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PSYCHIATRIC DISORDERS – WORLDWIDE ADVANCES

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Notice

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Meet the editor

Dr. Toru Uehara is currently an Associate Professor of mental health at the General Health Support Centre, Gunma University, Japan. He has been working in the area of neuropsychiatry, psychosomatic medicine and clinical psychology for over 20 years and published over 60 papers in English peer-reviewed journals, over 80 in Japanese journals, as well as 35 invited chapters in books. He is a board member of several Japanese societies or associations in these fields. His research and clinical interests focus on child and adolescent psychiatry, eating disorders, expressed emotion, family psychoeducation, neuroimaging, diagnosis and evaluations, psychosocial factors and campus mental health.

Contents

Preface

A psychiatric disorder is defined as any complex condition that involves the impairment of cognitive, emotional, or behavioral functioning. Aside from knowing the physical organic factors, its causal pathology has remained a mystery. Regarding recent advances in psychiatry and neurosciences, psychiatric disorders have been closely associated with socio-cultural, psychological, biochemical, epigenetic or neural-networking factors. Various classifications or diagnostic systems, such as the DSM or the ICD, are in use today. They apply different categories or hypothesis to temperament or human development. Most of the disorders present in Western societies can be divided according to similar criteria into psychosis, neurosis, substance use disorders, personality disorders and so on. However, they might sometimes also be interpreted as cross-cultural alterations present in the entire world. Consequently, a need for diverse approaches or support strategies arises, which should serve as common knowledge, empathetic views or useful skills for specialists in the filed.

As Puig mentions, the prefrontal cortex (PFC) controls the activity of many subcortical structures via the excitatory axons of pyramidal neurons. These projection neurons forward the output signals of a complex cortical microcircuit composed of distinct types of excitatory pyramidal neurons and numerous types of inhibitory interneurons. The author presents a summary of findings on anatomy, neurophysiology and pharmacology of serotonergic system in medial PFC of rats.

Yildirim describes “Radiologic Imaging in Psychiatric Disorders in the Light of Recent Developments” and gives us the information about current approaches in psychiatric disorders and essential imaging modalities. Innovational findings discussed in the section dealing with advanced brain MRI findings in psychiatric disorders, provided additional new methods to the conventional MRI.

Brain mechanisms underlying dissociation or impulsivity are in the focus of research on adolescent mental health. Uehara et al. investigated frontal activation during word productions using new near-infrared spectroscopy and examined correlations between relative changes of cerebral blood volume and psychopathology. The authors suggest that dissociation might be related to PFC and that the lack of anger suppression could be associated with stronger rostal PFC activation.

Schoepf and Neudeck present a comprehensive framework on Cognitive Behavioral Analysis System of Psychotherapy (CBASP), which is developed by McCullough Jr. as a specific outpatient protocol. CBASP integrates interpersonal and cognitive-emotional strategies for specific psychotherapeutic treatment of chronic depression. Consequently, a multi-step psychotherapy approach is represented that integrates CBASP`s intervention strategies in the therapy of chronic depressed patients with an inpatient history of therapy-refractory episodes.

Berget and Ihlebæk describe different aspects of human-animal relationship, with emphasis on positive impact that animals may have on human mental health. The effect on human mental health and its theoretical framework of animal-assisted intervention (AAI) are fully discussed. This chapter maintains its scientific and artistic integrity on AAI.

Pulido offers a general review of the most important empirical evidence about therapeutic alliance process in institutional settings and introduces the concept of Institutional Therapeutic Alliance (ITA) – clinical and empirical phenomenon that accounts for the working bond between the patient and the therapeutic staff perceived as a whole. The author also reports major results of a longitudinal study conducted to assess the ITA and explores the relationship with treatment outcomes.

Luzny comments that the quality of life (QOL) seems to be a good example of controversy present in modern medical science. Though the QOL may be too vague to be defined by conventional approach, and is viewed as an additional parameter present among many others, it represents integral feature which is connected to complex evaluation of therapy from patients' points of view, as the author mentions.

Myint and Schwarz present brief and basic immunology on inflammation, findings and mechanisms related to inflammatory state in psychiatric disorders, as well as the immune-endocrine interaction. This insightful chapter also covers immune-endocrine-tryptophan metabolism interaction and inflammation-tryptophan metabolism-neurochemicals interaction network.

Di Sciascio evaluates the clinical importance of cardiometabolic risk factors amongst people suffering from mental disorders, addressing the contribution of antipsychotic medications to increased cardiometabolic risk, as well as suggesting monitoring strategies for modifiable risk factors relevant to the treatment of serious mental illness.

Dalirsani et al. describe psychiatric comorbidity and pharmacotherapy in patients with lichen planus, which is a relatively common chronic mucocutanueons disease. Its exact etiology is not well understood. Therefore, this chapter is particularly important to readers interested in this topic.

It has been suggested that some infectious diseases can influence the development and course of several psychiatric disorders. Rackova and Janu describe the correlation between Borna disease virus and psychiatric disorders, asking whether viruses can

influence psychiatric disorders. Their backgrounds and relationships are discussed in a comprehensive and complete manner.

Zietsch gives us "Explanations for elevated psychiatric vulnerability in nonheterosexuals: Environmental stressors, genetics, and the HPA and HPG axes". This powerful review discusses greater risk of psychiatric disorders in nonheterosexuals, minority stress hypothesis, lifestyle, genetic factors, adverse childhood experiences and a novel neurohormonal explanation.

Dilley et al. describe the epidemiology, pathology and investigation of brain injury, with focus on findings in neuropsychiatric disorders. A discussion of difficulties in understanding aetiology in neuropsychiatry of mild traumatic brain injury, including postconcussional syndrome, is undertaken, providing an overview of key predisposing factors for long-term psychiatric presentations. A summary of pharmacological and practical treatment recommendations is also present.

Doria aims to assess the level of awareness, experiences and perceptions of Italian teachers with regards to their risks of developing work-related stress disorders. A new national body of legislation on work-related stress was introduced in the chapter, with a task to devise prevention programs for teachers.

This book is written by active clinicians and scientists from all over the world, making it fruitful for future development and collaboration in "world psychiatry". Finally, the editor would like to express his gratitude to the authors for their valuable contributions to this book project, and wish all the readers further collaborations in the field of psychiatry.

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Part 1

Brain and Psychiatry

1

Serotonergic Modulation of the Prefrontal Cortex: From Neurons to Brain Waves

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1. Introduction

Humans are remarkably proficient at some sophisticated and abstract tasks such as learning, memory and flexibility. These tasks depend on the prefrontal cortex, the cortical region most evolved in primates (Fuster, 2001; Miller & Cohen, 2001). The prefrontal cortex includes the most anterior structures of the frontal lobes, with some imprecise anatomical boundaries between different species of mammals. It has been defined across species according to its reciprocal anatomical connections with the mediodorsal nucleus of the thalamus (nucleus MD). The prefrontal cortex controls the activity of many subcortical structures via the excitatory axons of pyramidal neurons. These projection neurons forward the output signals of a complex cortical microcircuit composed of distinct types of excitatory pyramidal neurons and numerous types of inhibitory interneurons. It receives, along with the thalamus, dense innervation from many brain regions, including the serotonergic nuclei of the brainstem. During the last decade, research conducted by many laboratories has revealed that serotonin is a major modulator of prefrontal functions at the behavioral, neuronal and network levels. Its influences on cortical processing are implemented through multiple receptors expressed by pyramidal neurons as well as interneurons. These complex modulatory signals are altered in many psychiatric disorders such as schizophrenia and depression, where changes in receptor expression, neuron activity and brain waves have been observed. Furthermore, many psychiatric treatments -for instance, some antipsychotics and antidepressants- target the serotonergic system and the prefrontal cortex. Thus, understanding the role of serotonergic neurotransmission in prefrontal cortex function is of major importance. Here we present a summary of our findings on the anatomy, neurophysiology and pharmacology of the serotonergic system in the medial prefrontal cortex of the rat.

2. Serotonergic control of prefrontal cortex function

The involvement of serotonin in higher-order cognition is still poorly understood. Research conducted in non-human primates and rodents suggests that serotonin in the prefrontal cortex plays a modulatory role in spatial working memory (Williams et al., 2002) and is critical for cognitive flexibility, its depletion resulting in perseverative behaviours (Clarke et

al., 2004, 2005; Dalley et al., 2011; Robbins, 2000, 2005; Rygula et al., 2010). In addition, serotonin is relevant for behavioral inhibition, since elevated or reduced prefrontal serotonin is followed by deficits in impulse control (Dalley et al., 2002; Passetti et al., 2003; Talpos et al., 2005; Winstanley et al., 2003). Recent studies have provided some insights on the serotonergic receptors implicated in the regulation of cognitive flexibility and response inhibition (Boulougouris et al., 2008; Winstanley et al., 2003, 2004). Deficits in working memory, flexibility and control are associated with various psychiatric disorders, most notably schizophrenia, obsessive-compulsive disorder (OCD) and drug addiction. Thus, further work is required to investigate the specific roles of serotonergic receptors in these cognitive tasks.

The anatomy and neurophysiology of the serotonergic system, however, have been described in much more detail. The interconnections between the raphe nuclei, source of serotonergic neurons, and the distinct aspects of the prefrontal cortex in the rat brain are well known. Anatomical evidence indicates that medial prefrontal cortex neurons project densely to both the dorsal and median raphe nuclei of the brainstem. Conversely, serotonergic neurons of these nuclei send axons to the prefrontal cortex, where serotonin exerts its actions through several receptors expressed by a large population of neurons. These receptors are powerful modulators of cortical activity, both at a single neuron and network levels. In the following sections we describe the anatomy and neurophysiology of the serotonergic system in the rat prefrontal cortex.

2.1 Reciprocal connections between the raphe nuclei and the prefrontal cortex

Dense reciprocal connections exist between the dorsal and median raphe nuclei and the different regions of the medial prefrontal cortex: the cingulate, prelimbic and infralimbic cortices (Groenewegen & Uylings, 2000). Early anatomical studies utilizing retrograde and anterograde tracing methods revealed that all these cortices project to the raphe nuclei (Hajos et al., 1998; Peyron et al., 1998; Sesack et al., 1989). More recently, Vertes (2004) has reported that the prelimbic cortex sends denser axon bundles to the raphe nuclei than the infralimbic cortex. In turn, serotonergic neurons send ramified axons to many cortical areas, including the prefrontal cortex (Groenewegen & Uylings, 2000). This diffuse anatomy allows serotonergic neurons to modulate large cortical regions simultaneously.

The prefrontal-raphe descending pathway and the raphe-prefrontal ascending pathway have been functionally characterized *in vivo* in the anesthetized rat. Raphe projecting neurons in the prefrontal cortex were identified by stimulating electrically their terminals in the raphe nuclei and recording the action potential generated in the soma by the electrical wave travelling backwards along the axon, a phenomenon called antidromic activation (Amargos-Bosch et al., 2004; Celada et al., 2001; Puig et al., 2003, 2005, 2008). Similarly, serotonergic neurons were identified by antidromic activation from the prefrontal cortex (Celada et al., 2001). These approaches have yielded important insights into the relative conduction velocities of glutamatergic and serotonergic axons. The electrical stimulation of the prefrontal cortex was also used to investigate how prefrontal neurons control the activity of serotonergic neurons. A series of *in vivo* experiments indicate that serotonergic neurons in the dorsal raphe nucleus are strongly regulated by prefrontal afferents through a complex cellular mechanism. Prefrontal stimulation mainly inhibits serotonergic activity despite the descending projections are excitatory. This inconsistency may be explained by the presence of 5-HT1A autoreceptors on serotonergic

neurons: a small population of neurons is initially activated by direct excitatory inputs from the prefrontal cortex; this increases the release of serotonin within the dorsal raphe nucleus, which immediately reduces spiking of nearby neurons via 5-HT1A inhibitory autoreceptors. Another mechanism would involve direct excitation of inhibitory interneurons in the dorsal raphe nucleus by prefrontal afferents (Celada et al., 2001; Hajos et al., 1998).

2.2 Expression of serotonergic receptors in prefrontal cortex

The prefrontal cortex consists of a remarkably complex microcircuit composed of numerous types of pyramidal neurons and interneurons. According to Swanson (1998), the rat medial prefrontal cortex is composed of 5 layers. Layer 1 is the most superficial and contains the bodies of inhibitory interneurons and dendrites of pyramidal neurons. Layers 2 and 3 are full of somas of small pyramidal neurons and distinct types of interneurons, whereas layers 5 and 6 are packed with large pyramidal neurons -output neurons whose axons project to subcortical structures- and a myriad of different interneurons. Several classifications of GABAergic interneurons have been made based on their morphology, chemical neuroanatomy and electrophysiological properties (Gupta et al., 2000; Kawaguchi & Kubota, 1997, 1998; Markram et al., 2004; Uematsu et al., 2008).

Over the last 20 years, many efforts have been made to understand the expression pattern of serotonergic receptors in the heterogeneous neuron types present in the prefrontal cortex. Yet, we are still puzzled by the fact that many prefrontal neurons express at least one type of serotonergic receptor and oftentimes co-express several, despite these receptors may exert opposite effects on neuronal activity. For instance, 60% of pyramidal neurons in the rat prefrontal cortex express serotonin receptors 5-HT1A or 5-HT2A, particularly in layer 5 (De Almeida & Mengod, 2007; Kia et al., 1996; Lopez-Gimenez et al., 1997; Martin-Ruiz et al., 2001; Pazos & Palacios, 1985; Pompeiano et al., 1992, 1994; Santana et al., 2004; Weber & Andrade, 2010; Willins et al., 1997). Interestingly, around 80% of these co-express both receptors (Amargos-Bosch et al., 2004; Puig et al., 2010; Santana et al., 2004), although 5-HT1A receptors reduce whereas 5-HT2A receptors increase neuronal spiking (see below). The purpose of this co-expression has yet to be elucidated. However, the distribution of these receptors in different compartments of the pyramidal cell points to a specific role in action potential generation. 5-HT1A receptors are densely located on the axon initial segment (De Felipe et al., 2001), where they may downregulate the generation of action potentials; by contrast, 5-HT2A receptors are abundant on the apical dendrites (Jakab & Goldman-Rakic, 1998; Martin-Ruiz et al., 2001), where they increase excitatory currents (Marek & Aghajanian, 1999) (Figure 1). We have recently found that pyramidal neurons also express 5-HT2C receptors, but the degree of co-expression with 5-HT1A and 5-HT2A receptors is still unknown (Puig et al., 2010).

Cortical GABAergic interneurons are also innervated by serotonergic afferents from the raphe nuclei, as assessed by electron microscopy (De Felipe et al., 1991; Smiley & Goldman-Rakic, 1996). Consistently, populations of neocortical interneurons express serotonin receptors, in particular 5-HT1A, 5-HT2A and 5-HT3A receptors (De Almeida & Mengod, 2007; Jakab and Goldman-Rakic, 2000; Jansson et al., 2001; Morales & Bloom, 1997; Puig et al., 2004, 2010; Santana et al., 2004; Vucurovic et al., 2010; Weber & Andrade, 2010; Willins et al., 1997) (Figure 1). *In situ* hybridization histochemistry has revealed that, unlike pyramidal

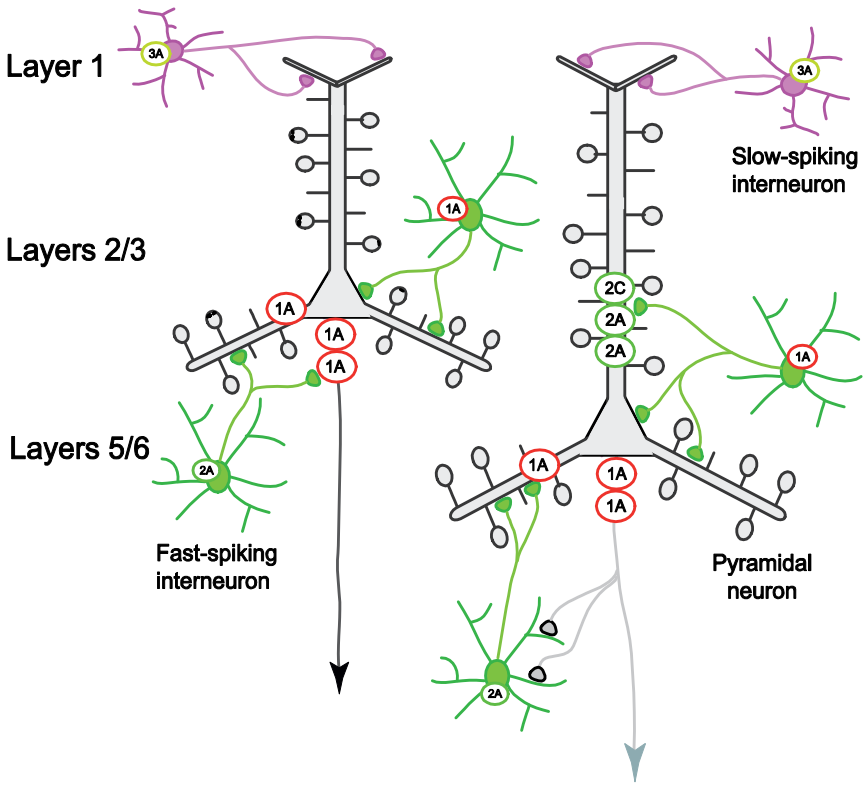

Fig. 1. Localization of serotonin receptors within the prefrontal cortex microcircuit. Many pyramidal neurons in deep layers co-express 5-HT1A and 5-HT2A receptors. In addition, distinct populations of local inhibitory interneurons that express serotonin receptors innervate different compartments of the pyramidal cell: 5-HT1A- and 5-HT2A-expressing fast-spiking interneurons are preferentially located in deep layers where they contact pyramidal neurons at the soma and proximal dendrites; slow-spiking interneurons that express 5-HT3A receptors are located in superficial layers where they innervate pyramidal neurons at the distal dendrites. Modified from Puig et al., 2008.

neurons, two separate populations of fast-spiking interneurons express 5-HT1A and 5-HT2A receptors and not 5-HT2C receptors. These interneurons are more abundant in layers 2, 3 and 5, particularly in layer 5, where each receptor subtype is expressed by 50% of interneurons (Puig et al., 2010). Thus, fast-spiking inhibitory neurons that express 5-HT1A or 5-HT2A mRNAs are enriched in layer 5, just as pyramidal neurons. In addition, a population of slow-spiking interneurons expresses 5-HT3A receptors (Ferezou et al., 2002; Morales et al., 1996; Morales & Bloom, 1997; Puig et al., 2004). These neurons are particularly abundant in layer 1, an area devoid of pyramidal cell bodies but full of their dendrites, where 40% of inhibitory cells express 5-HT3A receptors. In the rat, these neurons also express cholecystokinin (CCK), vasoactive intestinal peptide (VIP) or neuropeptide Y (Ferezou et al., 2002; Vucurovic et al., 2010), whereas 5-HT3 receptors have been localized to calbindin- and calretinin-containing small size interneurons in the monkey (Jakab & Goldman-Rakic, 2000). Therefore, the distribution of 5-HT3A-expressing interneurons is complementary to that of 5-HT1A- and 5-HT2A-expressing interneurons, through which

serotonin can control the entire pyramidal cell (Figure 1). This sophisticated expression pattern of serotonergic receptors in pyramidal neurons and interneurons allows serotonin to exert a profound control over the activity of prefrontal cortex microcircuits.

2.3 Serotonin modulates neuronal activity in prefrontal cortex

With the exception of the 5-HT3 receptors (ligand-gated ion channels), serotonin receptors couple to G-proteins to exert their effects (Hoyer et al., 1994). In the slice preparation, 5-HT1A and 5-HT2A receptors mediate inhibitory and excitatory responses, respectively, in layer 5 pyramidal neurons (Aghajanian & Marek, 1997; Araneda & Andrade, 1991; Arvanov et al., 1999; Marek & Aghajanian, 1998; Tanaka & North, 1993; Zhou & Hablitz, 1999). 5-HT1A hyperpolarizations involve coupling to G_i/G_o proteins and increase in potassium conductance (Gk). 5-HT2A-mediated depolarizations follow activation of G_q/G_{11} proteins and decrease in Gk conductance. Similarly, serotonin hyperpolarizes and depolarizes neocortical interneurons *in vitro* via 5-HT1A and 5-HT2A receptors (Foehring et al., 2002; Jakab & Goldman-Rakic, 1998; Xiang & Prince, 2003; but see Gulledge et al., 2007), and induces fast membrane potential depolarizations via 5-HT3A receptors (Ferezou et al., 2002; Foehring et al., 2002; Xiang & Prince, 2003).

To investigate the roles of these receptors *in vivo* we stimulated electrically the raphe nuclei – which induces measurable increases of prefrontal serotonin release (Gartside et al., 2000; McQuade & Sharp, 1995) - while recording the responses on identified pyramidal neurons and interneurons of the prefrontal cortex in anesthetized rats. Serotonin evoked three different responses on pyramidal neurons: inhibitions (66%), excitations (13%) and biphasic responses (20%), composed of an initial inhibition followed by an excitation (Puig et al., 2005) (Figure 2). Considering the proportion of inhibitions and mixed responses, serotonin exerts preferential inhibitory actions on the prefrontal cortex *in vivo*, similar to those observed in early microiontophoretic and stimulation studies (Ashby et al., 1994; Jacobs & Azmitia, 1992; Mantz et al., 1990). Pharmacological manipulations confirmed that the decreases and increases of activity were mediated by 5-HT1A and 5-HT2A receptors, respectively, and that the biphasic responses likely corresponded to pyramidal neurons co-expressing both receptors (Amargos-Bosch et al., 2004; Hajos et al., 2003; Puig et al., 2003, 2005). In addition, the administration of the 5-HT2A/2C receptor agonist DOI increased activity of pyramidal cells, an effect reversed in most neurons by a selective 5-HT2A receptor antagonist (Martin-Ruiz et al., 2001; Puig et al., 2003). However, in a small population of neurons the 5-HT2A receptor antagonist failed to reverse DOI's induced excitation. This suggests that 5-HT2C receptors also mediate excitatory responses *in vivo* in a subpopulation of pyramidal neurons, in accordance with their pattern of expression in the prefrontal cortex (Puig et al., 2010).

Noteworthy, the amount of biphasic responses (20%) recorded was smaller than the reported proportion of pyramidal neurons co-expressing 5-HT1A and 5-HT2A receptors (45-50%). So, possibly many pyramidal neurons that co-express these receptors are indeed inhibited by serotonin. A plausible explanation would involve the dense localization of 5-HT1A receptors on the axon initial segment of pyramidal cells (Azmitia et al., 1996; Cruz et al., 2004; Czyrak et al., 2003; De Felipe et al., 2001; Martin-Ruiz et al., 2001), coincident with the cortical GABAergic axo-axonic synapses between chandelier cells and pyramidal cells (De Felipe et al., 2001; Somogyi et al., 1998), and downstream of 5-HT2A receptors in the process of spike generation (Figure 1). This would assign a prominent inhibitory role to 5-HT1A receptors in the control of pyramidal activity.

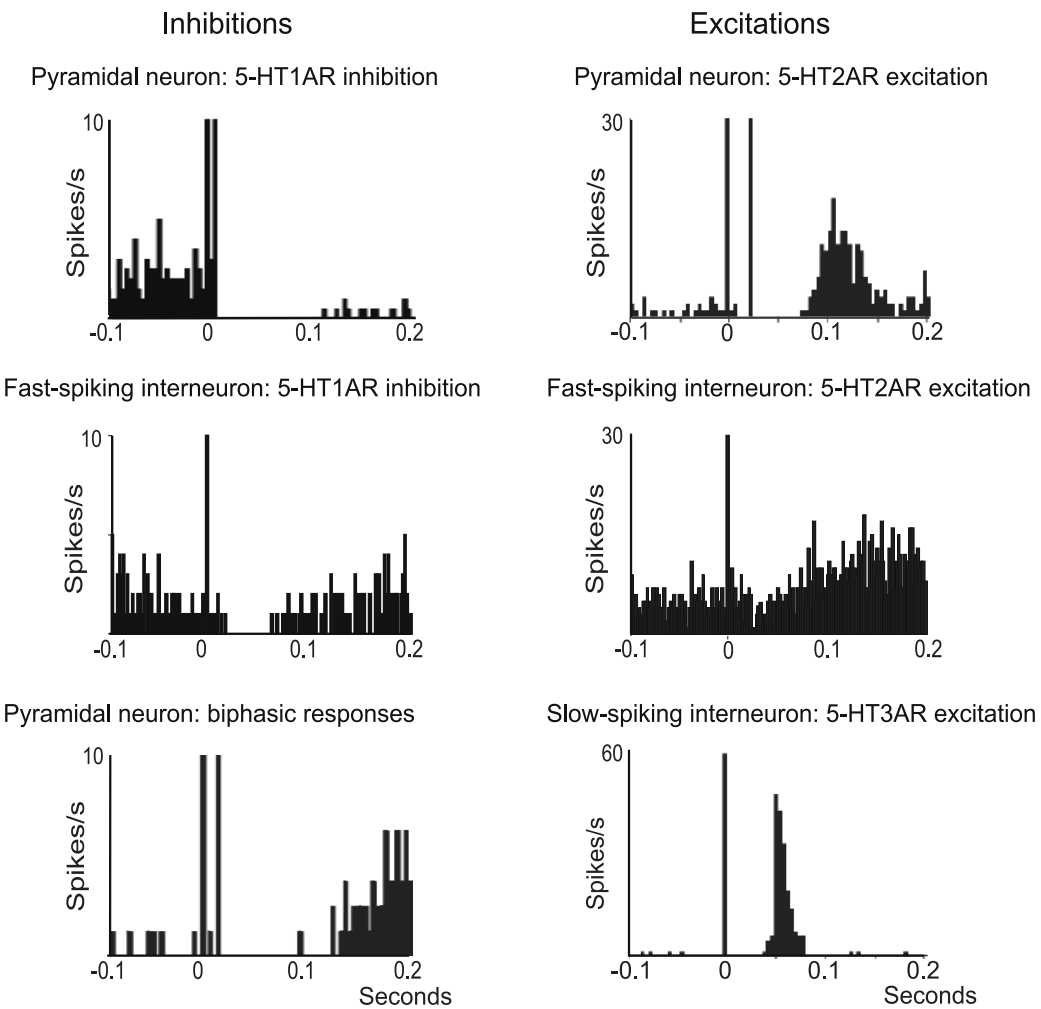

Fig. 2. Serotonin inhibits and activates distinct populations of prefrontal neurons. Peri-stimulus histograms depicting the firing rate of pyramidal neurons and different types of interneurons recorded in the prefrontal cortex of anesthetized rats during electrical stimulation of the dorsal raphe nucleus (time 0), which induces release of serotonin in the prefrontal cortex. Note that 5-HT1A-mediated inhibitions are shorter in fast-spiking interneurons compared to pyramidal neurons and that 5-HT3A-mediated excitations have a shorter delay and duration than 5-HT2A-mediated excitations. Modified from Amargos-Bosch et al., 2004 and Puig et al., 2004, 2010.

A second possibility entails an activation of non-serotonergic inhibitory afferents to the prefrontal cortex from the raphe nuclei. GABAergic projection neurons have been found in the dorsal raphe nucleus, and many inhibitions have an initial component independent of 5-HT1A receptors (Li et al., 2001; Puig et al., 2005). Moreover, the involvement of direct GABAergic projections to the prefrontal cortex is suggested by the short-latency (≤ 8 ms) inhibitions recorded in prefrontal pyramidal neurons that cannot be accounted for by the slow conduction velocity of serotonergic axons (Puig et al., 2005).

GABAergic interneurons may play an important role in the inhibitory effects of serotonin as well. We have recently shown that subgroups of prefrontal fast-spiking interneurons are modulated by 5-HT1A and 5-HT2A receptors *in vivo* (Puig et al., 2010). Akin to previous studies, we stimulated electrically the dorsal raphe nucleus and recorded the responses on parvalbumin-expressing fast-spiking interneurons of the prefrontal cortex. Parvalbumin is a calcium binding protein selectively expressed by this type of interneuron (Kawaguchi & Kubota, 1997; Uematsu et al., 2008). We observed 5-HT1A-mediated decreases and 5-HT2A-mediated increases of activity in 61% and 10% of the recorded cells, respectively (Figure 2). However, unlike pyramidal neurons, we found very few biphasic responses (6.5%; Puig et al., 2010). This may be due to the fact that separate populations of fast-spiking interneurons express 5-HT1A and 5-HT2A receptors. Again, a predominance of 5-HT1A-mediated inhibitions indicates that serotonin exerts a potent inhibitory drive on cortical fast-spiking interneurons, similar to that on pyramidal neurons. On a similar pace, we identified slow-spiking interneurons in superficial layers of the prefrontal cortex that are excited by serotonin through 5-HT3A receptors (Puig et al., 2004). Interestingly, the latency and duration of the 5-HT3A-mediated excitations were shorter than those elicited by 5-HT2A receptors in pyramidal and fast-spiking neurons of the same area (Figure 2). This is consistent with this receptor being an ion channel and not coupled to G-proteins. Thus, not only is the expression pattern of 5-HT2A- and 5-HT3A-expressing interneurons complementary, but the timing of their activation by serotonin is finely tuned as well.

2.4 Serotonin modulates brain waves in prefrontal cortex

We have recently uncovered that serotonin is a potent modulator of slow waves in the prefrontal cortex (Puig et al., 2010). Under chloral hydrate anesthesia, the predominant oscillatory activities recorded through intracortical field potentials are slow waves (< 2 Hz) that resemble the slow rhythms of natural slow-wave sleep. Slow waves are thought to be critical for memory consolidation (Ji & Wilson, 2007; Marshall et al., 2006; Landsness et al., 2009; Louie & Wilson, 2001; Stickgold, 2005), and are generated by synchronized neuronal ensembles that oscillate between periods of activity (UP states) and silence (DOWN states). UP and DOWN states reflect alternating periods of membrane depolarization and hyperpolarization of large neuronal networks (Contreras & Steriade, 1995; Mukovski et al., 2007; Steriade et al., 1993).

We stimulated the dorsal raphe nucleus at a frequency similar to the discharge rate of serotonergic neurons (1 Hz) in anesthetized rats. The stimulations consistently and reversibly increased in the frequency of slow waves: UP and DOWN cycles appeared more irregular and of shorter duration and the peak of the power spectra (that marks the predominant frequency) increased significantly from 0.74 to 0.94 Hz (Figure 3). This suggests that the 1 Hz stimulations were imposing their frequency onto the cortical network. In fact, increasing the release of serotonin into the cortex -by augmenting the intensity of the stimulations- reliably imposed a frequency of 1 Hz on slow oscillations. Remarkably, serotonin appeared to evoke this increase in frequency by promoting the initiation of UP states from DOWN states with a very short latency. Therefore, the activity of serotonergic neurons in the raphe nuclei may directly regulate the frequency of cortical slow oscillations by promoting UP states. Moreover, during raphe stimulations the amplitude of slow waves was reduced compared to pre-stimulation epochs, and the time that slow waves spent in UP states was greater than before or immediately after the stimulations (i.e. DOWN state

potentials were reduced; Figure 3B). Since UP states are generated by the synchronous depolarization of large ensembles of cortical neurons, these results suggest that serotonin might have excitatory actions on cortical networks.

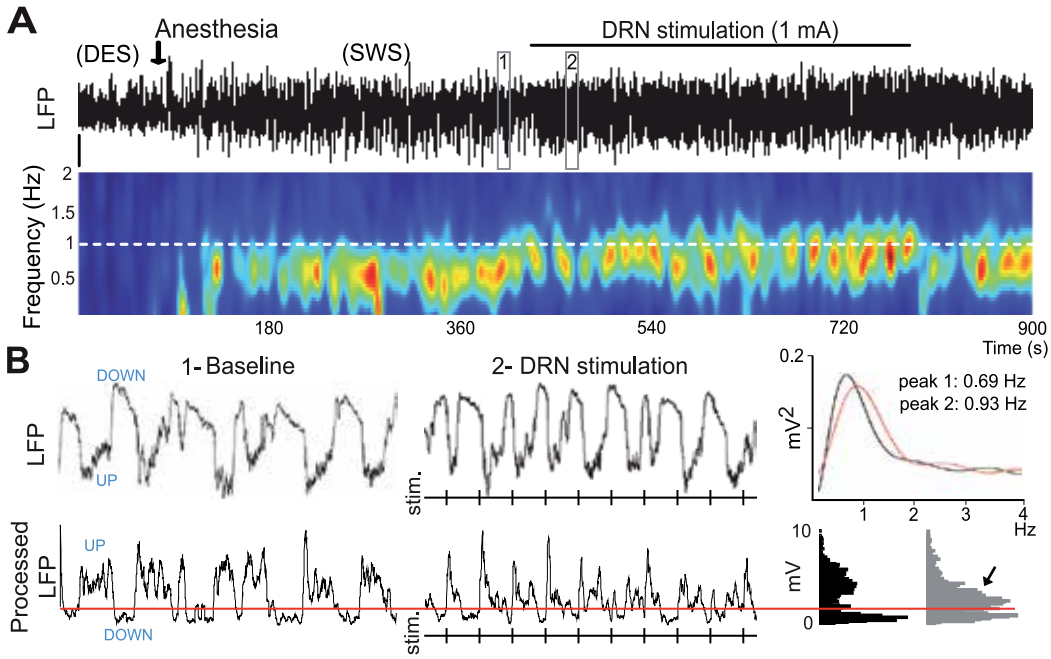

Fig. 3. Serotonin modulates slow waves in prefrontal cortex.
Electrical stimulation of the dorsal raphe nucleus (DRN) at 1 Hz increases the frequency and reduces de amplitude of cortical slow waves (< 1 Hz). (A) Top, local field potential (LFP) signal depicting an epoch of desynchronization (DES, absence of slow waves) and anesthesia-induced slow-wave sleep (SWS) following the injection of chloral hydrate anesthesia. Boxes 1 and 2 are expanded in (B). Bottom, time-frequency representation depicting the change in power (root mean square of the amplitude) over time (red indicates high power, blue low power). White dashed line marks the frequency of stimulation. Note that the predominant band increases in frequency towards the frequency of stimulation during DRN stimulation. (B) Top, expanded 10-second traces from (A). Vertical lines correspond to times of DRN stimulation. Power spectra for 1 min segments that contain the 10 s traces in boxes 1 and 2 are shown on the far right. Bottom, LFPs were processed off-line for an accurate measure of UP state duration. A threshold was set (red line) to discriminate - UP states. Note the increase in UP state potentials during the stimulations (arrow). Modified from Puig et al., 2010.

Indeed, high frequency stimulation of the dorsal raphe nucleus (100 Hz), which induces a massive release of serotonin in the cortex, completely suppressed cortical slow waves by eliminating DOWN states (Puig et al., 2010). These results support the proposed role of the serotonergic system in modulating the transition between sleep and awake states (Dringenberg & Vanderwolf, 1997; Portas et al., 2000). Furthermore, the administration of an antagonist of 5-HT2A/2C receptors altered slow waves, but not antagonists of 5-HT1A or 5-HT2C receptors (Figure 4). This implicates 5-HT2A receptors in the regulation of slow

waves. Blockade of 5-HT2A receptors desynchronized slow oscillations by reducing the number, duration and amplitude of DOWN states, which resulted in a significant increase of UP state potentials similar to that observed after raphe stimulation (Puig et al., 2010).

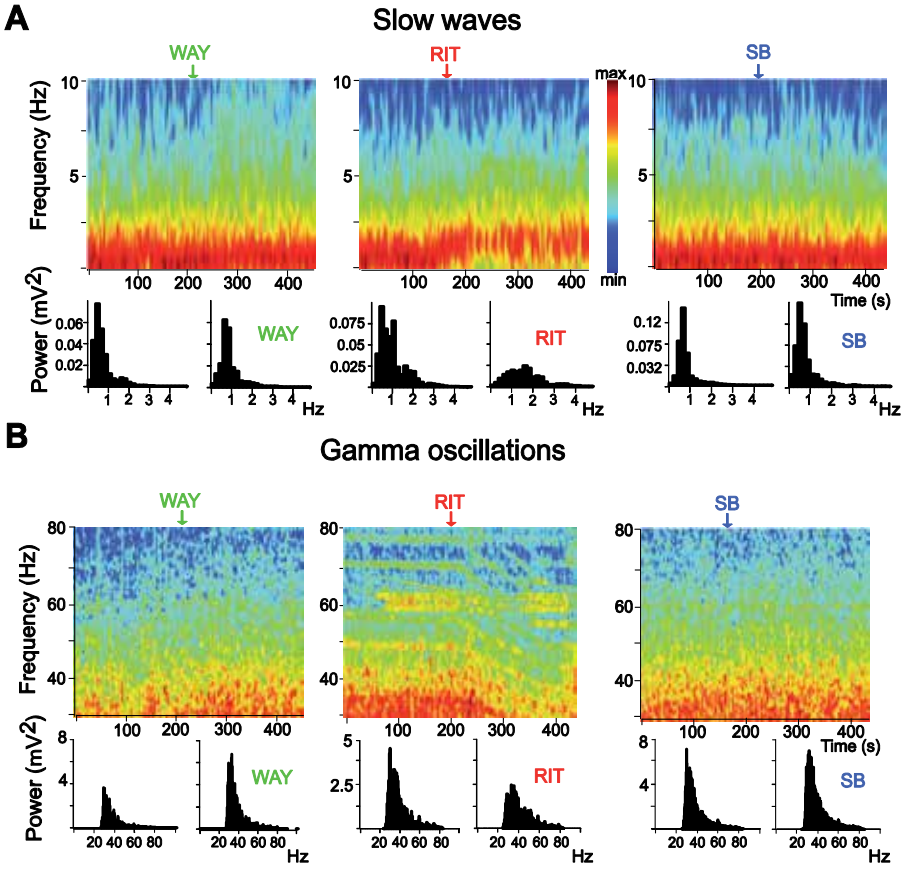

Fig. 4. Serotonin receptors modulate slow and gamma oscillations in prefrontal cortex. Effect of WAY (WAY100635, 5-HT1A receptor antagonist), RIT (ritanserin, 5-HT2A/2C receptor antagonist) and SB (SB242084, 5-HT2C receptor antagonist) on the power of slow waves and gamma oscillations in the rat prefrontal cortex. (A) The power of slow waves decreases after injection of RIT but not SB or WAY, indicating a modulation by 5-HT2A receptors. (B) WAY increases whereas RIT decreases the power of gamma oscillations. This suggests that serotonin regulates gamma rhythms both via 5-HT1A and 5-HT2A receptors. Modified from Puig et al., 2010.

In addition, serotonin exerts a strong modulation of prefrontal gamma oscillations (30-80 Hz). Gamma rhythms provide a temporal structure for cognitive tasks such as attention, sensory processing and working memory (Howard et al., 2003; Singer, 1999; Ward, 2003). We found that blockade of 5-HT1A receptors increases whereas blockade of 5-H2A receptors decreases the amplitude of gamma waves (Figure 4; Puig et al., 2010). Since networks of fast-spiking interneurons generate and are modulated by gamma oscillations (Bartos et al., 2007; Cardin et al., 2009; Puig et al., 2008; Whittington & Traub, 2003), we

hypothesize that serotonin regulates gamma rhythms through fast-spiking interneurons expressing 5-HT1A and 5-HT2A receptors. There are a number of observations that support this. First, high-frequency stimulation of the dorsal raphe nucleus reduces the amplitude of gamma waves in the prefrontal cortex and, as mentioned earlier, serotonin predominantly inhibits cortical fast-spiking interneurons. Second, blockade of 5-HT1A receptors increases the amplitude of gamma waves and the spiking of 5-HT1A-expressing fast-spiking interneurons, while sharpening the synchronization of these neurons to gamma cycles. Thus, stimulation of cortical 5-HT1A receptors would desynchronize gamma oscillations by reducing the activity and synchronization of 5-HT1A-expressing fast-spiking interneurons. Third, blockade of 5-HT2A receptors decreases the amplitude of gamma waves and desynchronizes 5-HT2A-expressing fast-spiking interneurons from gamma waves. Hence, stimulation of cortical 5-HT2A receptors would enhance gamma oscillations by synchronizing 5-HT2A-expressing fast-spiking interneurons. Fourth, fast-spiking interneurons in the prefrontal cortex do not express 5-HT2C receptors and, consistently, blockade of these receptors does not alter gamma oscillations. Finally, the interplay between pyramidal neurons and fast-spiking interneurons further enhances gamma oscillations. Thus, during anesthesia-induced sleep-like states serotonin may down regulate gamma oscillations simply because it inhibits most pyramidal and fast-spiking neurons.

2.5 Dual actions of serotonin on prefrontal cortex networks

The data presented above suggest that serotonin modulates neuron activity and network oscillations in the prefrontal cortex in remarkably different ways, at least during anesthesia-induced slow-wave sleep. It decreases spiking of a large population of neurons while exciting their membranes so that there is a switch from DOWN-hyperpolarizing to UP-depolarizing states during slow waves. How can these two opposing effects be reconciled? Serotonin may be acting upon 5-HT1A receptors on the soma and axon initial segment of pyramidal neurons to prevent generation of action potentials while promoting the increase of excitatory postsynaptic potentials (EPSCs) on their apical dendrites via 5-HT2A -and perhaps 5-HT2C- receptors. Oscillatory activities are recorded through local field signals that reflect the summation of postsynaptic potentials in dendrites, and recent studies suggest that they are independent of action potential generation. By contrast, spiking activity represents the results of local processing (Monosov et al., 2008; Nielsen et al., 2006). We propose that serotonin plays a dual action on cortical pyramidal networks by enhancing synaptic inputs onto the dendrites while down-regulating spiking at the axon level.

It is well documented that some interneurons are potent modulators of pyramidal membrane potentials and that they can innervate many pyramidal neurons simultaneously. Thus, it is fair to assume that interneurons may participate in the generation of UP and DOWN states by inhibiting large populations of pyramidal cells synchronously. Nevertheless, a role for inhibitory interneurons in the proposed dual model of serotonin actions is unclear. First, superficial layers of the cortex -that are rich in pyramidal dendrites- contain 5-HT3A-expressing interneurons, whose activation by serotonin should indeed decrease excitability of distal pyramidal dendrites. Second, it is unknown at this time what compartments of the pyramidal cell 5-HT1A- and 5-HT2A-expressing fast-spiking interneurons interact with. In a configuration consonant with our model, 5-HT2A-containing interneurons would preferentially innervate the soma and axon of pyramidal

neurons, whereas 5-HT1A-containing interneurons would do so on pyramidal dendrites (Figure 1). Clearly, further work is needed to elucidate the exact role of serotonin-modulated interneurons on the cortical microcircuit.

The proposed dual model described earlier is based on observations obtained during anesthesia-induced slow-wave sleep states. Although it has been reported a participation of serotonin in the transition between sleep and alertness, it is currently poorly understood how serotonin differentially modulates prefrontal microcircuits during distinct arousal states. In that sense, some of our recent work has shed some light into this issue (Puig et al., 2008, 2010). We recorded fast-spiking interneurons *in vivo* in the rat prefrontal cortex under chloral hydrate anesthesia. By adjusting the level of anesthesia we allowed short-lasting epochs of cortical desynchronization, periods of time with absence of slow waves that resemble awake states. This manipulation allowed us the examine the firing patterns of cortical neurons during sleep-like states (deep anesthesia) and wake-like states (light anesthesia). We identified two populations of fast-spiking interneurons based on the activity during cortical UP states and the difference in spiking between sleep-like and wake-like states. One population preferentially discharges during the first half of UP states ('early' cells) and decreases spiking during wake-like states. A second population behaves in the opposite manner: it predominantly fires on the second half of UP states ('late' cells) and increases dramatically the activity during wake-like states. This suggests that this latter population may be responsible for generating the gamma oscillations associated with cognitive processing during wakefulness. Intriguingly, these two populations of interneurons are coupled to different phases of gamma cycles, suggesting a sequence of activation from 'early' to 'late' neurons (Puig et al., 2008). Altogether, subpopulations of cortical interneurons may play different but complementary roles during sleep and alertness. We assessed the effects of serotonin on these two neuronal populations during sleep-like and wake-like scenarios (Puig et al., 2010). Although serotonin inhibited most fast-spiking neurons during both states, there was a remarkable increase in the proportion of excited cells during wake-like states. Consistently, the 'late' population (which is more active during alertness) showed a greater amount of excitations. Thus, serotonin may activate a larger population of cortical interneurons during alertness, exerting a more balanced inhibition and excitation which could provide a fine control of gamma oscillations during cognitive tasks.

3. Relevance for psychiatric disorders

Prefrontal function and metabolism is altered in patients with severe psychiatric disorders (Andreasen et al., 1997; Drevets, 2001; Weinberger et al., 1994). For instance, cognitive deficits in schizophrenia patients are mediated by derangements in brain circuits involving the prefrontal cortex (Bertolino et al., 2000; Elvevag & Goldberg, 2000), and an imbalance in glucose metabolism between prefrontal cortex and several anatomically related areas has been described (Andreasen et al., 1997). Similarly, abnormal glucose utilization has been consistently found in prefrontal cortex of patients with major depression (decrease) and post-traumatic stress disorder (increase). Several observations support a role for serotonin receptors in the pathophysiology of these mental illnesses. First, the expression of some serotonin receptors is abnormal in the frontal lobes of psychiatric patients (Arango et al., 1997; Gurevich et al., 2002); and second, hallucinogens such as LSD or DOI are 5-HT2A

agonists and atypical antipsychotics are potent 5-HT2A antagonists (Artigas, 2010; Kroeze & Roth, 1998; Meltzer, 1999; Meltzer & Huang, 2008).

The effects of the hallucinogen DOI have been examined on the activity of pyramidal neurons in the rat prefrontal cortex. DOI, via stimulation of cortical 5-HT2A receptors, increases and decreases the firing rate of distinct subpopulations of pyramidal neurons (Puig et al., 2003). Increases of activity might follow direct stimulation of 5-HT2A receptors, whereas the decreases likely involve nearby interneurons activated by this receptor. Thus, cortical interneurons expressing 5-HT2A receptors may play a crucial role in the actions of some hallucinogens and antipsychotics. Unfortunately, we are unaware of any study that has examined the *in vivo* effects of specific hallucinogens and antipsychotics on this particular population of interneurons. In our 2010 study (Puig et al., 2010) the effects of the selective 5-HT2A/2C antagonist ritanserin were assessed on a very small group of fast-spiking interneurons, rendering inconclusive results. The results yielded by these investigations would be very relevant considering that altered GABA neurotransmission has been reported in schizophrenia. Transcript levels of GAD65/67, enzymes responsible for most GABA synthesis in the cortex, are consistently lower in the prefrontal cortex of subjects with schizophrenia, especially in fast-spiking interneurons (Gonzalez-Burgos et al., 2010; Lewis et al., 2005, 2011).

It has been described in recent years that many psychiatric patients show altered brain waves in a variety of brain regions (Basar & Güntekin, 2008). For instance, the synchronization of slow (<1 Hz), delta (1-4 Hz) and gamma (30-80 Hz) bands is reduced in schizophrenia, major depression and bipolar disorder (Cho et al., 2006; Hoffmann et al., 2000; Keshavan et al., 1998; Spencer et al., 2003; Uhlhaas & Singer, 2006). Remarkably, the hallucinogen and 5-HT2A receptor agonist DOI reduces the amplitude of low frequency oscillations (slow and delta) in the prefrontal cortex of anesthetized rats (Celada et al., 2008). DOI's effects on cortical networks may derive from a depolarizing action on a large population of 5-HT2A-expressing neurons, consistent with the dual model presented earlier. This effect was reversed by a selective antagonist of 5-HT2A receptors, and by the classical and atypical antipsychotics haloperidol and clozapine. The attenuation of DOI-induced alterations of slow oscillations is possibly related to the ability of these drugs to suppress psychotic symptoms in schizophrenic patients. Interestingly, haloperidol was less effective than clozapine in reversing the effects, which may likely be explained by the higher affinity of the latter for 5-HT2A receptors. Surprisingly, the 5-HT2A/2C antagonist ritanserin reduces the amplitude of slow oscillations via blockade of 5-HT2A receptors as well (Figure 4; Puig et al., 2010). Thus, either pharmacological stimulation or blockade of 5-HT2A receptors with DOI and ritanserin, respectively, desynchronizes slow rhythms in the prefrontal cortex. This strongly suggests that a balanced activation of 5-HT2A receptors is critical for a stable synchronization of slow waves. Interestingly, a reduction in slow wave activity has been detected in patients with schizophrenia during sleep (Hoffmann et al., 2000). We propose that a potential source of this decrease could be an unbalanced stimulation of cortical 5-HT2A receptors. Impaired gamma oscillations and synchrony have been reported in schizophrenia patients as well (Basar & Güntekin, 2008; Cho et al., 2006; Gonzalez-Burgos & Lewis, 2008, 2010; Spencer et al., 2003; Uhlhaas and Singer, 2006). Unfortunately, the effects of DOI and antipsychotics were not assessed on cortical gamma oscillations in the studies described earlier. Detailed knowledge of the brain mechanisms underlying serotonergic modulation of gamma oscillations could provide valuable

information for our understanding of why most schizophrenia treatments are largely ineffective at improving cognition.

4. Conclusions

The prefrontal cortex is a key area for the control of higher-order executive tasks such as learning, working memory, flexibility and behavioral control. The prominent innervation by serotonergic afferents and the dense expression of serotonergic receptors in this region suggest that serotonin is a major modulator of prefrontal cortex function. Over the last decade we and others have unveiled the complex pattern of expression of the most abundant serotonergic receptors in this area, and have described in some detail how these receptors modulate the activity of pyramidal neurons and interneurons *in vivo*. From these series of investigations we can conclude that serotonin primarily inhibits pyramidal and fast-spiking neuronal activity via 5-HT1A receptors and excites a small population of these via 5-HT2A receptors. The exquisite expression pattern of 5-HT1A, 5-HT2A and 5-HT3A receptors in distinct populations of fast-spiking and slow-spiking interneurons allows serotonin to control the different compartments of pyramidal neurons more or less independently. Moreover, serotonin finely tunes the timing of its actions through the different properties of its receptors (G-coupled vs. ion channels) and the cell type that expresses them. This sophisticated mechanism of control might be important for the precise computations required during cognitive tasks.

Serotonin is also a potent modulator of brain waves in the prefrontal cortex. Serotonergic neurons of the raphe nuclei may play a role in regulating the frequency and amplitude of slow oscillations during sleep, a phenomenon critical for memory consolidation. Serotonin exerts an excitatory effect on cortical networks during slow wave sleep via 5-HT2A receptors. Thus, serotonin may play dual actions on large pyramidal ensembles by down regulating spiking while enhancing the inputs onto the dendrites. This is possibly accomplished by 5-HT1A receptors located on the axon initial segment of pyramidal neurons and 5-HT2A receptors located on the apical dendrites. Further studies are required to elucidate the exact involvement of interneurons in this complex modulation. Serotonin regulates the amplitude of gamma waves as well, perhaps through 5-HT1A- and 5-HT2A-expressing fast-spiking interneurons. Interestingly, the latter population tends to be more active during wakefulness whereas the former is active both during sleep and wakefulness. Therefore, serotonin may adjust the activity of these two populations of interneurons to control the amplitude of gamma waves during executive tasks.

The prefrontal cortex is altered in many mental illnesses and some psychiatric treatments target serotonergic receptors in this area. At this time, more work is needed to really comprehend the alterations of the serotonergic system in these disorders. In fact, the role of serotonin in the prefrontal cortex of the healthy brain is still poorly understood. Recent studies have revealed that GABAergic neurotransmission in interneurons may be altered in some of these mental conditions. The fact that interneurons in the prefrontal cortex express serotonergic receptors and most likely play a critical role in modulating cortical activity and brain waves makes them good candidates as targets for future psychiatric treatments.

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2

Radiologic Imaging in Psychiatric Disorders in the Light of Recent Developments

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1. Introduction

Psychiatric disorders account for a great majority of overall health problems. Therefore, psychiatric conditions have become of great importance for today's world. It is a known fact that quality of life is substantially determined by the mental health of an individual. A great number of physical diseases have also important mental component. As its importance has been defined here, psychiatric science has shown considerable change particularly in the second half of the current century, and making a diagnosis has become available not only via physical examination, but also by detecting underlying organic factors. In line with the advances in clinical psychiatry, neuropsychiatry and biologic psychiatry, considerable progression has been achieved both in diagnosis and also in treatment. In this process, structural and functional imaging techniques have remarkably contributed to the etiology of psychiatric diseases to be understood better, as well as to the development of diagnostic approach. Owing to the current development in radiological imaging modalities, certain anatomical or functional abnormalities could be assessed, from now on, in the psychiatric diseases that could have not been predicated upon any organic basis previously. In many studies conducted until today, diagnosis or follow-up in the course of the treatment has focused on development process of the disorder, pathophysiology, underlying progressive picture, and neural process, as well as potential factors, rather than imaging methods.

Since the invention of X-rays, available information due to the advances both in radiology and in computer technology has become sharable as well. With the new methods, other than old or conventional modalities, it has been possible to not only anatomically visualize but also functionally evaluate the tissues or organs. Exposure to ionized radiation is not a matter of question with such modalities developed in MRI field. Moreover, these techniques and experiences in this field are gradually becoming available day by day. Operator and software dependent variability of these methods that has been relatively going on would be solved in time and be standardized. Current advanced MRI modalities that can be used in addition to routine examinations include high resolution imaging (3Tesla), functional magnetic resonance imaging (f-MRI), perfusion MRI (p-MRI), diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS). It is aimed to review the functional (f-MRI) or microanatomical structure (DWI, DTI) or metabolite (MRS) changes in imaging of the

psychiatric disorders. Moreover, metabolic alterations in structurally preserved normal areas can also be measured with PET/MRI fusion imaging. The next stage of brain imaging is estimated to be the molecular methods. Now, imaging at neuroreceptor level, as well as at neurotransmitter synthesis and transport stages, is aimed with advancing molecular imaging and is under research. All of the anatomic, metabolic or functional information obtained from all these modalities is helpful in directing the radiologists and/or psychiatrists to the origin of the abnormality, especially in the cases whose having normal conventional cross-sectional images.
In this section, firstly, the information about current approaches in psychiatric disorders and essential imaging modalities will be discussed completely, but briefly. Subsequently, innovational findings under the title of "advanced brain MRI findings in psychiatric disorders" provided additional new methods to the conventional MRI findings.

2. Information about basic imaging methods in psychiatric patients: Current methods and advances

Until today(now, bence), current psychiatric diseases have been studied under the topic of neuropsychiatry. Radiological modalities (**Table 1**) were used in the psychiatric diseases to investigate, eliminate, and to assess the prognosis of acute stroke, as well as to diagnose brain death, for trauma evaluation, to identify the focus in epilepsy, in the differential diagnosis of dementia, to investigate Parkinsonian syndromes, and to evaluate mass or recurrence, which are more evident pathologies with partially defined spectrum (Kwon et al., 2004). Before introducing the main subject, we thought that it would be necessary to summarize conventional modalities that have been used in the psychiatric and neuropsychiatric cases so far(in order to notice the contribution of advances discussed in this section). Of note, although the topic of this section has focused on "Advanced MR Imaging", general tendency in current technology is to perform all the examinations by multiparametric imaging until the pathology is detected before the patient leaves the radiology unit.
It should be kept in mind that, patients hospitalized for physical diseases or underwent invasive or non-invasive procedures experience fear and anxiety and these experiences sometimes lead to anxiety or depressive disorders (Krzyaowski et al., 1998). Considering that 30% to 60% of hospitalized patients were reported to have diagnosable psychiatric disorders, we should know that various stages of imaging might also cause psychiatric symptoms, in addition to the data mentioned up to now. Therefore, patients with anxiety, clostrophobia, or with known psychiatric disease should undergo radiological processes under the supervision of an auxiliary team including companion, consultant and security (Krzyaowski et al., 1998).

2.1 Computed tomography

The chance of imaging with multidetector subsecond systems has become available due to the acceleration in CT technology. This enables the completion of the process without problem in the patients with poor cooperation. In addition to being used for the elimination of urgent intracranial pathologies, it may also be used in the patients that are non-cooperated as a guide in placing special electrodes to stimulate ventral intermediate nucleus

of thalamus with high frequency stimulators (3D volumetric CT, **Figure 1**), which are used in the treatment of Parkinsonian symptoms (Schulz et al., 2005). Moreover, CT-perfusion may be an alternative problem solver in the cases, in who MRI is absolutely contraindicated (CT-perfussion, **Figure 2**).

Modality	**Explanation**
MRI	Magnetic Resonance Imaging 3 Tesla MRI unit Dynamic-contrast MRI, MR-Angiography MR-perfusion (MRP) MR-Spectroscopy (MRS-Proton, MRS-Phosphorus) Diffusion Weighted MRI (DWI) Diffusion Tensor Imaging and Tractography (DTI) Sensitivity Weighted Imaging (SWI) Magnetic Transfer Imaging (MTI)
CT	Computed Tomography Guidance to the surgical or radiotherapic ablation of local lesions via multidetector CT technology, advanced applications such as calculations at submillimetric level and navigation in neurostimulation therapies are its characteristics expected to step in standard routine. CT-angiography, high-resolution three-dimension imaging and CT-perfusion in the cases in which MRI is contraindicated are possible with this modality.
PET/CT	Positron Emission Tomography/Computed Tomography In this system, PET and CT are fused and the images of these two modalities can be either obtained separately or combined. This method as well presents anatomical data of sectional and functional activity. Changes in brain metabolism developed in the epilepsy, of which the focus could not be found with other methods, and in many other disorders can be investigated with this method. With the fusion of PET/MRI in the new systems, it is possible to obtain high resolution anatomic and physiologic images, and preoperative consultation is possible.
MEG	Magnetoencephalography In this system, it is possible to visualize action potentials, as well as the localization of the pathology magnetically. It is known as a current and new modality that spontaneously measures stimulated brain waves more sensitively than EEG and clinical examinations. Sometimes it may be more effective than the sectional analyses, and magnetically localize the abnormality and guides for successful epilepsy surgery.

Table 1. A summary of modalities which are used in a radiology unit to visualize psychiatric diseases and the modalities which are expected to make more contribution in the future with their main characteristics.

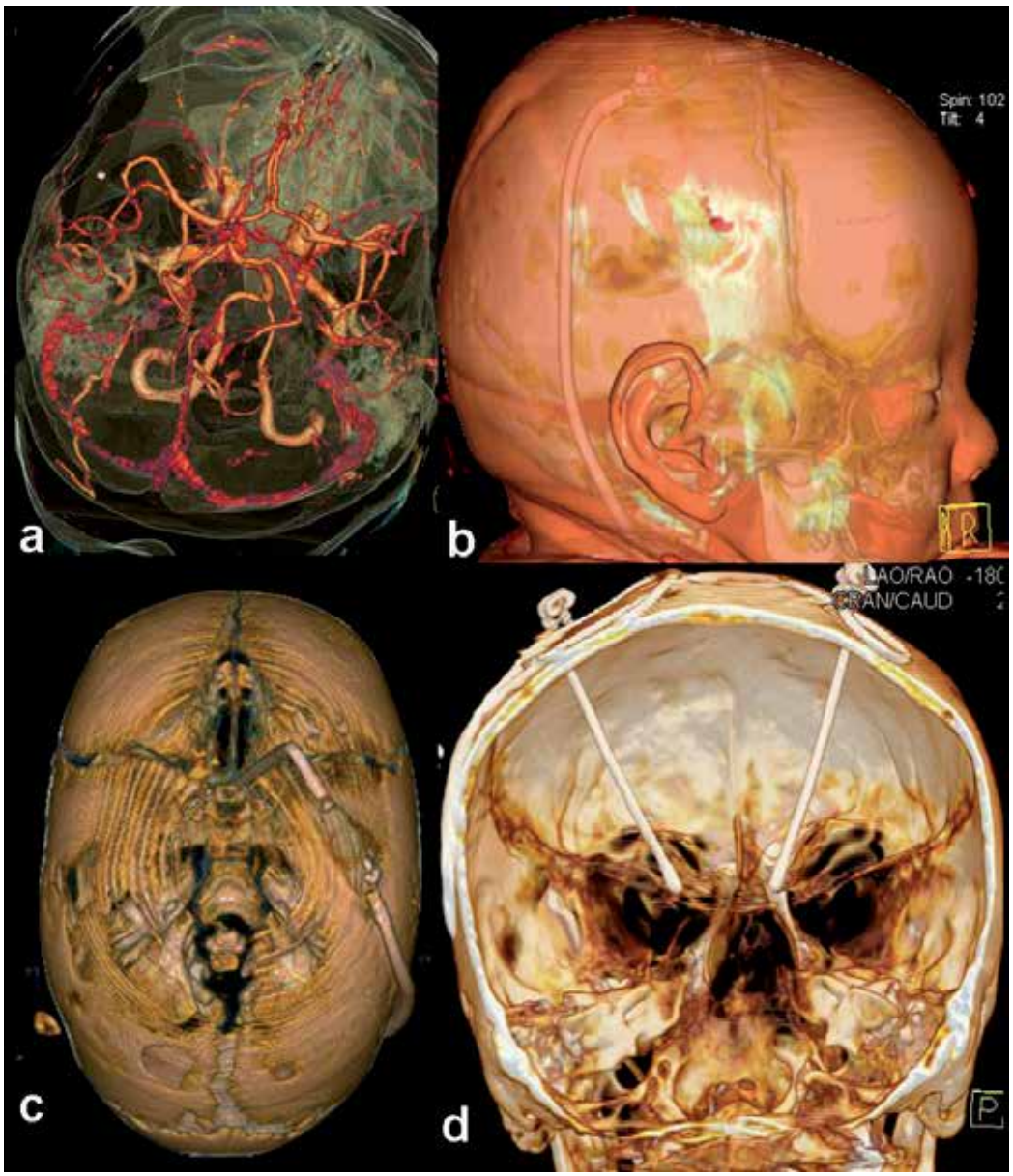


Fig. 1. Guidance in the surgical therapy using multidetector system with dual source CT (64x2). **a**) Main vascular anatomy is seen quite clearly on the three-dimensional computed tomography (3D-CT) image. **b-c**) These images were obtained by the same parameters with those of the previous case, revealed clear image of projection and trace of the ventriculoperitoneal shunt. **d**) Image of a case with Parkinson Disease, obtained by a virtually sliced section of the frontal half of the scalp. It shows neurostimulator electrodes.

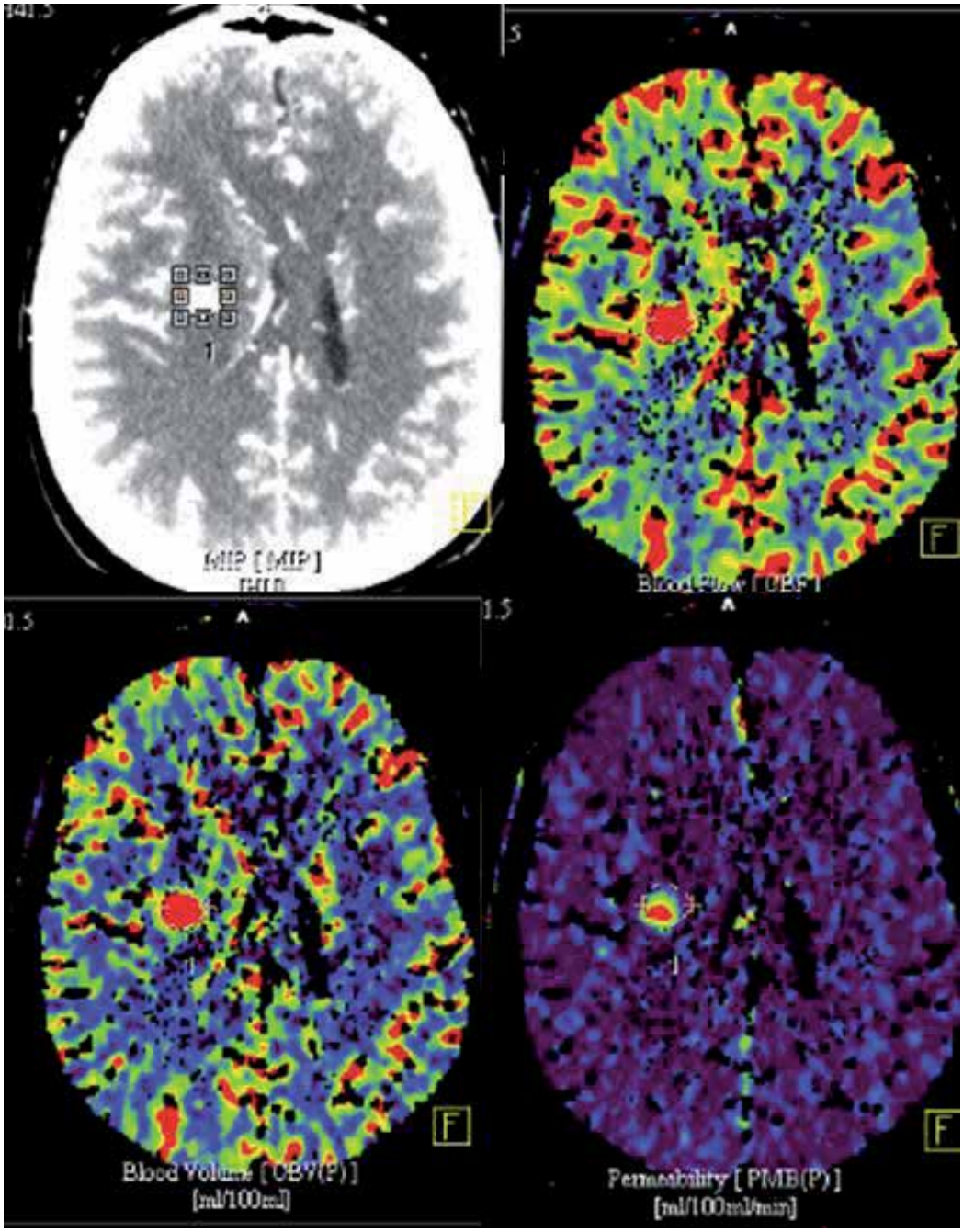


Fig. 2. Operated lung carcinoma. The case that presented with numbness, weakness and dullness on the 2nd year control. Right basal ganglionic mass has been detected on the contrast sections of the case that could not undergo MRI because of cardiac battery. The patient that could not undergo MR perfusion underwent CT perfusion in the same session, and the findings were consistent with right basal ganglionic metastasis.

2.2 PET, PET/CT, PET/MRI and other molecular-metabolic imaging methods

Recent studies show that it is possible to detect the neural progenitor cells in-vivo. This finding offers to foresee genetic therapy and to follow the outcomes in the near future (Seidenwurm et al., 1997). Along with the information at the level of neuromediator, transporter gene, and receptor that would be introduced by the studies on molecular neuro-imaging science, an expectation has appeared for finding an answer to the questions also in the field of biological underlying disorders of psychiatry (Sevin et al., 2007).

PET, which is an indirect metabolic imaging method, is commonly being used as PET/CT fusion modality. This method is usually used in early detection of Alzheimer's disease, in detecting the epileptogenic foci, and also in the evaluation of the effects of medical-surgical therapies (**Figure 3**). It detects the degree of uptake in the tissues, in which radioactive FDG (fluorodeoxyglucose) is injected via intravenous route to the patients with predicted pathology, and fuses this metabolic data on concurrent CT images.

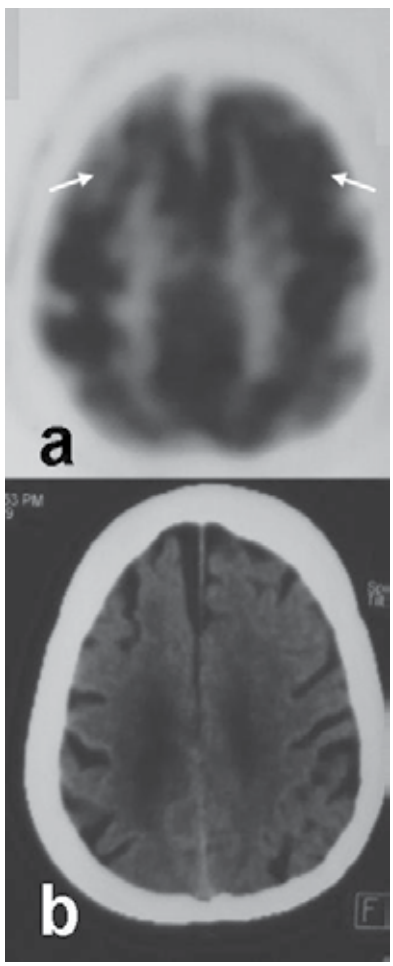


Fig. 3. PET (**a**) and related CT (**b**) sections of a case with Alzheimer's disease. There were lots of corticosubcortical asymmetrical FDG uptake areas (aroows) show "the hypoactivity" which is in harmonious with the clinical examination findings.

PET technology has been advanced such expeditiously that imaging reached to the receptor level. That is to say, experimental metabolite studies performed to lay speaking, memory, learning, cognitive functions and cerebral distribution of related receptors, as well as their activities have been successfully completed (Adachi et al., 2008).
The outcomes of the studies that focused on PET/MRI fusion modality, which has been theorized because of inadequate image resolution of CT, have ended positively and PET/MRI fusion systems are currently begun to be used particularly in the cranial localizations.
At this point, it must be emphasized that, multiparametric and fused systems, which are begun to be used extensively, require the multi-disciplinary collaboration (of a radiologist, psychiatrist, nuclear medicine specialist, physicist and molecular biologist) especially in investigating psychiatric diseases.

2.3 Magnetoencephalography (MEG)

Magnetoencephalography, which combines the high resolution anatomical images with electrophysiologic data can successfully test and visualize the dynamic cerebral functions. Thus, the focus that complex neural network shows dysfunction can be clearly localized and accordingly be treated; such that, a single region or action potentials produced by a single cell clump can be evaluated using this method. By this means, local neural effects of drugs with specific efficacy can be tested (Seo et al., 2011). The major disadvantage of this method is the fact that it remains to be able to evaluate only superficially localized cerebral pathologies.

2.4 Magnetic Resonance Imaging (MRI)

In line with the systems that perform very quick dynamic analysis in CT, techniques have been rapidly advanced and revised in MRI as well. In addition to the conventional sequences, MRI is able to analyze even anatomic-functional etiopathogenesis of various disease groups with numbers of modalities (**Table 2**). Here, the technical and clinical characteristics of the above-mentioned methods will be briefly discussed in terms of following topics.

MRI methods	Explanation	Psychiatric practicability
Conventional sequences (T1, T2, fat-saturated sequences, dynamic examinations)	Give opportunity to obtain high resolution anatomical information. Contrast patterns of the lesions can be shown with dynamic examination modalities.	Intracranial normal and abnormal formations can be detected with higher sensitivity than CT can. Moreover, it is easier with MRI to make differential diagnosis in the nervous system lesions.
MR-Angiography	Visualization of main vessels	It can be applied both with and without contrast. Availability to perform without contrast allows visualization of vascular anatomy without injection in the patients unable to coordinate and cooperate.

MRI methods	Explanation	Psychiatric practicability
Magnetization transfer imaging	It makes the basal signals, particularly those abnormal and those developed later, more prominent with a kind of subtraction.	By this means, abnormal contrast uptake foci that have not been exposed yet with conventional sequences can be detected early.
MR-spectroscopy	It allows the detection of metabolite content of a wide area, a lesion, or surroundings in the brain.	This method can detect the metabolite content of neural parenchyma without causing anatomic imaging anomalous. There are studies performed on many psychotic and neurotic disorders showing that metabolite concentrations show differences in various localizations as compared to the normal population.
MR-perfusion	A method that relatively introduces the differences in the vascularization of cerebral regions as different maps. Here, it is possible to detect the altered blood pool foci despite the preserved anatomy by forming rCBV (relative cerebral blood volume), rCBF (relative cerebral blood flow), MTT (mean transit time), and TTP (time to peak) vascularization mapping.	This method is able to differentiate malign tumors from benign, efficacy of medical-surgical therapy from radiotherapy, and the residue from relapses.
MR-diffusion	A method that detects micromolecular water motion and motion restriction.	A method that detects the nature of ischemic lesions (acute or chronic), as well as the cellularity of mass lesions. By this means, diffusion limitation of cortically localized lesions can be detected and dysplasia-cortical mass can be differentiated.

MRI methods	Explanation	Psychiatric practicability
Diffusion tensor imaging-tractography	A technique that identifies the nerve fiber traces via special software by changing the power of diffusion gradient and the direction of diffusion.	By this method, we can detect the nerve fibers and pathways by differentiating afferent and efferent fibers, although they have been considered normal via conventional examination modalities. DTI technology has been advanced to illuminate the etiopathogenesis of cognitive disorders (113).
SWI (susceptibility weighted imaging-high-sensitive imaging)	A modality that detects the abnormal foci in the brain quite before appearing on the known and routinely used sequences.	It is of great importance to early detect the calcific or hemorrhagic foci in the brain, although they are extremely small. This sequence will early detect the amyloidal angiopathy, or hypertensive encephalopathy, or calcification of basal ganglion, as well as the organic pathologies that might affect the cognitive functions in the diseases such as migraine.
fMRI cortical activation measurements (BOLD)	A method that monitors both motor and functional processes. The patients are asked to do the motor and sensorial paradigms they have been taught during special and rapid (EPI) sequences, and the cortical regions are detected, in which alterations (hemoglobin, loses O2 to become deoxyhemoglobin) are observed with blood oxygenation level dependent (BOLD) effect.	In the controlled trials, it is known that quite specific signal recordings (increasing and decreasing), different from the normal population, are obtained particularly in the prefrontal cortex in both the psychotic and affective diseases on the functional examinations that the activity created by word repetition and thought is recorded.

Table 2. Points that might contribute to the problem solving with psychiatric point of view in the MRI sequences, which have been frequently used in routine and in current MRI applications.

2.4.1 High resolution (3T) MRI analysis, dynamic contrast MRI (Dyn-MRI), diffusion weighted imaging (DAI), MR-angiography

Although its quality may vary due to the movement or other artefacts while investigating other organs, it is possible to early detect pathological process via high-resolution images obtained on the craniospinal axis by 3T. In addition to the conventional sequences, high

resolution images can distinguish the abnormal signal changes earlier (**Figures 4-6**). These anatomical structures or pathologies (infection, inflammation, and neoplasia) can be evaluated by contrast analyses, signal dynamics, and DWI. So the cellularity of the lesion can be detected. Main arterial and venous anatomy can easily be exposed noninvasively.

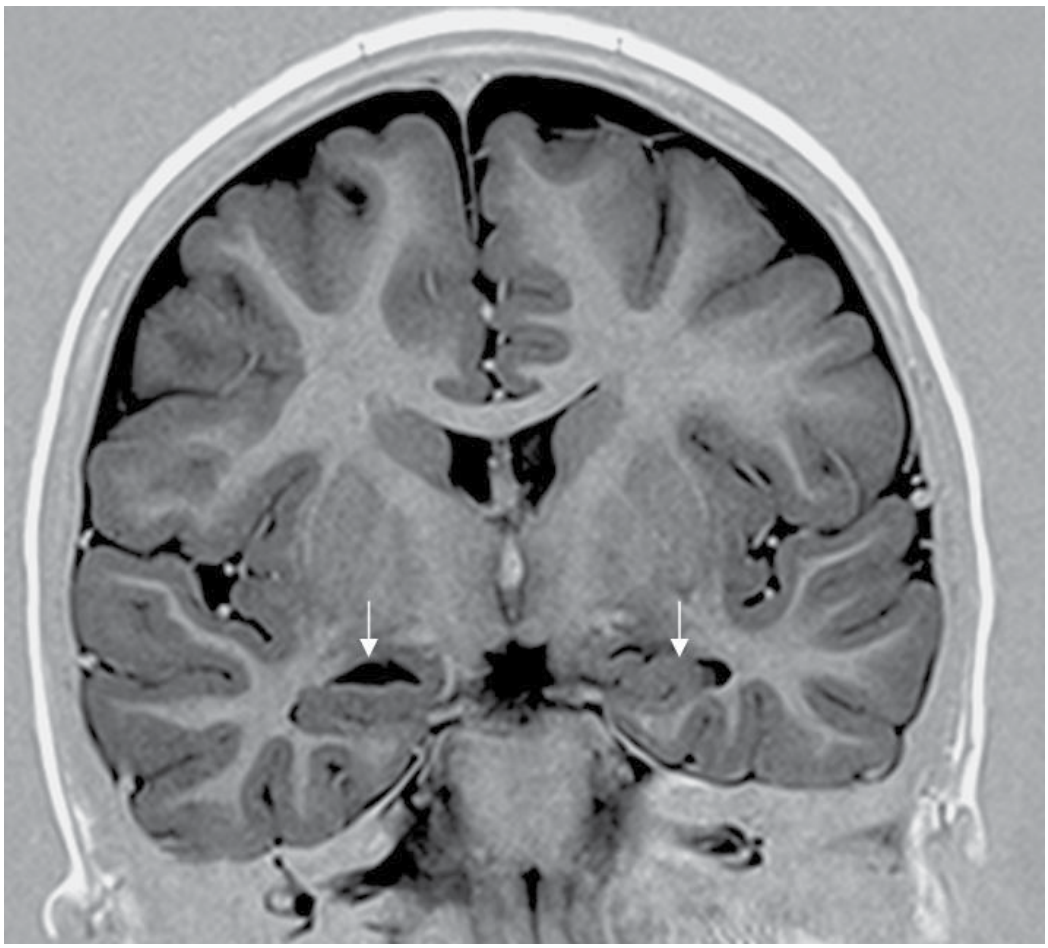


Fig. 4. A male patient with mild mental retardation and temporal epilepsy (age: 29 years). Coronal T1W brain MRI-1.5 Tesla obtained by high-resolution. Asymmetry between choroid fissures can be seen clearly (arrows).

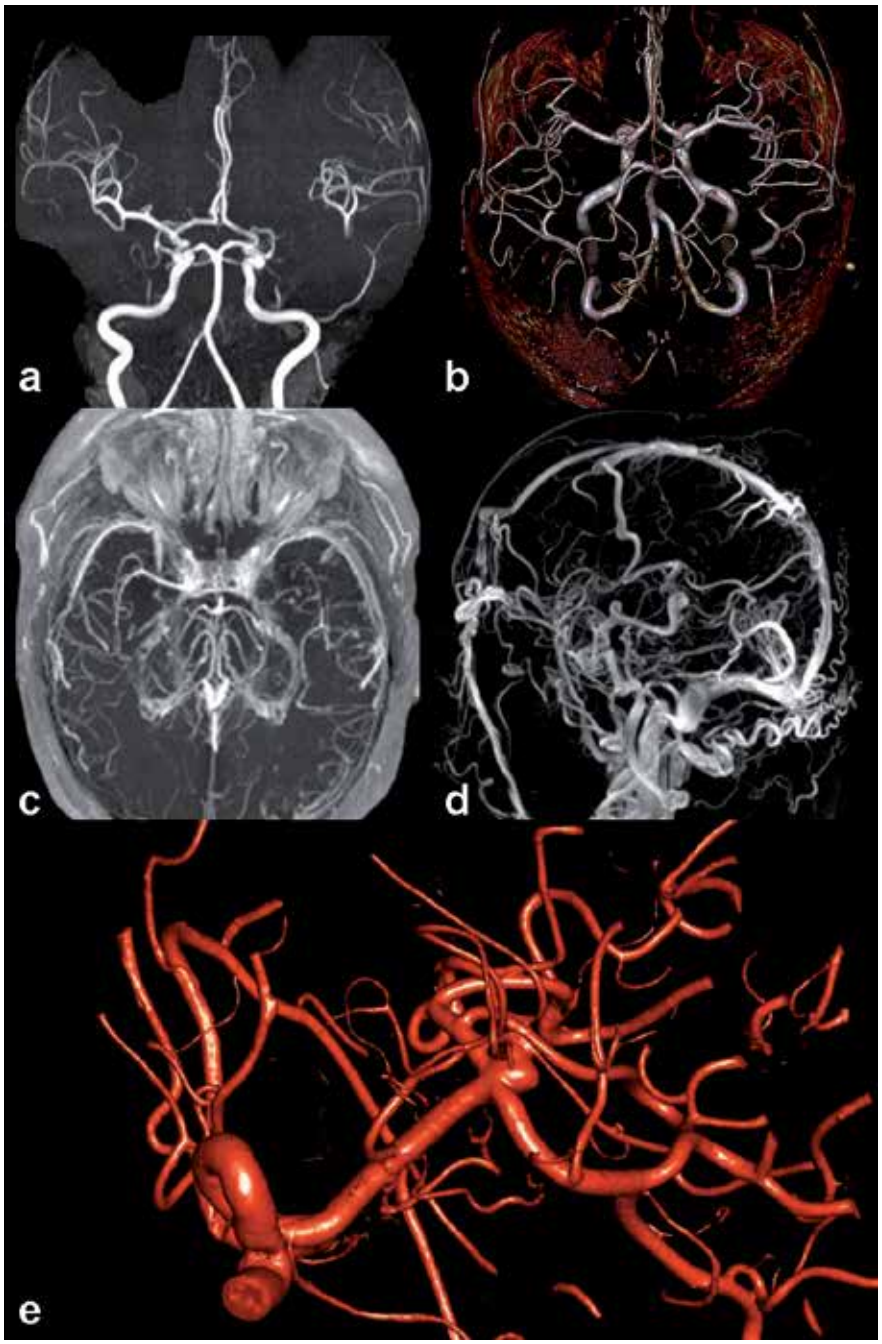


Fig. 5. On the coronal thick MIP (a), colored axial VR (b), posterior fossa axial thin MIP (c), sagittal thick MIP and (d) MRI imaging of different cases, it is conspicuous that extremely complex network can also be visualized in detail. Despite the advanced MRI technology, it is understood that more complex traces can be visualized with higher quality which is shown on the VR/3D biplane angiographic image.

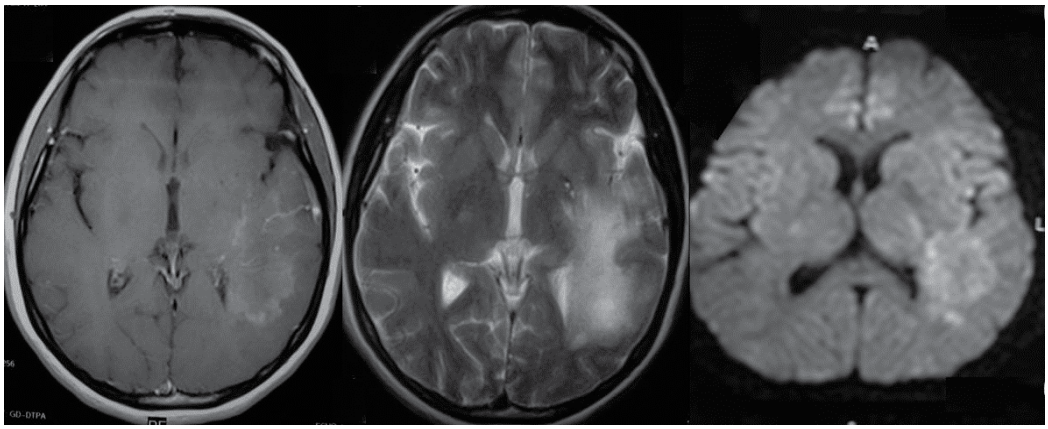


Fig. 6. Although it gives mass impression on the diffusion-based images, large heterogeneous contrast fields in the left temporal lobe of a case presented with atypical psychotic complaints has been considered acute-subacute infarction due to the limited diffusion in the vascular supply field.

2.4.2 Functional MRI (fMRI) and related sub-modalities

MRI spectroscopy that can measure certain cerebral metabolites.
Perfusion MRI can measure regional cerebral blood flow using different parameters such as time of arrival, time to peak, blood flow, transit time, delayed enhancement.
Blood-oxygenation level-dependent (BOLD) MRI measures regional differences in the oxygenated blood over time. Newer commercially fully integrated MRI systems are now available. With these units, it is possible to perform a variety of well-documented paradigms for motor, language, and visual mapping. Moreover, the possibility of fusing 3D DTI-BOLD and conventional images brings the development to its peak.
Diffusion weighted MRI, which measures random movement of water molecules through the axonal fibers. So, this method is capable to obtain tractographic images with additional tensor imaging software.

2.4.2.1 Magnetic Resonance Spectroscopy and basic principles

Proton MR-Spectroscopy is a useful in vivo examination for analyzing the metabolites of the human brain that are in small concentrations. The aim of this method is to detect the metabolite composition of the tissue. Particle content can be evaluated by a sensitivity one in a million, using the differences in Larmor frequency at horizontal axis caused by special frequencies. Previous studies have reported that the NAA level can be altered by neuronal cell death or other neuronal damage in the gray matter (Tzika et al., 1997). NAA is an amino acid, located exclusively in the neuronal cell bodies, dendrites and axons. In contrast, the Cho level has been regarded as a marker of cellular density, since Cho is the precursor for phosphatidylcholine, which is a major component of the cell membrane. Thus, the NAA/Cho ratio is regarded as a significant indicator in assessing neuronal activities, because it represents the relative ratio of neuronal density to cellular density.
1H-MRSI now offers the ability of directly correlating abnormal imaging findings with a presumptive measure of neuronal pathology. Quantitative differences in metabolite content can be investigated by whole brain MRS that can be obtained particularly in the new

technological systems (**Figures 7, 8)** (Bertolino et al., 2000). The status of different metabolites can be investigated by changing the parameters. As a neuron-specific surrogate marker of cellular integrity, NAA levels have been examined in numerous neurological disorders. In schizophrenia as well, reduced NAA in PFC (prefrontal cortex) has been shown to predict the abnormalities in dopamine metabolism (Callicott et al., 2000). Although, all the findings of the cases are seem sometimes as normal, but a pathology being reflected as low NAA ratio in PFC (Callicott et al., 2000).

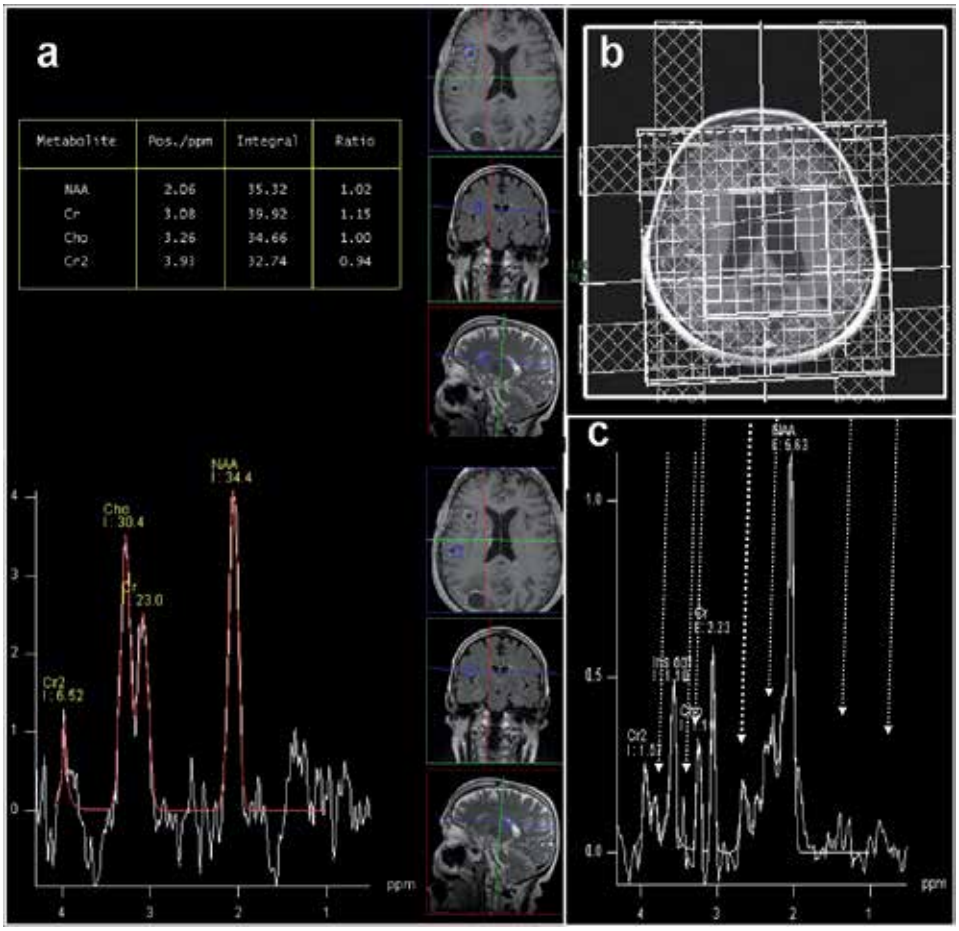


Fig. 7. **a**) It seems possible to evaluate various lesions and fields at the same time by whole brain spectroscopy, as well as to obtain metabolite peaks and proportional information concurrently with new software in the cases with multiple cystic intracranial lesions. Screening the whole brain via large multivoxel windows in that way may enable diagnosis of certain metabolic diseases perhaps along with the first psychiatric symptoms, as well as decreasing the dose and shifting to the treatment (such as dialysis for lithium toxicity). **b**) In this evaluation, in which all the fields that remained out of the investigation must have been suppressed, because increased susceptibility would lead to artefactual measurements. **c**) When the imaging is done using short "time of echo = TE" values, it is likely to obtain peaks of more metabolites (showed with long arrows).

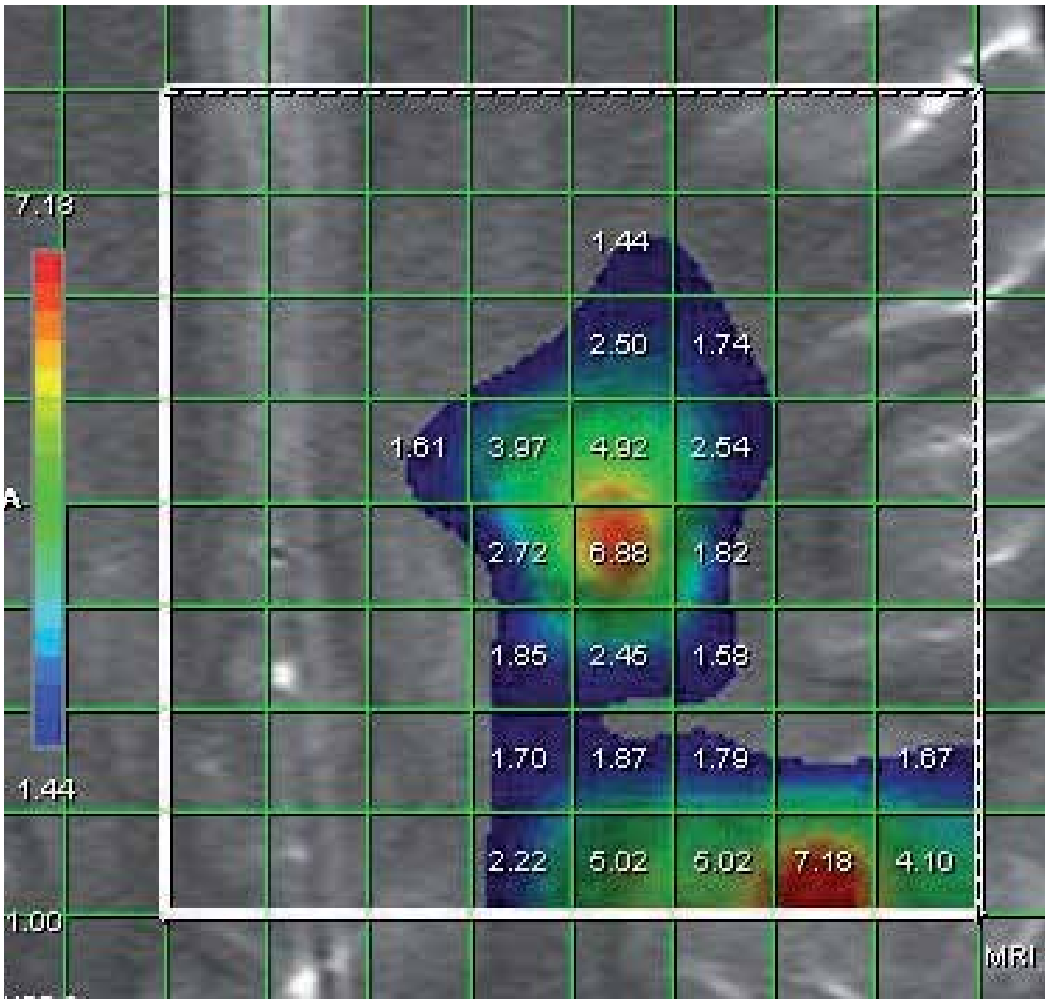
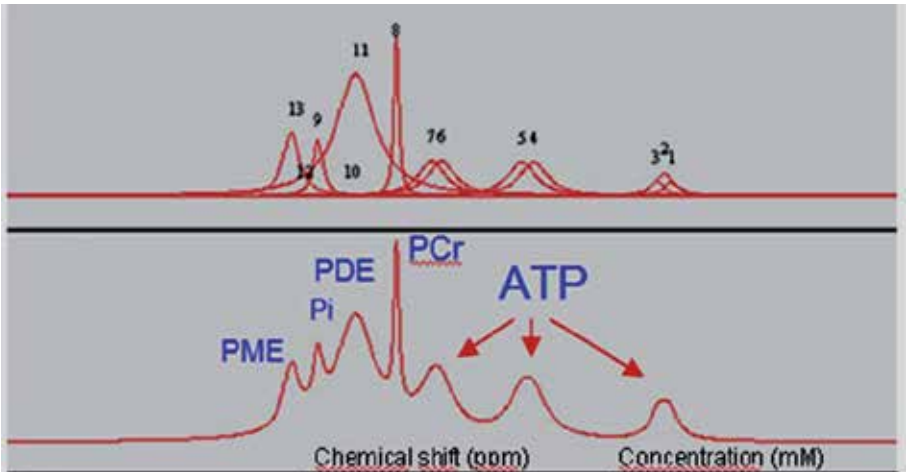


Fig. 8. Involvement of deep white matter in the left frontoparietal region that displays normal signal characteristics in a case with encephalitis. Cho elevation that indicates increased devastation on the color Cho/Cr maps; it may be changed into a more demonstrative form that a clinician could orientate him/herself.

It is known that spectroscopy can detect also the metabolites that contain phosphorus which play a role in energy metabolism. The basic elements of energy metabolism such as ATP (adenosine triphosphate), phosphocreatinine (PCr), inorganic phosphate (Pi), phosphomonoester (PME), and phosphodiester (PDE) can be measured by 31P-Spectroscopy (**Figure 9**) (17, 18). Beside the indirect information about energy metabolism, it is known that this method can also assess intracellular pH and Magnesium (Mg) levels via indirect ways (19).



	Chemical shift (ppm)	Concentration (mM)
PME	6.4	3-4
Pi	4.7	~1
PDE	2.7	9-14
PCr	0	3-4
ATP	-2.6	~3

Fig. 9. Distribution of the peaks obtained on a normal *brain-phosphorus spectroscopy*, and the resonance values and the amount of resonance are seen in the table attached.

Benefiting from the changes in this metabolite map, not only the grade of tumoral lesions or neoplasias is estimated, but also information can be obtained about the energy metabolism of a special region.

2.4.2.2 Perfusion weighted MR-Imaging (p-MRI)

Perfusion is the blood volume that passes through a certain amount of tissue in a unit of time. T1A or T2* type perfusion analysis can be done by labeling this blood volume with an exogenous marker including gadolonium. In more modern systems, which the studies are going on and which are newly being used in clinical practice (arterial spin labeling), blood cells are magnetically labeled with special radiofrequency bands, instead of using an exogenous agent, and are monitored. Again, in these systems, the degree of cerebral perfusion can be analyzed both qualitatively and quantitatively. Since all these signal recordings have to be done within a time shorter than two seconds, ultra-rapid software named EPI (Echo Planar Imaging) sequence are used in the perfusion weighted analyses. In the cerebral system, perfusion means oxygen delivery level to the tissue.

Tissue perfusion is an indirect indicator of metabolic activity. Physiologically, perfusion occurs in an adult's brain between 40-60 ml/100g/minute (Rostrup et al., 2005). At that point, it is important to make a shoot (particularly for perfusion and spectroscopy) including both hemispheres in ROI field in order to make a comparison between the symmetric regions. Consequently, distribution of cerebral blood flow can be calculated on the perfusion weighted MRI examination by certain automatic programs that use multiple parameters, such as CBF, CBV, TTP, MTT, and TOA, based on the changes in the microenvironment caused by the contrast substance while passing through the capillary network (**Figure 10**).

In terms of convenience, the common unit for CBF is milliliters of blood per 100 grams of tissue per minute, and a typical average value in the human brain measured is approximately 50 mL/100 g per min., the gray matter being approximately three times higher than the white matter (Rostrup et al., 2005). For imaging applications, it is often convenient to express this as the flow delivered to a unit volume of tissue rather than a unit mass of tissue, because a signal is measured from a particular volume in the brain. Since the density of brain is close to 1 g/mL, CBF values expressed in these units are similar.
Cerebral blood flow is a measure of arterial blood delivery. Blood flow is controlled by varying vascular resistance. In the vascular system, the resistance is not uniformly distributed among all of the branches of the network but, instead, is dominated by the arterioles and the capillaries. The arterioles are the seat of vascular resistance control.

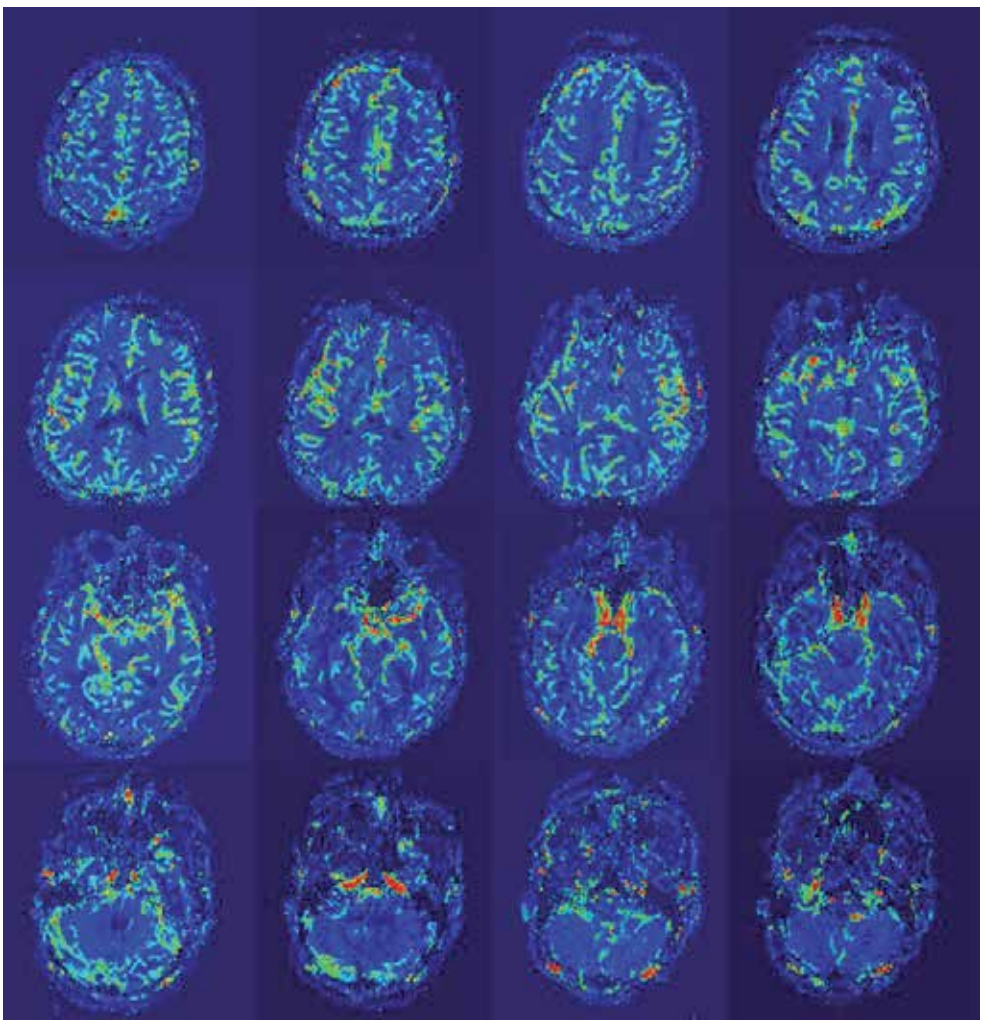


Fig. 10. Color perfusion images that show the rCBV map of a healthy subject. Here, signal decrease due to T2* effect gives information about the vascular bed in capillary network and is expressed as relative (r) because it indirectly reflects the perfusion.

Perfusion analysis has been mostly used for ischemic or tumoral cases since its first use (**Figure 10, 11**). Despite, in time, it was begun to be used in various psychiatric diseases for trial purposes including metabolic diseases, neurodegenerative diseases (Alzheimer), and attention disorder and hyperactivity, the fields in which it has been studied utmost due to its higher resolution than PET/CT and ability to localize better and offering quantitative information (Patrella&Provenzale, 2000). For example, decrease in rCBF has been reported in the anterior cingulate, temporal gyrus and precuneus, the fields associated with attention, in the attention disorder and hyperactivity syndrome. In schizophrenia, rCBV elevation has been reported in the occipital cortex, basal ganglia and cerebellar level (Leinsinger et al., 1997). Cerebral blood volume (CBV) is the fraction of the tissue volume occupied by blood vessels, and typical value for the brain is approximately 4% (CBV= 0.04) (Leinsinger et al., 1997).

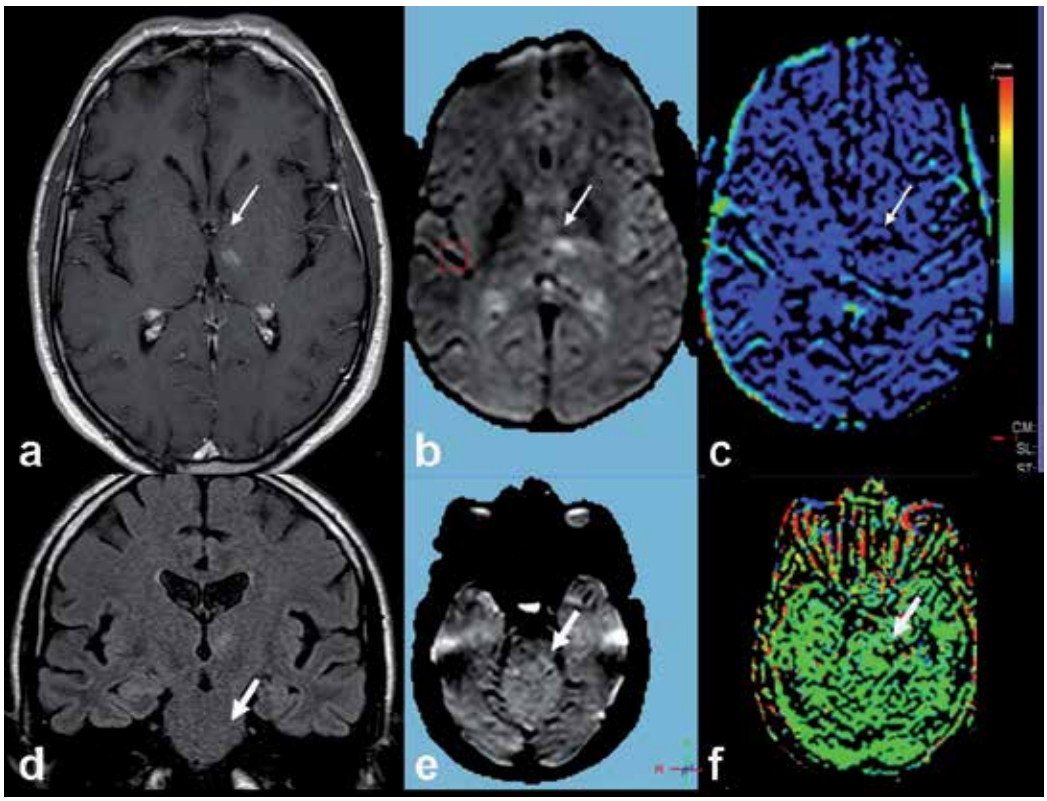


Fig. 11. Despite the presence of dullness and flight of ideas in the case presented with behavior disorder that developed recently, systemic and cranial screening is required because of concurrent attacks and sweating. On the T1W-C$^+$ axial section (**a**), thalamic focus that uptakes contrast agent (arrow) has displayed T2-shine through effect on the perfusion sequence (**b**, arrow), and presented completely as non-perfused on the rCBV map (**c**, arrow). The same focus is visualized on the coronal FLAIR sequence (**d**). Although the pons is seen normal on this sequence (**d**, arrow), it is seen as a suspicious field on the basic perfusion image (**e**, arrow) and again as non-perfused on the rCBF map (**f**, arrow). Left thalamic subacute infarction.

The CBV roughly represents milliliters of blood vessel, regardless of dimension, per milliliter of tissue. Since an indirect neural activity indicator increases the local rate and products of energy metabolism, it in turn triggers increased flow to deliver more glucose and O2. That is to say, the process progresses backward. Instead of energy consumption first and then blood flow, increase in neural activity and metabolism products (NO is the most important trigger that increase CBF causing arteriole dilatation) occurs first and then increase in blood flow. A striking aspect of the brain is the relatively uniform Axygene Extraction Fraction = OEF at rest (Gusnard et al., 2001). This suggests that, during development, CBF to each region is adjusted to the basal level of energy metabolism (extraction fraction of O2 is the same, approximately 40%). What we summarized herein is that, this system seems to be affected, in fact, by numerous micromelocular, anatomic and sub-systems that have not been known yet (Perthen et al., 2008).

Recent studies have been focused on neurovascular unit and mentioned about the presence of more complex synaptic connection network of glial cells (Haydon&Carmignoto, 2006). It raised the thought that these astrocytes, which are in association with synaptic space and at the same time are located in the close neighboring of arteriole junction, work as hard as neurons and that have important functions in the regulation of neural activation. With these end-feet connections, astrocytes form a bridge between neuronal activity and blood flow (Filosa&Blanco, 2007). Considering that these hypothetic changes occur in a complex environment, neuronal cells should work patently together with overall neurovascular unit during the initiation and progression of neural activation, instead of working alone.

2.4.2.3 Functional MRI (f-MRI) with blood-oxygenation level-dependent (BOLD) technique

Failing to visualize underlying pathologies with old imaging methods has led psychiatric diseases to be considered medically only in the functional category and thus, the opinion that the absence of any organic pathology has been accepted (by mistake) (Rajkowska et al., 1998). This opinion has been confused with quite confirmed studies in the recent times; methods that can detect cortical thinning by 8% and the volume loss in postmortem schizophrenic brain as compared to the normal are in question (Selemon et al., 1998). In addition to this gross anatomic change, it should be known that perfusion abnormality alone, without the presence of any other micromolecular anomalous, is likely to cause abnormal potentials impairing the function. Functional MRI, which is a method that can illuminate the pathology by detecting perfusion abnormalities, steps in at this point.

In the beginning of the researches, positron emission tomography was the only technique that provide human brain mapping by measuring the changes in energy metabolism. But, more recently, fMRI methods have dominated the field of functional neuroimaging, primarily based on a phenomenon called as blood oxygenation level dependent (BOLD) effect (Bohning et al., 2001). In this frame, when hemoglobin loses O_2 to become deoxyhemoglobin, the magnetic properties are changed in a subtle way. When an area of brain is activated, the blood flow increases much more than the metabolic rate of O_2. This leads to a reduction in the extraction fraction of oxygen, seemingly a paradoxical scenario, in which the venous blood is more oxygenated. This phenomenon is known as BOLD (blood oxygen level dependent) effect, a local increase in the MR signal owing to a reduction in the OEF during increased neural activity (**Figure 12**). Recent research has emphasized the key role played by the astrocytes, cells that function projecting both neurons and blood vessels. This has led to the concept of the neurovascular unit, a close interaction between neurons, astrocytes, and blood vessels (Bohning et al., 2001).

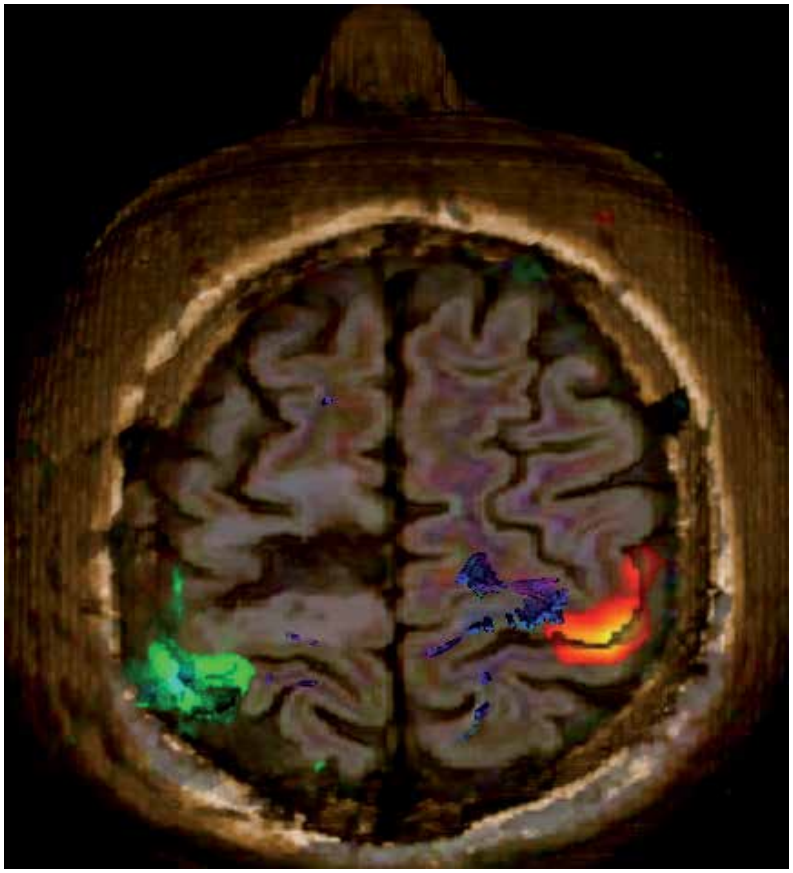


Fig. 12. Attention should be paid to the BOLD color scatter occurred on the right due to the contribution of remodeling that developed in time, in the motor area affected by encephalomalasic region, at the origin of the motor activity that occur during snapping. As the result, although this information gives simple impression on a color map, it, in fact, indicates signal decrease caused by the deoxygenation of the erythrocytes while passing throughout a capillary network with decreased diameter up to 6-8 μ and subsequent increase in the reactional blood flow.

Despite the relative difficulty for the patient in adapting to the MR gantry in the psychiatric diseases, non-invasiveness, no radioactivity, widespread availability, and virtually unlimited study repetitions make fMRI ideally suit to the study of in vivo brain function in psychiatry.

In the controlled studies, the functional examinations, in which the activity created by word repetition and thinking has been recorded, showed a decrease in signals in the prefrontal cortex (sensorineural) in schizophrenic patients, whereas the signals associated with motor cortex remained the same and constant (Callicott et al., 1998). Additionally, in the uniparameter system, which is stimulated by sensorial stimulation (visual) such as photic stimulation and finger tapping and motor stimulation (finger motion), significantly increased regional cerebral blood volume was detected in the left occipital cortex and left caudate of schizophrenic subjects. Despite the sensorial asymmetry in this study,

schizophrenia-associated motor abnormalities (decreased magnitude of fMRI) have been reported more frequently (**Schröder J** et al., 1999). Although, in some of the studies antipsychotic medication was thought to cause this lateralization asymmetry, neuropathological examination of postmortem motor cortex has revealed both abnormal and normal cortex (Braus et al., 2000). In addition to the studies designed for the general hypoactivation of prefrontal cortex, there are studies performed with fMRI that have been specifically focused on the symptoms. For example, there are studies, in which abnormal temporal cortex activation in response to external speech was detected in some schizophrenia cases with auditory hallucinations (Woodruff et al., 1997). Moreover, some studies that have focused on the limbic system, other than the underactivation of prefrontal cortex, showed reduced amygdala activation in schizophrenic patients during sad-mood induction (Maas et al., 1998).

Along with the Ogawa et al.'s finding that deoxyhemoglobin has signal reducing effect on T2*, fMRI is first used in early 1990s and hundreds of studies have been performed on this subject since that time. In this system, fMRI is achieved via two methods. One of them is T1 perfusion effect; the other and more commonly used one is the BOLD (Blood Oxygenation Level Dependant) technique (Ogawa et al., 1990).

During functional MRI applications, staying still in a relatively narrow gantry unit and complying with the instructions in a dark medium with closed eyes are difficult, particularly for psychotic patients. Furthermore, the sensitivity of the region and the paradigm (motor, sensorial) may technically change the outcomes. Finally, a technical team and equipment qualified to perform shooting and a program able to process the images are required. Evaluation of function enables the activation in the motor pathways to be tested by finger movements. Since speaking will impair the quality of analysis due to "misregistration artifact" caused by head movements, it is performed as silent speaking and usually is maintained by word repetition and lexicalization. Despite the difficulty in evaluating the information about memory and limbic system, information about the pathophysiology of these systems can be obtained particularly by perfusion-weighted evaluation (Aksoy et al., 2000). At this point, it is obvious that fMRI evaluation in the pediatric age group would be difficult and post-processing evaluation of the parameters that are evaluated by the reactions such as anxiety, fear and crying would be artifactual in children. However, it has been reported in the literature that pediatric population over the age of eight years have similar results to those of adults (Patrella et al., 2000).

With its increased flexibility due to advanced technology, fMRI may allow us to map a sufficiently wide dynamic range. Thus, pathological cortical regions may be visualized more clearly during both rest and activation by evaluating all the measurements together. As seen on arterial MR-angiography on the Figure 5, major cranial arteries course decreasing from a calibration of few millimeter. They deliver glucose and O_2 to the brain with the blood they carry. Since they have been separated into thin branches, vascular system become more complex turning into an intensive collateral network with a diameter of generally 6-8 µ, and sometimes is decreased down to 2 µ. New MRI sequences have the sensitivity to show the reflex responses of capillary blood flow abnormalities against large-diameter venous system; thus, pathologies such as migraine, encephalitis and subarachnoid bleeding can be detected earlier as compared to the conventional sequences. Therefore, the aura, hallucination, or acute phases of these diseases can be recognized before overt clinical symptoms without being mistaken with panic attack and other conditions (**Figure 13**).

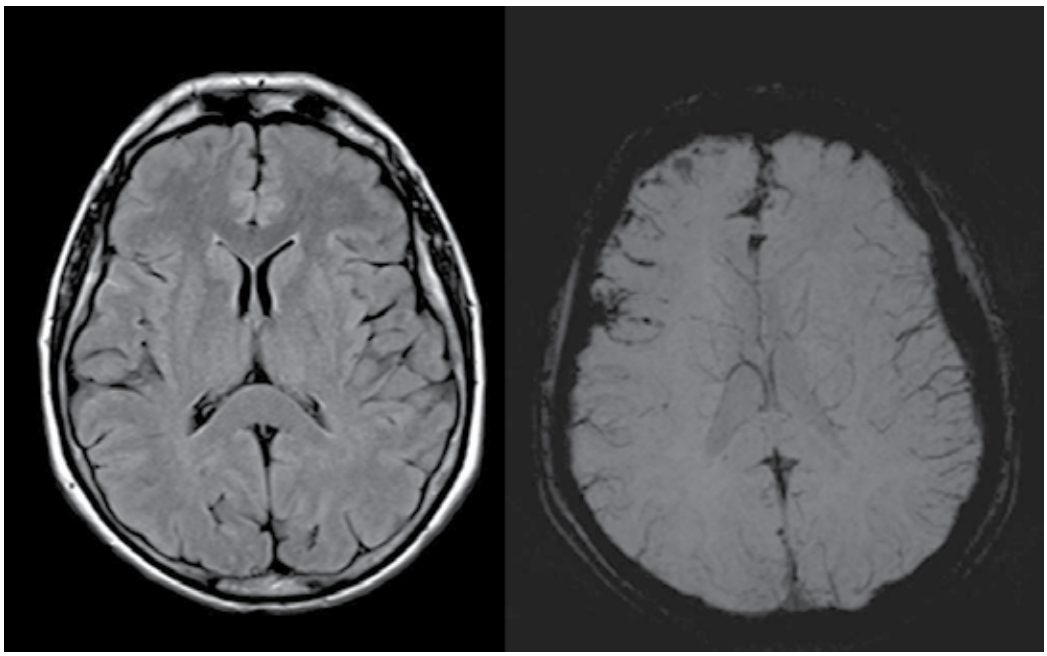


Fig. 13. In the case that has been brought to the emergency room with such an intensive headache that he could bump his head on the wall, FLAIR sequence image sensitive to the lesion and pathology showed no abnormality; however, axial section from SWI sequence showed signal loss in the right extra-axial spaces due to the presence of hemorrhagic products.

2.4.2.4 Fractional anisotropy and tractography, Diffusion Tensor Imaging (DTI)

Tractography can be made over fractional anisotropy maps that are obtained by applying diffusion gradient in multiple ways (varies between 6 and 30 directions). Diffusion tensor imaging is an MR technique that can be used to characterize directional properties of the diffusion of water molecules (Beaulieu, 2002). With the application of this technique, it is possible to obtain microarchitectural anatomy of white matter tracts exceptionally. So, DT fiber tractography has been reported to be robust for visualizing and evaluating connectivity in the brain (**Figs. 14, 15**) (Lee et al., 2005).

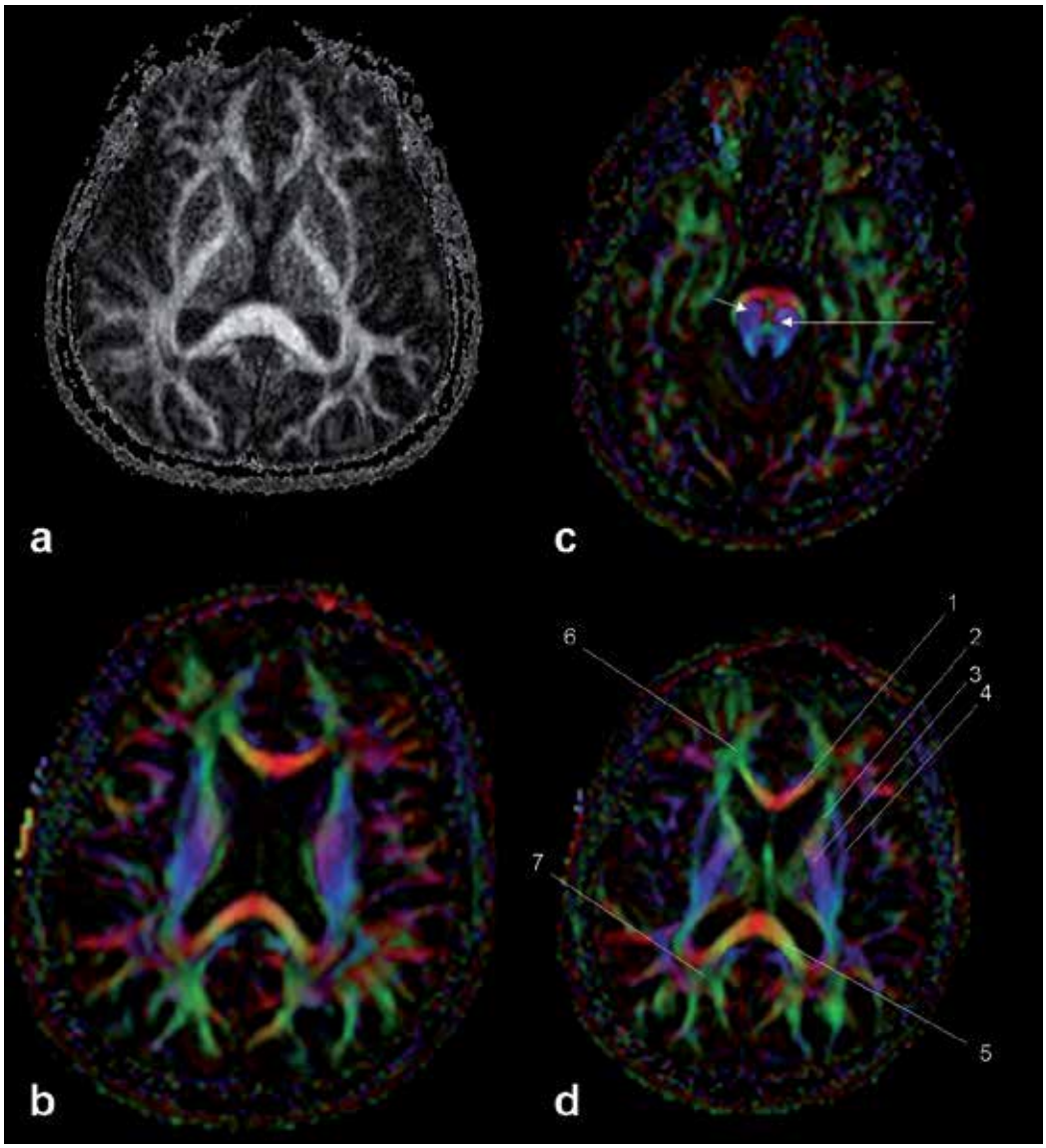


Fig. 14. Axial fractional anisotropy gray scale (a) and colored maps (b) show the restricted water diffusion crossing the fibers. Color-coded fractional anisotropy images of DTI. c) A section through the brain stem: pontine crossing fibers (long arrow) and corticospinal plus corticopontine fibers (short arrow) are shown. d) Supraventricular hemispheric section: genu of the corpus callosum (1), anterior (2) and posterior (3) limb of internal capsule, external capsule (4), splenium of the corpus callosum (5), forceps minor (6) and forceps major (7) are shown respectively. It may be possible to see the other minor fiber tracts also in detail.

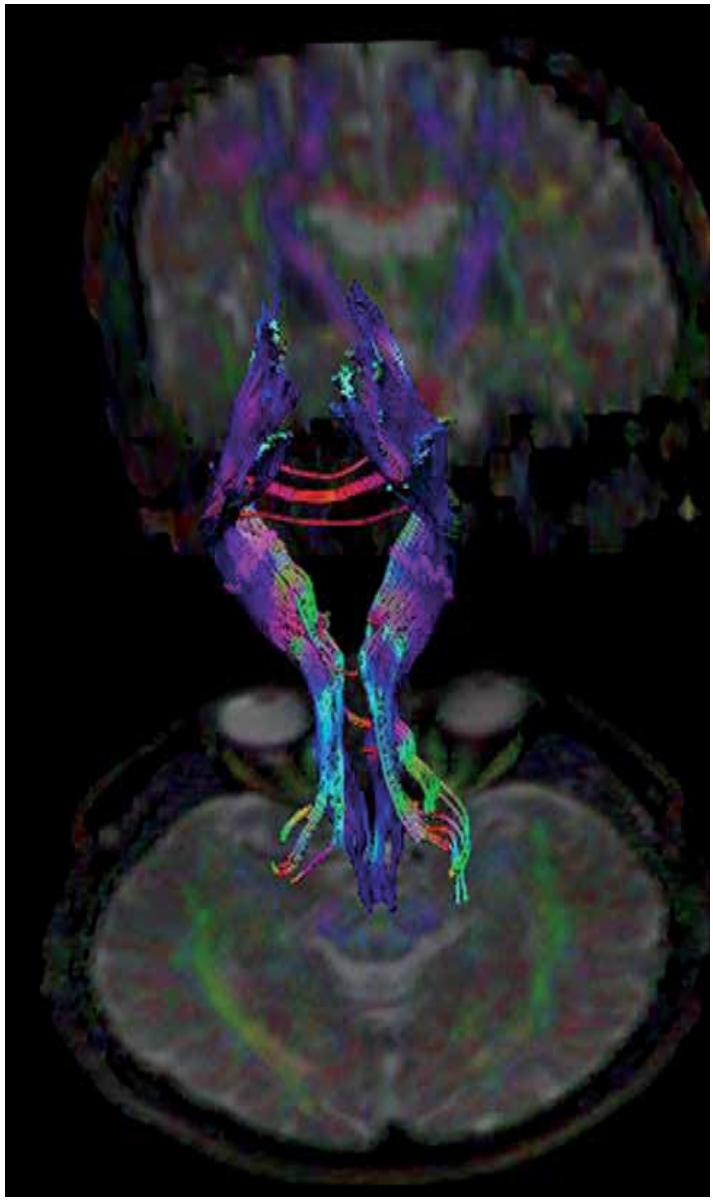


Fig. 15. After processing these fractional anisotropy maps with special softwares, it is possible to detect the tracts alone or as superposed on 3-dimension parenchyma floor labeled in different colors, as is seen in the picture.

The advent of diffusion tensor imaging (DTI) and fiber tractography has opened an entirely new noninvasive window on the white matter connectivity of the human brain. DTI and fiber tractography have already enhanced the scientific understanding of many neurologic and psychiatric disorders, and they have been applied clinically for the pre-surgical mapping of eloquent white matter tracts before resecting intracranial mass, also as a complementary metod fused with fMRI data (**Figs 16**).

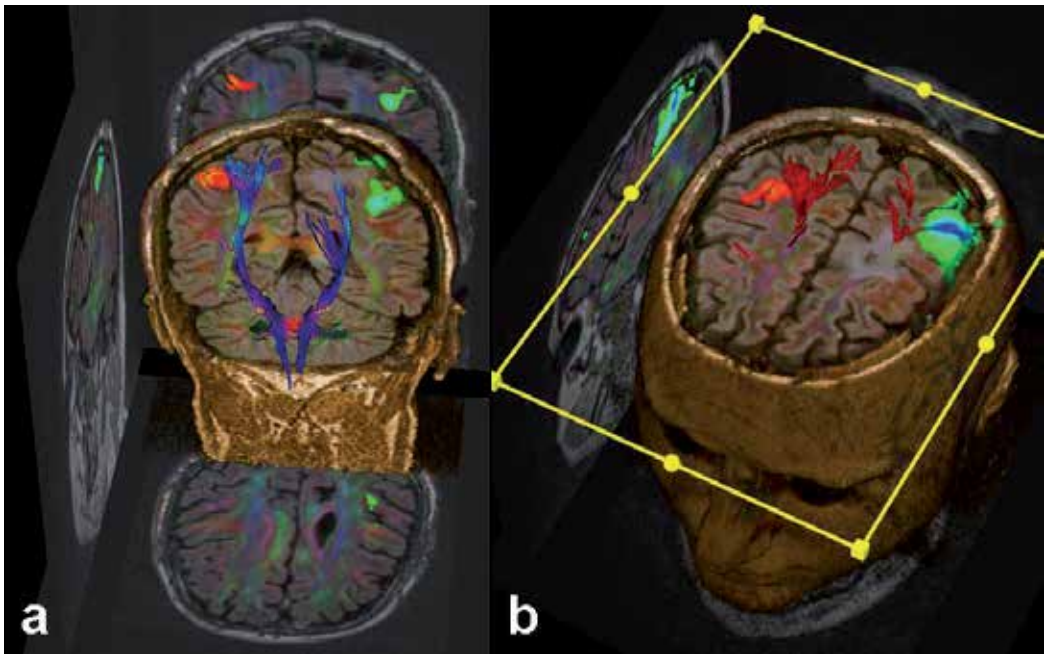


Fig. 16. fMRI-DTI fusion image. On the schema the BOLD signal characteristics that occurred during fMRI with sensory motor paradigms are recorded, the opportunity provided by three-dimensional evaluation of multiparametric data at the same time by coding the fractional anisotropy maps on DTI images offers quite advantageous information.

In this context, the basic principles of diffusion work according to the "Stejskal-Tanner Diffusion Encoding" system. A diffusion-weighted pulse sequence is constructed by adding a pair of diffusion-sensitizing gradients, also known as motion-probing gradients, to a T2-weighted spin-echo sequence. The diffusion gradients are applied along the same directional axis both before and after the 180° refocusing pulse (Stejskal&Taner, 1965). The objective of DTI fiber tracking is to determine intervoxel connectivity based on the anisotropic diffusion of water (Parker et al., 2003).

By this means, axonal traces are followed clearly and fiber tracking can be achieved in condition showing schematically on 3D images. DTI provides only microstructural information at relatively low spatial resolution. DTI fiber tracking is often combined with higher resolution anatomic images to delineate specific pathways. In this way, it is possible to depict virtual information about anatomic connectivity (which called virtual dissection) with 3D DTI tractography.

DTI Fiber Tracking is usually used before the tumor surgery to investigate the association between the mass and main corticospinal tracts (**Figure 17**). In general, if 1 cm space is left between the lesion and main corticospinal tract, there will be enough chance for the intervention. Besides, it can be used in certain developmental disorders as well (in scoliosis, absence of normally decussating pontocerebellar fibers). In addition to all these anatomical evaluations, quantitative DTI tractography studies have examined the microstructure of white matter tracts in pediatric individuals, in the patients with schizophrenia and in Alzheimer's disease (Hess et al., 2006).

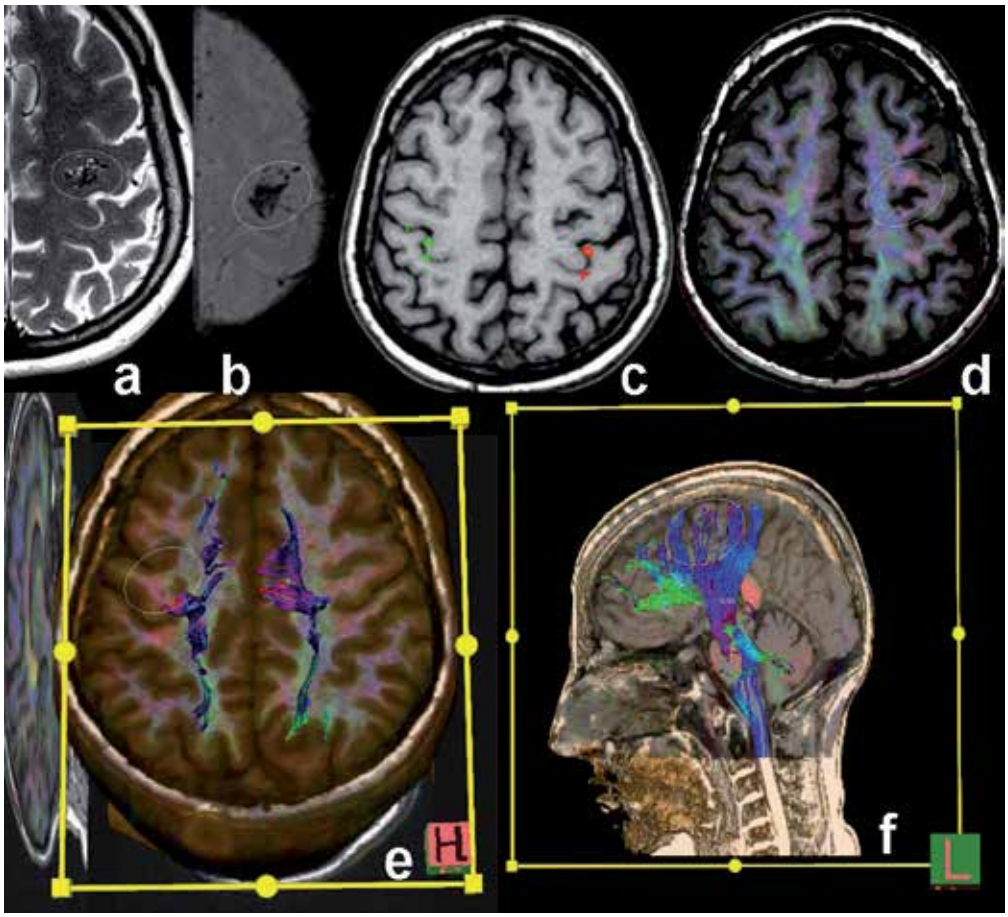


Fig. 17. A lesion localized in the left posterior frontal white matter is seen as hypointense on T2A images (a), and is more clearly visualized on SWI image (b) Cavernoma. This lesion, which is localized in the anterior aspect of motor speech region on the fMRI examination, superposed on the axial section (c), thins the related subcortical fibers on fractional anisotropy map (d), on MPR color VR image through superior vision (e), and on sagittal (f) DTI images. However, it does not cause a remarkable deformation in the course and arrangement of main corticospinal fibers.

Since the DWI principals are used in combination with advanced equipments in the fibertractography technique, microstructural information about biologic tissues, which could not be shown with other coventional techniques, can be obtained. However, even as sophisticated as a mathematical construct, this technique has limitations that affect the ability of DTI fiber tractography to fully delineate an axonal pathway and may lead to the generation of spurious tracks. These problems have led to the introduction of more advanced methods such as high angular resolution diffusion imaging and whole-brain connectivity networks. The asymmetry of diffusion anisotropy of the uncinate fasciculus between the subjects compared may reflect neurodevelopment-originated structural and functional differences between the two hemispheres. This asymmetry can be set forth demonstrating the course of DTI fibers (Kubicki et al., 2002).

In summary, functional MRI, 1H-MRS, Perfusion MRI, and DTI represent significant technical advances for functional neuroimaging. These tests, which yet require more experience about its usage, as well as observation of the results, should not be used for exact diagnosis, but used to confirm the diagnosis and to manipulate the treatment. Although their usage as the methods for exact diagnosis is not valid currently, both fMRI and 1H-MRSI are able to characterize statistical deviation from the normal. Under the light of 3T MRI systems and DTI, which is being advanced day by day with applicable properties, we think that radiological findings for psychiatric-neuropsychiatric diseases and the resolutions would be enhanced.

3. Advanced imaging findings in specific psychiatric disorder groups

3.1 Imaging in psychotic disorders

Initiation of the symptoms in cerebral diseases has been reported to be mainly within the frame of psychiatric picture (50). In fact, a single specific disease (such as encephalomyelitis, epilepsy, arachnoid cyst, Wilson's disease) has been associated with psychosis and there is information characterized by extensive studies and reviews only on this subject (Abbott&Bustillo, 2006).

The most consistent finding obtained from the brain imaging studies performed on schizophrenic cases is the decrease in brain volume and cortical grey matter volume and increase in the lateral ventricular volume (Kubicki et al., 2005). It has been thought that impaired connection between various parts of the brain is the main origin of pathology in schizophrenia (Stephan et al., 2006). Some literature data calculated by the ratios of MRS and DTI (diffusion tensor imaging) and MT (magnetization transfer) actually showed decreased neuronal content in corpus callosum in particular and decreased NAA (a neuronal marker) content in the frontotemporal pathways between the two hemispheres.

Studies on the cases with schizophrenia showed that such cases had changes in certain brain functions plus to structural alterations (Allen&Courchesne, 2003). In this field, it has been most commonly studied on the cellular, molecular and structural pathologies of temporal and frontal lobes (Allen&Courchesne, 2003). It was shown that N-acetylaspartate (NAA) levels were decreased in the temporal lobes of the patients with chronic schizophrenia. Moreover, it was reported that the asymmetric form of the brain was impaired due to the volume loss in the left temporal lobe in particular. However, the temporal lobe-associated neurobiological basis of schizophrenia has not been identified yet. Conflicting outcomes have been obtained from the temporal lobe 1H-MRS studies, in which schizophrenic cases were compared with the control groups. It was found that NAA/choline and NAA/creatinine levels were decreased in the right lobe in schizophrenia, whereas they were normal in the left lobe (Wong&Van, 2003).

In fact, different from the recent past, now we at least think that pathologies can be detected identifying the microstructural abnormalities with advanced techniques, in the studies, in which conventional sequence findings were normal (Kanaan et al., 2006). Despite a number of pervious conflicting studies, methods that measure brain glucose consumption have shown that, measuring glucose metabolism or blood flow during task performance have yielded more consistent findings. Hypofrontality has been demonstrated on Wisconsin Card Sorting Test performed on the schizophrenic adults (Kanaan et al., 2006). Hypofrontality is particularly associated with deficit symptoms, which is thought to result from the

schizophrenic patients' inability to activate frontal regions. Proton spectroscopy (1H-MRS) represents another in vivo imaging methodology that has been utilized to test the neurodevelopmental hypothesis of schizophrenia. With this technique, reductions in NAA levels in the hippocampal area and in the dorsolateral prefrontal cortex have been demonstrated in the patients with adult-onset schizophrenia.

In the recent studies performed with DTI, decreased diffusivity that involves whole white matter is in question. This is a consistent finding with loss of orientation and organization of fiber tract distribution; this technique requires to be developed more in order to obtain detailed in-vivo information in the further DTI studies (Huang et al., 2005).

Nonspecific hyperintense studies on the deep white matter and periventricular regions in psychiatric patients should be comprehensively performed using DTI or fMRI and be explained being purified from its current nonspecific nature.

Diffusion tensor tractography, combined with the information from conventional and functional MR imaging, can provide a powerful tool for neurosurgical planning, especially when surgery is performed close to the vital nerve fiber tracts. Particularly for the cases with signal abnormalities in the white matter, the guidance of tractography may be very necessary during radical operations in the name of preserving the critical fibers that were left in limited number. Using DTI, which offers indefinite but additional information to those from the conventional methods, may be beneficial in suspicious or overlapping symptomatology, as well as in manipulating pharmacological therapy that will be used in the treatment (Huang et al., 2005).

Atrophic volume changes in the various lobes of the brain or in the gyri of the schizophrenic cases have been discussed with speculative data that were contradictory sometime. In addition to these data, there is also a growing body of evidence suggesting a disturbance in the connection between different brain regions, which was just a theory, approximately 5 to 10 years ago. Here, with DTI, a technique that would roughly solve these connections at least for now, it is possible to evaluate the organization and coherence of fiber tracts of white matter (Peters et al., 2010). Although the techniques are insensitive to fiber tract, there are studies that DSI (diffusion spectrum imaging) could reflect the information about direction on the screen as differences in color-coding (Konrad et al., 2010).

DTI techniques are generally used to investigate frontotemporal connections in schizophrenia. Because, a number of studies have shown that functionally a disconnection is in question between frontotemporal connections, as well as volume loss and asymmetry in white matter. Some DTI studies have shown that involved tracts in schizophrenia include uncinate fasciculus, which is one of the greatest pathways, cingulum that enables connection in limbic system, fornix that connects hypocampus to prefrontal cortex and to thalamus, and arcuate fasciculus that connects the motor and sensorial speech centers. If we briefly talk about future directions concerning imaging in Schizophrenia, it should also be combined not only with other structural imaging techniques, but also with functional MRI and PET imaging in order to characterize and to understand more fully the relationship between functional and structural abnormalities in schizophrenia. Along with the standardization of multiparametric evaluations in neuroradiology field to put forward the lesion or pathologies in each organ, success in schizophrenia, which has been achieved within the last five years, would continue increasingly (Tang et al., 2007).

The onset of schizophrenia in childhood, usually defined as onset by age 12, is extremely rare. It has been estimated that the prevalence of childhood-onset schizophrenia may be 50

times less than that of adult-onset schizophrenia. When the structural brain imaging findings are primarily taken into consideration, lateral ventricle calibration in pediatric schizophrenia cases have been reported more stuffed than the normal in a study performed previously; however, later MRI studies did not corroborate this finding. Studies have shown decreased amygdala and temporal cortex volumes, but normal hippocampal, ventricular, frontal and total brain volumes (Shenton et al., 2001). In a study on childhood-onset schizophrenia, enlarged basal ganglia volumes at the beginning of the study were found normalized after patients were switched to atypical antipsychotic medication.

Very few functional brain imaging studies have been conducted in patients with childhood-onset schizophrenia. This can be attributed both to the fact that the disease is rarely seen and that it is difficult to evaluate pediatric cases via MRI. However, changes in favor of hypofrontality have been obtained in small study groups. Moreover, cerebellar hypermetabolism in childhood-onset schizophrenia, seen with these data analytic approaches, is notable in the light of recent evidence implicating the cerebellum in higher cortical processes (Akbarian et al., 1996).

As other functional imaging modalities, few 1H-MRS studies have been conducted previously in childhood-onset schizophrenia. As was observed in adult-onset schizophrenia, the ratio of NAA/Cr was significantly lower in the frontal lobes of the schizophrenic children in childhood-onset schizophrenia (Akbarian et al., 1996).

Functional imaging studies as well provide valuable evidence that the underlying pathophysiology in this disorder is similar to that in adult-onset schizophrenia. Studies on rCBF have provided evidence about task-related hypofrontality in early-onset disease, which were consistent with the findings in adult schizophrenia. MRS imaging findings in childhood-onset schizophrenia are in consistent with adult-onset schizophrenia that showed regionally specific reductions of NAA in mesial temporolimbic and prefrontal cortices suggesting neuronal involvement in these areas.

Clearer images are available with newly introduced propeller (motion free) sequences to reduce extensive movement artifacts in pediatric cases; thus, child-related minor inconsistency is likely to be tolerated in this way. No doubt, an individual that the child can trust, who would be helpful in case of potential problems that could occur particularly during the examination (narrow MR gantry and high-decibel noise), is extremely advantageous and required, particularly in the cases who mainly have delusional and hallucinational symptoms. Although studies with current technologically advanced modalities have been going on, early radiological diagnosis might be possible by directing to the systems more molecular and with larger studies in the subjects with early and suspicious symptoms.

In summary; overall imaging findings within schizophrenia spectrum show that, deviation exists both in the early and late period of brain development, which begins from the childhood and continues along with the adult life, and that, advances primarily in functional and molecular imaging methods are required for the pathophysiology of schizophrenia. There are studies that used advanced modality and multiparametric facilities, in which fMRI, MRS and DTI reveal common and consistent findings (White et al., 2008).

3.2 Imaging in affective disorders

Along with the advances in MRI technology, particularly within the last 10 years, brain anatomy and pathologies have begun to be understood better both structurally and

functionally. In this context, it should be identified that adult depression needs different progress and intervention from that of geriatric depression, whereas psychotic depression needs different progress and intervention from that of nonpsychotic depression. In general, brain volume measurements have shown that subcortical white matter volume and the volume of basal ganglionic nuclei are decreased with age in addition to the cortical atrophy (Kumar et al., 1999). In the studies on total brain volume, no significant difference has been identified between the depressive and normal groups in terms of age-related volume changes. It has been reported that atrophy process was more prominent in the frontal and temporal poles in the normal aging population and developed secondary to the volume loss in the central white matter (Palsson et al., 2001).

On the other hand, studies have shown that, frontal lobe is mainly responsible for the emotion and executive functioning and that volume loss particularly in the orbito-frontal cortex and in the subgenually located prefrontal cortex is a common finding in the depressive cases. Furthermore, the prominence of psychotic component that accompany depression has been found to be associated with the degree of frontotemporal atrophy (Simpson et al., 1999). Despite the conflicting results in the studies concerning the whole temporal lobe, only hipocampoamigdala related bilateral minor volumes have been found to be associated with major depression (Sheline et al., 1996). In addition to cerebral volume calculations, the studies that investigate hyperintense lesions located in the white matter reported that these lesions are in close association particularly with cardiovascular and metabolic risk factors. However, despite this association, regression analysis showed that the intensity of such lesions is related to depression (Lenze et al., 1999).

Despite the extensive studies on depression, studies on bipolar affective disorders are limited. However, bipolar subjects generally exhibit no frontal or parietal lobe volume abnormalities. Major depression, as a quite common disorder (the lifetime prevalence is 4.4%), requires early diagnosis and treatment. In one hand, late-onset bipolar subjects may differ from early-onset subjects; increased left sylvian fissure volume and bilateral temporal sulcal enlargement have been observed in the late-onset subjects as compared to the controls (Rabins et al., 2000). Deep midline cerebral structures have been suggested as the mediators of affective experiences and thus "Emotion and Mood" (Palsson et al., 2001). There are neuroimaging studies performed on many affective disorders ranging from aggression to antisocial personality disorder. At this point, studies have been extended from brain imaging to exposing the temperament elements (Taylor et al., 2001).

Studies on mood disorders are usually nonspecific, and volume-related atrophic changes have been reported. Ongoing studies on mood disorders showed that neurobiological developments progress in terms of illuminating the physiopathology of the diseases. In addition to these nuclear medicine based studies performed by PET/CT using special metabolites, functional imaging technologies as well are begun to be used in this field for diagnostic purpose. As previous anatomical researches, these studies were also aimed particularly at the circuits that are important contributors in affective processing like prefrontal and anterior paralimbic basal ganglia-thalamocortical circuits (McGowan et al., 2004). Functional brain imaging studies have consistently yielded insights into the neural substrates of affective processes. Neuroanatomically oriented functional brain imaging methods include positron emission tomography (PET) with fluorine-18-deoxyglucose C8FDG), which can determine the cerebral metabolic rate of glucose (CMRglu), and with oxygen-15 water, which can assess CBF. Single photon emission computed tomography

(SPECT) with technetium-99m-hexamethylpropyleneamineoxime (99Tc-HMPAO) or technetium-99m-exametazime (99Tc-EMZ) can determine cerebral CBF. fMRI studies also yield data that was considered to be related to cerebral activity. Different from the type and distribution of transmitter, we can calculate the information of a complex network by use of fMRI based on the regional cerebral changes. For example, one of the interesting findings on MRI due to the facial expression was the fact that, activation of the amygdala was most consistently related to fear processing. The main circuit responsible for the facial expression is anterior cingulate-medial frontal gyrus-basal forebrain (Kiosses et al., 2000). In addition to the anatomical variations (volume loss, local-generalized atrophy, and white matter-related sequel signal changes) efficacy of treatment (psychotherapy, antidepressants, mood stabilizers, and sleep deprivation) of existent abnormalities can also be evaluated via fMRI (Kennedy et al., 2001).

Mood disorders may follow a unipolar course in which only depression occurs or a bipolar course in which normal mood alternates with both depression and mania. Co-morbid entities (such as anxiety) may alter the nature of fMRI findings. In appropriately applied tests, fMRI can detect the hypofunction in the ventral striatum, slowed motor manifestations in the dorsal striatum or thalamus, and amygdalar hyperactivity or hypersensitivity developed in anxious cases. In a study performed with fMRI, BOLD-fMRI has been performed with block design to reveal left amygdala activation during emotion. In the study, which has been performed by showing the photos of the actors taken in different facial expressions, it is found in general that medial prefrontal cortex, retrosplenial cortex and cingulum, and temporal pathways were involved in depressive patients and thought that hipoactivity might be the main underlying cause of hypoactivity (Dougherty&Rauch, 1997).

On the other hand, in addition to the standard motor or sensorial stimulations given by the technician, it is possible to stimulate noninvasively a brain region and to image simultaneously regional brain activity via transcranial magnetic stimulation (TMS) within the fMRI scanner, in the studies performed with more advanced systems. It was found in these studies that prefrontal brain TMS and thus the connectivity features showed variations in the depressive cases as compared to the normal control groups (Kito et al., 2008). On the other hand, vagus nerve stimulation (VNS) is a new technology that serves as an effective antidepressant. Moreover, the fact that activity shows an increase with VNS in the orbitofrontal and hypothalamus and in the prefrontal cortex may serve as a reference for the confirmation of fMRI data (Bohning et al., 2001).

In addition to this system, in which micromolecular system has been indirectly and noninvasively investigated without being exposed to ionizing radiation, brain imaging studies can also be done being oriented biochemically with a special radiotracer using PET and SPECT modalities. Data on this subject that is not within the scope of this paper can be obtained from the literature.

MRS studies in mood disorder showed that patients had metabolite alterations in prefrontal and anterior paralimbic basal ganglia-thalamocortical circuits. We can also calculate cellular construction and degradation products and metabolite contents with Phosphorus-31 magnetic resonance spectroscopy as well as conventional 1H-proton spectroscopy. In addition to the findings detected by 1H-MRS (Increased basal ganglia choline and decreased bilateral dorsolateral prefrontal NAA levels), studies that used phosphorus spectroscopy have found that bipolar patients had lower prefrontal phosphomonoesters (PMEs) (Yildiz et

al., 2001). This is an indicator of altered signal transduction putatively related to the pathophysiology of bipolar illness (Yildiz et al., 2001). Studies on adults, in whom affective illnesses have been developed after brain injuries, showed related abnormalities in the frontal or temporal lobes. Mania may be related to the right frontotemporal or left parietooccipital lesions, whereas depression is related to the left frontotemporal and right parietooccipital lesions (Castillo et al., 2000). Proton MR Spectroscopy provides information about tissue biochemistry and metabolic changes in vivo. MR Spectroscopy has been used with success in psychiatric illnesses limited to understanding some metabolic changes and to assessing the effects of lithium in the treatment of bipolar affective diseases.

White matter abnormalities are one of the components of the network dysfunction that underlies affective disorders. DTI can uniquely study the direction and integrity of white matter tracts and is thus an ideal tool to shed light on white matter abnormalities also in affective disorders. DTI studies on affective disorders consistently identify reduced anisotropy in the frontal and temporal lobes as well as reduced number of tracts in the patients with affective disorders as compared to the control subjects (Sexton et al., 2009).

Owing to the combination of fMRI studies and other neurostimulation methods such as TMS and VNS, it is thought that data obtained from the studies on this subject would be increased. Current techniques (BOLD fMRI, perfusion, diffusion, and spectroscopy) would be enhanced more in time; perhaps, more information about direct function would be obtained due to combined methods with the advances that we still could not predict. Organic data might also be obtained for the diseases, the physiopathology of which remained imaginable only, and the solutions would be put forward more clearly. This is not such a distant prediction, and in fact, appears frequently with simple mechanisms. For example, perfusion MRI of a case presented with depressive mood disorder and had contrasted nonspecific thalamic lesion on the MRI showed isointense millimetric non-perfusion foci in the left half of the pons on the above-mentioned contrasted focus; it was determined that atrial fibrillation and microembolus have caused the existing alterations. Although, numbers of symptomatic overlaps are likely between the two groups, the differences between mood disorders and schizophrenia in terms of anatomical changes of the brain are estimated to be clarified with detailed studies that would be performed on this subject. However, it should be kept in mind that current studies greatly have focused on the neurotransmitter and that in fact there are many numbers of transmitters and steps during the stages of forming and maintaining thought and behavior.

In summary, despite the advances that have rapidly been introduced to the routine use, estimations on the functional process are still being done indirectly by measuring blood flow and energy consumption, rather than directly via neurotransmitter formation and axonal conduction. Current studies investigate direct methods studying on the metabolites associated more directly. It has been suggested that clearer and adequate anisotropy maps and tractography imagings can be obtained in the future with high-resolution diffusion spectrum imaging due to the potential advances in DTI techniques. In this context, it is thought that adequate connections between the anterior cingulate cortex-basal ganglia and the frontal cortex could be identified by coding the afferent-efferent fibers in different colors with planned software.

3.3 Imaging studies in Attention Deficit and Hyperactivity Disorder (ADHD)

ADHD is a disorder of unclear pathophysiology mainly characterized by hyperactivity, impaired impulse control and attention deficit. ADHD is one of the most common

psychiatric disorders among children. Symptoms continue in the adulthood in 30-50% of ADHD cases diagnosed during childhood. As was shown in the studies that will be mentioned later, dysfunction of fronto-striatal formations and significant differences in metabolite concentrations in certain regions (such as caudate nucleus) have been put forward with fMRI and MRS in addition to the anatomic differences. Contrary to the autistic cases, decrease in total brain volume has been shown in many studies performed until today on the children with ADHD (99). In some studies, this volume decrease has been particularly stressed on (Critchley et al., 2003). In the studies with fMRI, differences have been identified between the children with ADHD and the control group in terms of the activations of prefrontal cortex, anterior cingulate cortex and striatum (Konrad et al., 2010). Some studies have revealed that differences in the blood flow prior to the therapy showed improvements such as returning to the normal levels after methylphenidate therapy, as compared to the normal population (101). It was shown with fMRI that both the clinical picture and decreased basal ganglia activation have improved in the cases presented with ADHD and learning difficulty as compared to the healthy subjects (Coryell et al., 2005). It was also shown with specific SPECT studies, which can obtain receptor-based information, that there was a decrease in the dopamine transportation intensity in the basal ganglia after the therapy (MacFall et al., 2001). All these studies showed that functions such as integrity of frontostriato-thalamic circuit and dopaminergic pathway are abnormal in the cases with ADHD and that, are improved with therapy.

Recent studies indicated a role for the basal ganglia (caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and ventral mesencephalon) in a variety of neuropsychiatric conditions involving motor and attentional dysfunctions. It is known that striato–thalamo–cortico–striatal loop is associated with motor, somatosensory, oculomotor, executive, emotion, and motivation functions in daily stimuli. Studies performed with fMRI suggested decreased perfusion in the dorsolateral prefrontal cortex of hyperactive children as compared to those nonhyperactive. Furthermore, asymmetry was found in the motor-timing and response phases of anterior cingulate activation during cognitive interference task in these hyperactive children as compared to those normal and non-hyperactive. Decrease in the perfusion of basal ganglionic region has been objectively demonstrated in the group including the children with ADHD. Attention-deficit and hyperactivity disorder (ADHD) is characterized by persistent inattention and/or situational excessive motor activity, and accompanying impulsive behaviors. It is the most prevalent childhood psychiatric disorder (3–11% of the school-age population). Some studies raised the thought that there is a problem with basal ganglia in some of the psychiatric diseases as well as in certain motor disorders. Ignoring molecular basal ganglionic communication cycle, which is out of the scope of this section, striatum is separated into two up to the cortical conduction type. The first is prefrontal cortical and associative areas including visual and auditory cortical regions projecting the dorsolateral head of the caudate and the anterior putamen. The second is extensive projections from the anterior cingulate and medial orbitofrontal cortex. This more complex cycle, which we have summarized, is the point, in fact, where the functional neuroanatomy is bound as would be in the future. As a general principle, examination must be suspended for 48 hours to 2 weeks prior to a functional imaging study in the children with ADHD.

Since the basal ganglia produce signals initiated by the commands of frontal-originated fibers, studies that investigated the activity and volumetry of DLPFC are not limited. In addition to these many conventional alterations, regional cerebral blood flow (rCBF) studies showed it is anomalous in both children and adult cases with ADHD. In these studies, greater frontal activation was found in the subjects with ADHD during response-controlled condition (Teicher et al., 2000). Decreased volume and altered asymmetries of the caudate nucleus in children with ADHD have been reported in several studies (Teicher et al., 2000). In addition to the volume loss, greater motor hyperactivity has also been found correlated with lower perfusion, assessed with resting state fMRI, in the right caudate of the children with ADHD. In some of these studies, the activation was measured increased in some brain regions, including the right caudate nucleus in the cases with ADHD, whereas no activation was identified in the normal cases receiving psychostimulant. Since putamen always plays an essential role in the sensorimotor activity, it has become a component studied in ADHD. Besides, an influence is in question also in globus pallidus and anterior cingulate region in the cases with ADHD (Filipek et al., 1998). On the other hand, cerebellum is an important organ, but neglected in ADHD. Despite the considerable number of evidences that indicate the role of dopaminergic system in ADHD, the underlying mechanism remains unclear. Although it is among the targets in current fMRI studies, PET methodology allows direct examination of dopaminergic function in vivo (Ernst et al., 1999). The current aim should be trying to visualize directly the functional pathology beginning from the "task development" stage, and to study with large series by standardizing the functions. The above-mentioned studies performed with fMRI were consistent with each other. The fMRI studies on children and adults with ADHD have shown that frontal lobes, basal ganglia and cerebellum are the regions most likely to be involved.

Current evidence suggests that ADHD involves dysfunction of a wide functional network of brain areas associated with attention and cognition. Cases with ADHD show greater fractional anisotropy in white-matter regions that underlie inferior parietal, occipito-parietal, inferior frontal, and inferior temporal cortices. Tractography may reveal that these regions generally form a part of white-matter pathways connecting prefrontal and parieto-occipital areas with the striatum and cerebellum. Again, when the information both from fMRI and from DTI studies is evaluated together, it was found that in ADHD some cortical regions that have previously been shown is dysfunctional or hypoactive (Silk et al., 2009). In another study, it was suggested that alterations in brain white matter integrity occur in frontal and cerebellar regions in ADHD. The pattern of decreased fractional anisotropy might implicate the corticopontocerebellar circuit in the pathophysiology of ADHD (Ashtari et al., 2005). In the ongoing studies of the same research group, it has been theoretically claimed based on the controls performed with DTI and MRI that these disorganized or spoiled grey matter pathways can be relatively repaired after appropriate treatments.

3.4 Imaging studies in the autism

Within the time from the first definition of autism until now, many structural and functional brain-imaging studies have been performed to investigate either the neuroanatomic disorders or the pathophysiology. In the structural brain-imaging studies, a decrease was detected in both the white and grey matter volumes mainly in the frontal, temporal and parietal lobes, as well as in the total brain volume, and this was attributed to an extensive

damage in the neuron networks that might have been developed in the early developmental period. In the functional brain imaging studies, efficacy differences have been detected in the temporal lobe and amygdala, which function in the language and social cognition fields, whereas an increase in the efficacy has been detected in the posterior cortical regions (Nugent et al., 2006). Despite this volume increase, some studies reported a decrease in the gray matter volume particularly in the ventromedial and superior temporal regions, in which emotional and sensorial stimuli are processed, and in the cingulate gyrus and superior temporal sulcus (Baumann et al., 1999). The studies on the autistic cases have been conducted within such a wide spectrum that one of the studies has reported an increase in the amygdalohypocampal volume in the parents of pediatric cases involved by the disease. There are studies suggesting that cerebral blood flow variation during language use in the autistic patients shows difference as compared to the normal population (Vostrikov et al., 2007). In the cerebral functional MRI studies that tested auditory data processing mechanism, it was found that the activity of left posterior insular region is less, but contrarily the right Wernicke homologous accompanies more activities. These data have led to the neurophysiological studies to understand why emotional component less accompanies speech in autistic subjects (Sanacora et al., 1999). Activations during human face identification and facial expression processing were found different in autistic children, adolescents and adults on the encephalographic fMRI studies (Hasler et al., 2007). Interestingly, it attracted attention in some fMRI studies that cerebellar functions as well showed an increase during motor activation (Filipek et al., 1997). Despite the conflicting results in the literature, studies performed with MRS reported that NAA concentration has been increased in the hypocampus-amygdala and in cerebellar level in autism (Durston et al., 2003). In a study that evaluated serotonin synthesis capacity via PET, it was expressed that this capacity was more intensive and long-termed in the autistic subjects (Schultz et al., 2000).

Although temporal lobe-originated abnormalities have been defined approximately and significant results have been obtained with these detailed data, it seems that DTI and molecular based studies that would be conducted on larger samples are needed to clarify the pathophysiology of autism. Studies have been performed on many topics in addition to these common, more extensive and perhaps popular study fields. Although the mechanisms were similar in all these extensive studies, patient groups and the focal region investigated were different. For example, FDG affinity was found lower in the medial temporal lobes of the cases described as aggressive on the psychiatric evaluations (Tamm et al., 2004). In many consecutive case reports or in the research papers, it has been reported that the symptoms mostly began within a psychiatric picture in congenital enzyme deficiencies, in metabolic or idiopathic cerebral diseases, or in systemic diseases (Shafritz et al., 2004). Furthermore, there is information characterized by large researches and reviews on this topic, in which an association between a single specific disease (such as encephalomyelitis, epilepsy, arachnoid cyst, Wilson's disease) and psychosis has been established (Barnea et al., 2004).

Autism is a developmental disorder defined by the presence of a triad of "communication, social, and stereotypical behavioral characteristics" with onset before 3 years of age. It is difficult to scan young children and to obtain appropriate age-matched controls. Studies have been mostly performed on mild and conformist autistic cases and thus, we have been restrained to obtain more current and extensive information (Heh et al., 1989). Although the

first results of the studies mentioned about increase in global glucose consumption of the brain, presence of basal ganglionic uptake imbalance has also been reported (Heh et al., 1989). Phosphorus-31-MRS showed that decrease in phosphomonoester levels, increase in phosphodiester levels and decrease in ATP levels were associated with increased ATP consumption (Minshew et al., 1993). On the other hand, proton (1H) MRS has showed that NAA is significantly lower in cerebellum in the autistic group (Prather et al., 2001). Since autism is most commonly recognized in the second year of life, later on during autism process, behavioral manifestations of autism change with age, and therefore, functional brain abnormalities as well might change in time, although autism is not a progressive disease. In the studies performed with DTI, white matter organization abnormalities were frequently detected particularly on frontal fractional anisotropy and apparent diffusion coefficient maps (Sundaram et al., 2008). Besides, many studies have mentioned about disappearance of normal asymmetric tract anatomy and reduced interhemispheric connectivity pathology between two hemispheres via demonstrative images.

3.5 Imaging in the extracranial pathologies that clinically present as psychiatric disorders

In this section, we are going to summarize the information in a table (**Table 3**). Findings about certain organic-extracranial diseases, the clues of which would be found also with other laboratory findings, as well as the psychiatric symptoms they caused, which would

Extracranial pathology	**Related psychiatric disease**
Hypothyroidism	Somatization, obsessive-compulsive disorder, anxiety, and paranoid thought are more common in hypothroidic cases (Vyas et al., 2010).
Hperthyroidism	Thyrotoxic encephalopathy (Brownlie et al., 2000).
Parathyroid malfunction	Mental dimness, imbalance and depression (Pollard et al., 1994).
Vitamin B12 deficiency	Depression, mania, psychosis, dementia (McCall et al., 2009).
Adrenal cortex hyperfunction (hyperplasia, adenoma)	As is known, hypercortisolemia is toxic for hypocampus and certain cortical regions, and may play a role in the development of psycopathologies such as posttraumatic stress, depression and dementia. Adrenal medulla-originated lesions may first present with fear and anxiety attacks (Schüle et al., 2009).
In most common endocrinologic diseases	Symptoms that mimic psychosis such as psychomotor retardation depersonalization and cognitive changes, depression, and anxiety (Roy et al., 1994).
In some extracranial tumors (such as lung carcinoma)	Some paraneoplastic substances may cause psychiatric symptoms due to their encephalopathic effect (Alamowitch et al., 1997).

Table 3. Certain organic extracranial diseases and related psychiatric symptoms they caused.

disappear when treated. To these brief data, psychiatric symptoms should be cautiously evaluated since they might be the reflection of underlying endocrinological disease or paraneoplastic syndromes with systemic signs, and the imaging spectrum should be widened if needed. As the result, such psychiatric symptoms that sometimes appear before the organic symptoms may have been used in early diagnosis.

3.6 Psychiatric symptoms and imaging of intracranial lesions

It was known also before the development of modern imaging techniques that intracranial space-occupying lesions and some other structural pathology lead to psychiatric symptoms. Based on their localization in the brain, space-occupying lesions cause personality changes, affective disorders and disorganization of intellectual functions. At least half of the cases with space-occupying lesion show psychiatric symptoms; furthermore, psychiatric behavioral changes appear as the first sign of the disease in 18% of the cases. In the postmortem studies conducted on the chronic patients or on psychiatric patients under treatment, cerebral lesion was detected by 3.5-5%. This rate is consistent with that found in the general population. However, in detailed examinations, change in mental status may appear as the initial symptom in 15-20% of the patients with space-occupying lesion. These are high cortical functions including attention, memory, emotion, personality, concrete thought and confusion. Symptoms such as a single epileptic seizure, change in the daily activities and interests, and not hearing high-frequency sounds may cause the physician to suspect space-occupying lesion. Using contrast MRI and CT, although the order is changed according to the centers, unveils the suspicious conditions in such cases. However, it is important to understand the underlying factor of the symptom; because, the association between space-occupying lesion and psychiatric symptoms may be developed primarily due to the direct invasion of the tumor, as well as secondarily due to the increased intracranial pressure caused by the edema and space-occupying character.

It is seen that the majority of space-occupying lesions that cause psychiatric symptoms are located in the frontal, temporal and limbic lobes (Feinstein et al., 1998). Along with the enlargement of the frontal lesions and disappearance of inhibition in time, personality changes such as irritability, impaired judgment and lack of interference, as well as neurologic symptoms, begin to appear. Whereas the right frontal ventral region is associated with manic behaviors, lesions of dorsolateral prefrontal cortex were found associated with apathy, lack of interest and psychomotor retardation (Feinstein et al., 1998). Temporal lobe lesions commonly cause complex partial (characterized by impaired conscious, repetitive psychomotor and autonomic motions) and simple partial (characterized by smell and taste hallucinations, deja vu, feel of fear) epileptic seizures. Lesions of temporolimbic region (likely due to the involvement of limbic formations such as hypocampus, fornix, mamillary corpuscle, mamillothalamic bundle, anterior thalamic nucleus, cingulate gyrus, and parahypocampal gyrus) are known to be frequently associated with psychosis and schizophrenia-like disorders (148). Parietal and occipital lobe lesions are rarely accompanied by psychiatric disorders.

Whereas, only localization of the lesion can be detected by tomography, differential diagnosis of the mass is available by MRI and functional techniques, and extremely beneficial information that might direct the therapy can be obtained. Tumoral metabolic activity can be identified by PET/CT, PET/MRI, and SPECT examinations. Examination by

DTI is a method that could identify the deformities of nerve tract caused by the edema-invasion-infiltration effects of the lesion.
In case of inconsistent mass lesion and psychiatric symptom, other likely anomalies that accompany the current psychiatric disorder can be investigated in the same session. The pathologies without mass lesion have been summarized under separate topics in the further sections of the review.
As a well-known entity; Alzheimer's disease: It is possible to differentiate the brain of healthy elderly from AD with conventional sequences. However, signal changes in the posterior segments of corpus callosum in early AD identified by DWI are consistent with pre-atrophy initial changes and are reasonable (Backman et al., 2001). On the other hand, DTI studies conducted in the early stages of the disease have revealed significant connection disruptions in the junction of white matter fiber tracts, including the temporal stem (uncinate fasciculus), cingulate fasciculus, corpus callosum, and superior longitudinal fasciculus, as well as the hippocampus (Volkow et al., 2000). The general rule up to now is; studies on AD have been performed with BOLD, and the degree of regional activity in mesial temporal lobe has been studied comperatively. In these studies, decreased mesial temporal lobe activity in mild AD cases, in which the volume loss was not manifest yet, as compared to the normal healthy population attracted attention (Kantarci et al., 2001). Additionally, magnetization tranesfer ratio measurements are more specific than visual analyses in detecting structural damage of the hippocampus in the patients with AD (Hanyu et al., 2000).

4. Conclusion

In conclusion, advances in molecular imaging technologies, in addition to the sectional radiologic imaging that provides anatomo-morphologic and functional information, have the ability to detect, diagnose and follow the neurophysiologic axis abnormalities that are reflected as psychiatric disorders. What is important is which of these methods are usable in what extent and which points the method would illuminate in the pathophysiology of the investigated disease. The aim of radiologic imaging in psychiatry should be to detect the specific findings of each disease and to allow differential diagnosis. Various algorithm templates that are appropriate for each clinic may be in question on this subject (**Figure 18**). For any of the imaging center, with routine or further radiological evaluation if needed, under the light of the literature information or experiences, this might be possible with the available modalities.
With regard to neuroimaging in psychiatry, numerous ongoing developments suggest that it may be possible to scrutinize the underlying anatomopathological or molecular abnormalities with radiologic imaging. By the emerging studies with 7 Tesla MRI, it may be possible to delineate subfield morphological abnormalities especially hypocampal regions. Besides, using DT-MRI in-vivo, under the ultra-high field MRI system, the tracts that form the white matter can be visualized noninvasively. Although, only the structural alterations have been studied previously, current technology aims to obtain metabolic, functional and consequently molecular information beyond the anatomic information. However, different from the other internal and surgical fields, the process in psychiatry is more complex and variable. Since there might be a severe metabolic-functional underlying organic etiology without presence of anatomomorphologic alteration, it is impossible, at least for now, to make the diagnosis easily with a "gold standard" imaging modality. With further advances,

optimization and standardization of radiological diagnostic systems for psychiatric diseases may be required in the near future.

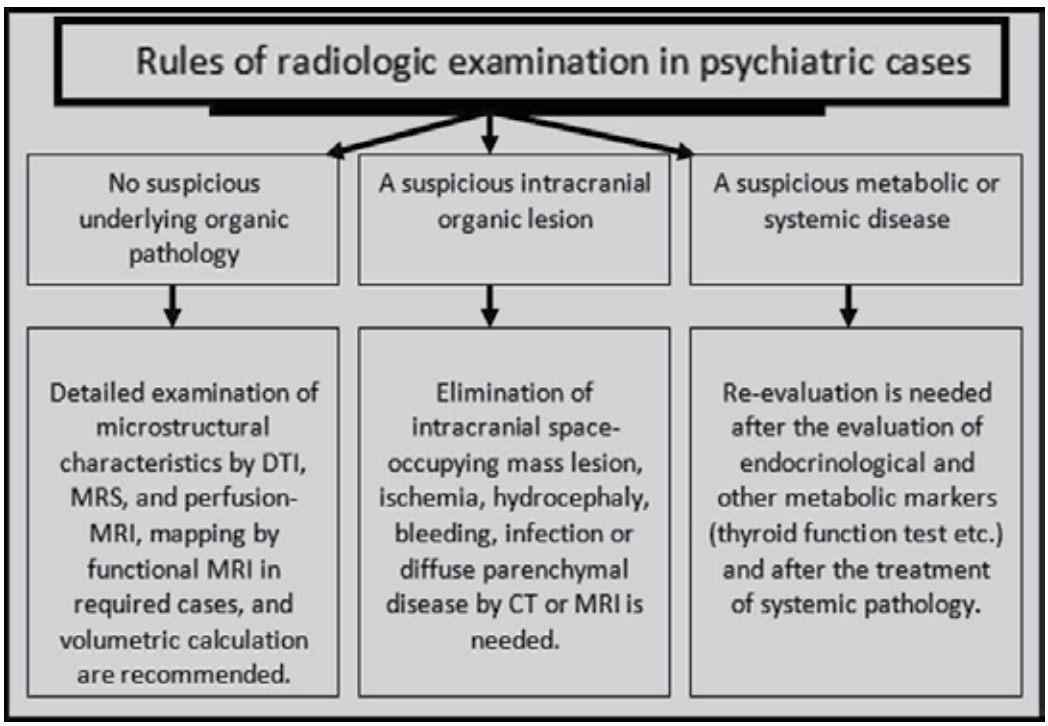


Fig. 18. A practical and applicable schema that indicating the simple algorithm that can be applied to radiological evaluation in psychiatric disorders.

With new modalities, the distribution of psychiatric medications that are considered relatively serious can be investigated by giving marked medications, in terms of not only the disease could be foreknown, but also potential toxicity and which organ it would affect most. It is already possible to measure the concentration of lithium or fluoxetine metabolites by detailed MRS examination.

Since the course of the fibers can be known and predicted in the examinations performed with DTI in particular, it can be used as a guide in stereo-ataxic neurosurgery that is used in the treatment of therapy-resistant obsessive-compulsive disorder or major depression. DTI guidance can be used to preserve the risky tracts prior to the procedures such as anterior cingulotomy, anterior capsulotomy, and limbic leucotomy. Moreover, efficacy of therapy (particularly in epileptic cases) can also be evaluated with this method. At this point, therapy-resistant obsessive-compulsive disorder and depression can be treated more appropriately with transcranial magnetic stimulation (TMS) for the regions that abnormally matched DTI/fMRI. It can be said in all contexts that knowledge about imaging in

psychiatry would be improved and, as in many fields, routine use of MRI sub-modalities for diagnosis might be in question in the near future, although not so close.

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3

Dissociative Tendency, Anger Expression, and Frontal Activation During a Verbal Fluency Task

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1. Introduction

Dissociation in adolescence has been described as a part of severe psychopathology with a complex comorbidity or serious trauma including sexual abuse (e.g., Chu and Dill, 1990; Sar et al., 2006). In contrast, it is also possible for healthy subjects to experience nonpathological (nonclinical) dissociation including daydreams or defense from strong stressors (de Ruiter et al., 2006). It is important to clarify the etiology of dissociative experiences. For example, a lack of integration of consciousness, amnesia, derealization, or depersonalization, and some neural mechanisms underlying dissociation could be reasonably hypothesized as core features of dissociative disorders (DD). Particularly, self-reference related regions such as the medial prefrontal or ventral frontal area might be involved in identity diffusion or multiple identity disorder (Reinders et al., 2003). Actually, recent advances in neuroimaging technology enable us to explore the brain functioning of dissociation. Although it is ideal to examine a patient with DD who is experiencing dissociation in vivo, it is simultaneously intrusive to induce pathological dissociation using reminders or stressors. According to the spectrum of dissociative experiences, another option would be to examine nonclinical dissociation or dissociative tendencies in a typical setting. Dissociative experiences usually begin in childhood, and less than 8% of the DD diagnoses are made in adolescents between the ages of 12 and 19 (Kluft, 1984). Some of the experiences are not subjectively distressful; therefore, dissociation might be underestimated as a clinical phenomenon (Foote et al., 2006). Furthermore, recent campus mental health professionals in Japan have often indicated that a trend for defence mechanism is "to dissociate from repression" in young adults (e.g., Takaishi, 2000). Based on these assumptions, the present study focused on nonclinical dissociative tendencies and investigated frontal functioning during a cognitive task in healthy university students.

Aggression or impulsivity is another important mental health topic in youth including attention-deficit hyperactivity disorder (ADHD) or childhood bipolar spectrum including temper dysregulation disorder. Impulsivity is related to the loss of response inhibition, particularly to the lack of frontal functioning (e.g., Chamberlain and Sakahian, 2007). A recent study concluded that slower cortical thinning in the prefrontal cortex during adolescence is characteristic of ADHD, providing neurobiological evidence for the

dimensionality of this disorder (Shaw et al., 2010). Anger is the most relevant emotion closely associated with impulsivity or aggression. Activity in the dorsal anterior cingulate cortex is positively related to self-reporting of anger and individual differences in general aggression (Denson et al., 2009). Another study (Hewig et al., 2004) reported that subjects with relatively greater left than right frontal cortical activity showed higher anger-out scores and lower anger-control scores. Furthermore, anger induction was uniquely associated with increased regional cerebral blood flow to the right temporal pole and thalamus. Based on these studies, it appears reasonable to investigate functional correlates of anger expression in youth.

Interestingly, one descriptive study reported a relationship between dissociative experiences and anger proneness in late adolescent females (Calamari and Pini, 2003). The authors stated that significant correlations were obtained between the Dissociative Experience Scale (DES) and the State-Trait Anger Expression Inventory (STAXI), confirming a connection between anger proneness and dissociation described in patients with dissociative disorders in a nonclinical sample. We also speculate that dissociation may be one of the defence mechanisms to cope with anger, impulsivity, or aggression. Consequently, frontal functioning may determine individual styles including expression, control, and suppression.

Near-infrared spectroscopy (NIRS) and the newly developed optic brain functional imaging are promising techniques because of their non-invasiveness and convenience. NIRS employs near-infrared light emitted and detected on the skull skin (Boas et al., 2004). It allows the monitoring of hemodynamic changes, which include both cerebral blood volume changes and oxygenation state, using a small apparatus with a high time resolution of about 0.1 s. It also allows the monitoring of changes in both oxygenated haemoglobin concentration [o-Hb] and deoxygenated haemoglobin concentration [d-Hb]. NIRS is suitable for studies of higher brain function because it enables measurements in a natural setting compared with other brain imaging techniques. For example, subjects can undergo an NIRS examination in the sitting position, with their eyes open, or while speaking (Suda et al., 2009). Taking advantage of these characteristics, several NIRS studies on psychiatric disorders, such as schizophrenia (Grignon et al., 2008; Takizawa et al., 2008), depression (Matsuo et al., 2005), eating disorders (Suda et al., 2010a; Uehara et al., 2007), and ADHD disorder (Ehlis et al., 2008), have been conducted. These characteristics of NIRS have also enabled the investigation of subjective experiences in healthy subjects such as conversation, subjective sleepiness, and psychological fatigue (Suda et al., 2008, 2009, 2010b).

The present study aimed to examine cortical activation using a verbal fluency task, which has been applied widely in clinical and nonclinical samples as a standard and specific paradigm to activate the frontal lobe. We used a newly developed multi-channel NIRS machine specified for frontal regions to explore differences in frontal activation according to the dissociative tendency. In addition, we examined correlations among frontal functioning, dissociation scores, and anger expression styles measured by self-report.

2. Material and methods

2.1 Participants

The study participants were 44 healthy university students (29 females), with a mean age of 20.5 years (SD, 2.0). They were all Japanese, and two students were left-handed. None of the

participants had any significant medical/psychiatric history. The participants were voluntarily recruited as subjects for this scientific study, and were paid 1,600 yen for a 2 hours exam as a co-operator as per the official provision. All subjects gave written informed consent prior to their participation in the study, which conformed with the provisions of the Declaration of Helsinki revised in Edinburgh in 2000. Privacy and anonymity of all participants were carefully preserved. The data was collected from August to December in 2009 and 2010.

2.2 NIRS (Fig. 1-3)

NIRS allows the calculation of changes in [Hb] parameters, including [o-Hb] and [d-Hb], by measuring the attenuation of near-infrared light at an approximate 800 nm wavelength. Neural activation induces regional hemodynamic changes in brain tissue, almost identical in pattern to spontaneous cerebral neural activity. Cortical activation is typically detected as an [o-Hb] increase or an [d-Hb] decrease; however, the direction of change in [d-Hb] can be ambiguous in the frontal lobe (Sato et al., 2007). Mainly changes in [o-Hb] at a depth of 2–3 cm from the scalp, that is, the surface of the cerebral cortex, are correlated with positron emission tomography (PET) hemodynamic changes (Ohmae et al., 2006) and blood-oxygenation-level-dependent signal changes in functional magnetic resonance imaging (fMRI) (Toronov et al., 2001; Mehagnoul-Schipper et al., 2002). NIRS does not measure cerebral luminescence but measures the attenuation of irradiated light intensity. Therefore, the combination of optical irradiation and photon detection determines the resolution. It characteristically measures not the 1:1 combination of irradiation and detection, but the light from one light source with 2 or more detectors arranged geometrically in the measurement system of NIRS. Thus, information on which detector measures the signal of which portion becomes important. Some methods are available for judging this channel separation. The first method, time division multiple access, makes a light source turn on in order, and separates the signal on a time axis. The second method, frequency division multiple access, is for modulating and irradiating two or more light sources with different frequencies and separating a signal based on frequency information after detection. The third method is code division multiple access (CDMA), using spectrum diffusion attenuation, which is applied in such applications as global positioning system or mobile phone. A new machine, OEG-16 (Spectratech, Inc, Yokahama, Japan), uses CDMA and is very convenient and portable. It can generate NIRS data under natural conditions noninvasively, and artifacts induced by hair can be avoided because of the adjustments only on the front of the head. The OEG-16 measures 16 channels on the frontal lobe (according to Broadman's map, provides data on 10, 11, 12, 44, 45, and 46). Its time resolution is 0.5 s, and space resolution is 2 cm. A headset was placed on the participant's head according to the 10/20 system, by which a central hole was coordinated with Fz. The measurement points for channels 1 to 8 were placed from the right lateral to the central pole. For channels 9 to 16, the measurement points were placed from the ventral/rostral to the left lateral (refer to the video content). These placements provided for relative changes in [Hb] concentration, and the values obtained were in arbitrary units (concentration × path length).

Details of NIRS methodology have already been described in major publications in Japan (Fukuda, 2009; 2011).

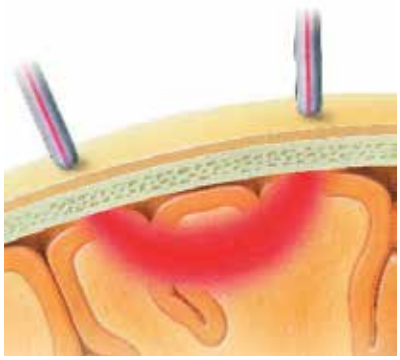

Fig. 1. Estimated areas for measuring the blood volume changes of cerebral cortex. (© Hitachi Medical Corporation, http://www.hitachi-medical.co.jp/info/opt/qa.html#q1)

Fig. 2. OEG-16 (18×17×4 cm, Spectratech, Inc.)

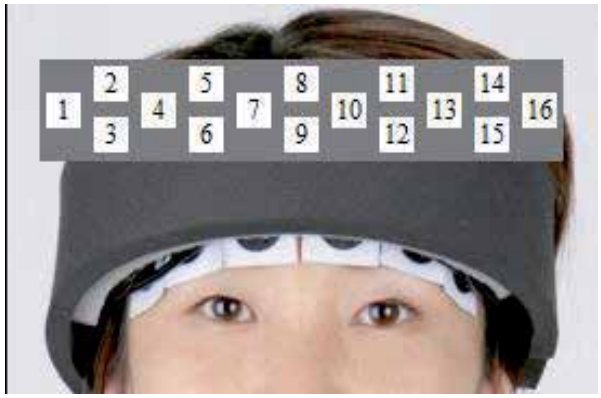

Fig. 3. Measuring points and headset. (Spectratech, Inc.)

2.3 Verbal fluency task

This standardized activation task is employed internationally for NIRS measurements, and it has been confirmed that this method provides widespread frontal activation reliably (Kono et al., 2007; Schecklmann et al., 2008; Kakimoto et al., 2009). The frontal activation task was a modified version of the verbal fluency task. A subject sat on a comfortable chair in a quiet room with their eyes open throughout the measurement. The activation task consisted of a 15-s pre-task baseline, a 30-s verbal fluency period, and a 15-s post-task baseline. During

the verbal fluency period, the subjects were instructed to verbally generate as many words as they could whose initial Japanese syllable (mora) was either /a/, /ki/, or /ha/. These three initial syllables were used in the above-mentioned order and changed every 10 s during the 30-s verbal fluency period to reduce the time during which the subjects remained silent. The number of words generated during the verbal fluency period was determined as a measure of task performance. During the pre-task and post-task baseline periods, the subjects were instructed to repeat the syllables /a/, /i/, /u/, /e/, and /o/ as the Japanese counterparts of A, B, and C in English. Two sets of this task were performed, and the respective data were superimposed and averaged.

Fig. 4. One epoch of the verbal fluency test (VFT).

2.4 ADES and STAXI

The ADES was developed solely for adolescents by Armstrong et al. (1997) to detect dissociative behaviour in children between 11 and 17 years of age. It is a 30-item self-reporting scale composed of an 11-point scale ranging from 0 representing "never" to 10 representing "always". The total ADES score is equal to the mean of all item scores. A subject circles the number that best describes how often a given experience happens. On the title page, respondents were instructed not to count experiences that occur under the influence of any drugs. Several versions of the ADES are available in Japanese (e.g., Tanabe, 2004). We used the one developed by Matsumoto et al. (2004) because of its excellent psychometric properties.

The STAXI tool evaluates anger isolated from hostility and aggression, covering anger experience and expression (Spielberger, et al., 1998). The STAXI is a self-reported 44 items, and individuals answered on a four-point Likert scale (score range: 0–132) to assess either the intensity of their angry feelings or the frequency as state, trait, anger-in, anger-out, and anger-control subscores (expression of anger toward other persons or objects in the environment is anger expression-out; holding in or suppressing angry feelings is anger expression-in; and controlling angry feelings by preventing the expression of anger toward other persons or objects in the environment, or controlling suppressed angry feelings by calming down or cooling off is anger-control). The Japanese version was developed by Mine et al. (1997), and the first STAXI was used in the present study.

2.5 Data analysis

The continuous waveforms of the [Hb] changes on all 16 channels were acquired from all subjects during the paradigm. The individually averaged [Hb] waveforms were obtained as the average sum of two trials; a baseline realignment for 5 s before and after the task periods, and a task segment averaging two sets of 15-s image viewing periods. Thereafter, the grand average values of the baseline and task segments for each channel were calculated for all data. Figure 5 is an example of a grand average waveform for three parameters; the

red polygonal line indicates the relative changes in [o-Hb], the blue indicates those of [d-Hb], and the green indicates the changes in the total-Hb (sum of o- and d-Hb).

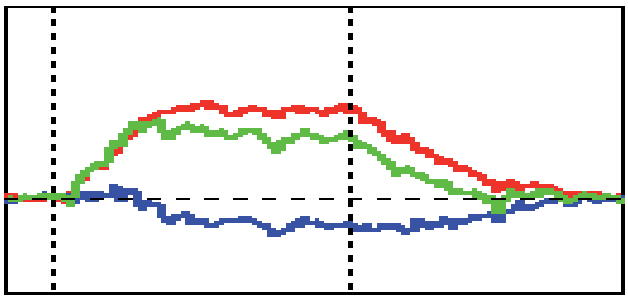

Fig. 5. The red polygonal line indicates the relative changes in [o-Hb], the blue indicates those of [d-Hb], and the green indicates the changes in the total-Hb (sum of o- and d-Hb).

We used only [o-Hb] values as cerebral blood volume changes for statistics, based on previous reports (Suto et al., 2004; Kameyama et al., 2006). Topography (video content) was presented on the frontal portion according to the time course. In this grand average data, channels that carried significant activation were analyzed between the pre-task and task periods using the t-test (http://www.brsystems.jp). Differences in the mean values were tested by combined variance, as the number of samples for the two periods was not equal.

Combined variance: Ue2 = { (na - 1) ua2 + (nb - 1)ub2}/{na + nb-2}
Variance and numbers of sample a: ua2 and na
Variance and numbers of sample b: ub2 and nb
T-value: t0 = |mXa - mXb|/root{ue2(1/na + 1/nb)}
Average of each sample: mXa, mXb

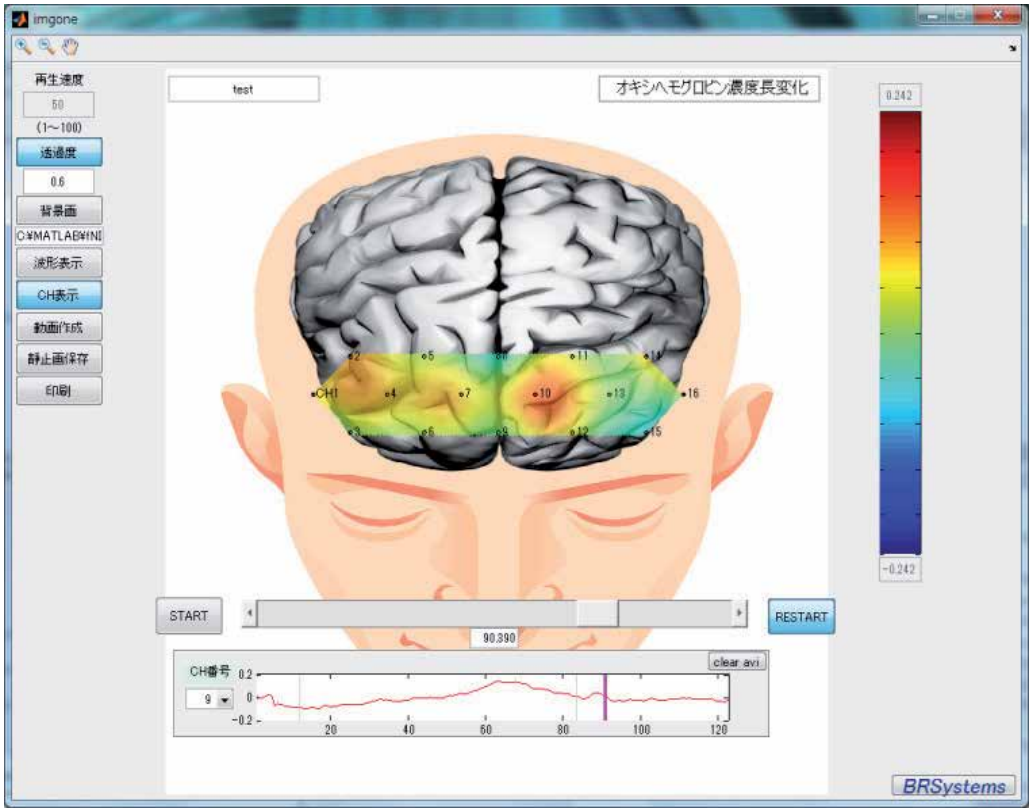

Fig. 6. An presentation using the Data Viewer (BR Systems, Inc.).

In the next step, differences were investigated according to dissociative tendencies followed by the t-test for each channel during the task period between the sample grand average data divided by the ADES mean scores ("strong" and "weak"). In the last step, the relationships between the [o-Hb] changes, the STAXI subscales, and the ADES scores were investigated. The channels, with significantly correlated changes, were analyzed by a nonparametric Spearman's correlation coefficient (two-tailed). Imaging software was used to analyze the NIRS parameters, and figure 6 shows an example of demonstration by this software (Data Viewer ver.1.1a, BR Systems Inc., Tokyo, Japan). The other statistical analyses were conducted using SPSS version 17.0 (SPSS, Inc., Tokyo, Japan).

3. Results

3.1 Waveform and dissociation

Figure 7 shows the grand average waveforms for the [Hb] changes for all participants, and figure 8 indicates the comparisons of waveforms according to the ADES average scores (mean = 13.9, S.D. = 12.8). 27 students scored under the mean as "weak" on the left, and the others as "strong" on the right. The red polygonal line indicates the relative changes in [o-Hb], the blue indicates those of [d-Hb], and the green indicates the changes in the total-Hb (sum of o- and d-Hb). The video content depicts the topography of the [o-HB] changes ("weak" on the left and "strong" on the right side), and redder areas represent greater

activation (grading to yellow, green, and opposite in deeper blue). Overall, gradual increases and fluctuations were generally observed in widespread channels during the task. The video file can be viewed on this website.
http://www.youtube.com/watch?v=g7IG5HG8q_U

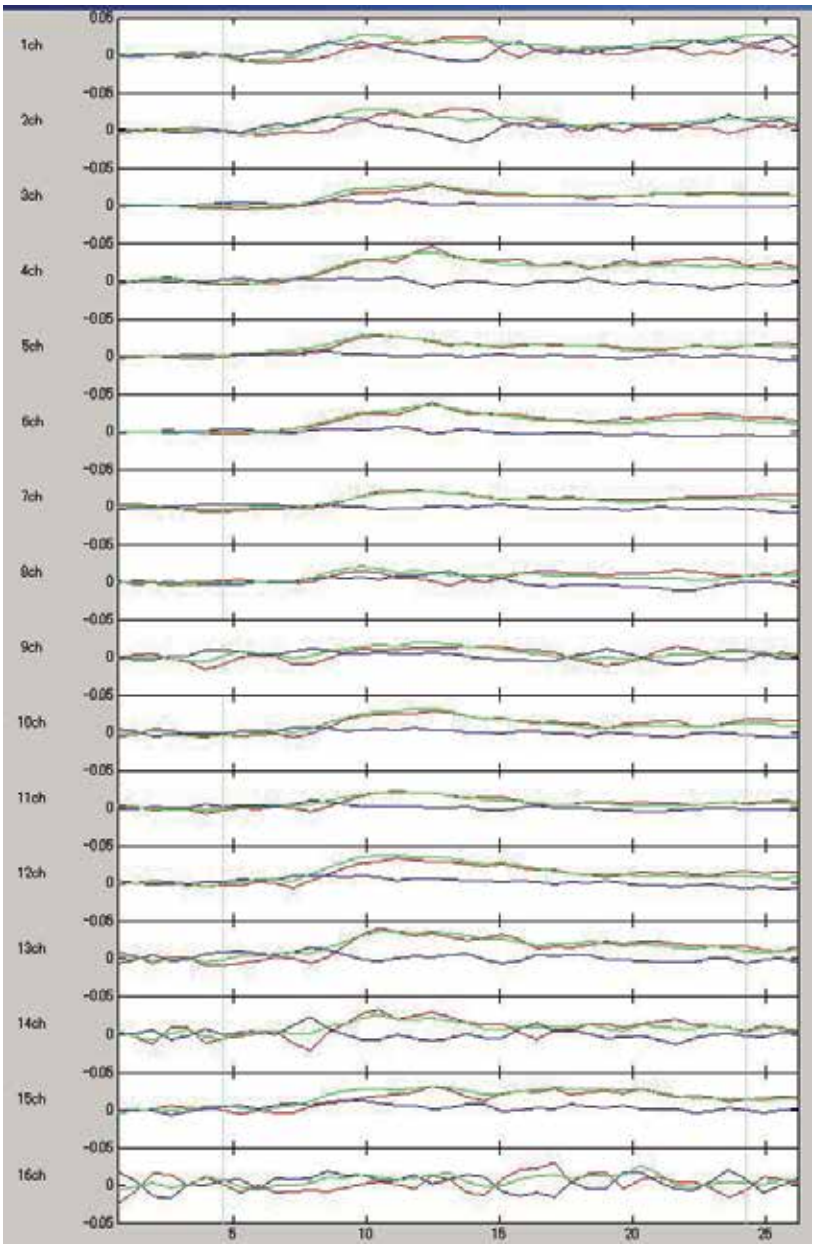

Fig. 7. Grand average waveforms

This demonstrated grand average waveforms of [Hb] changes for all participants' data. The red polygonal line indicates [o-Hb], blue indicates [d-Hb], and green indicates the total [Hb] (sum of o-HB and d-HB) relative changes. The vertical axis represents the relative changes in [Hb] (mMmm), and the vertical grey lines represent the start and end of task periods. The numbers on the abscissa indicate measurement time points (seconds). The data of the respective channels was placed according to each number from the top to the bottom.

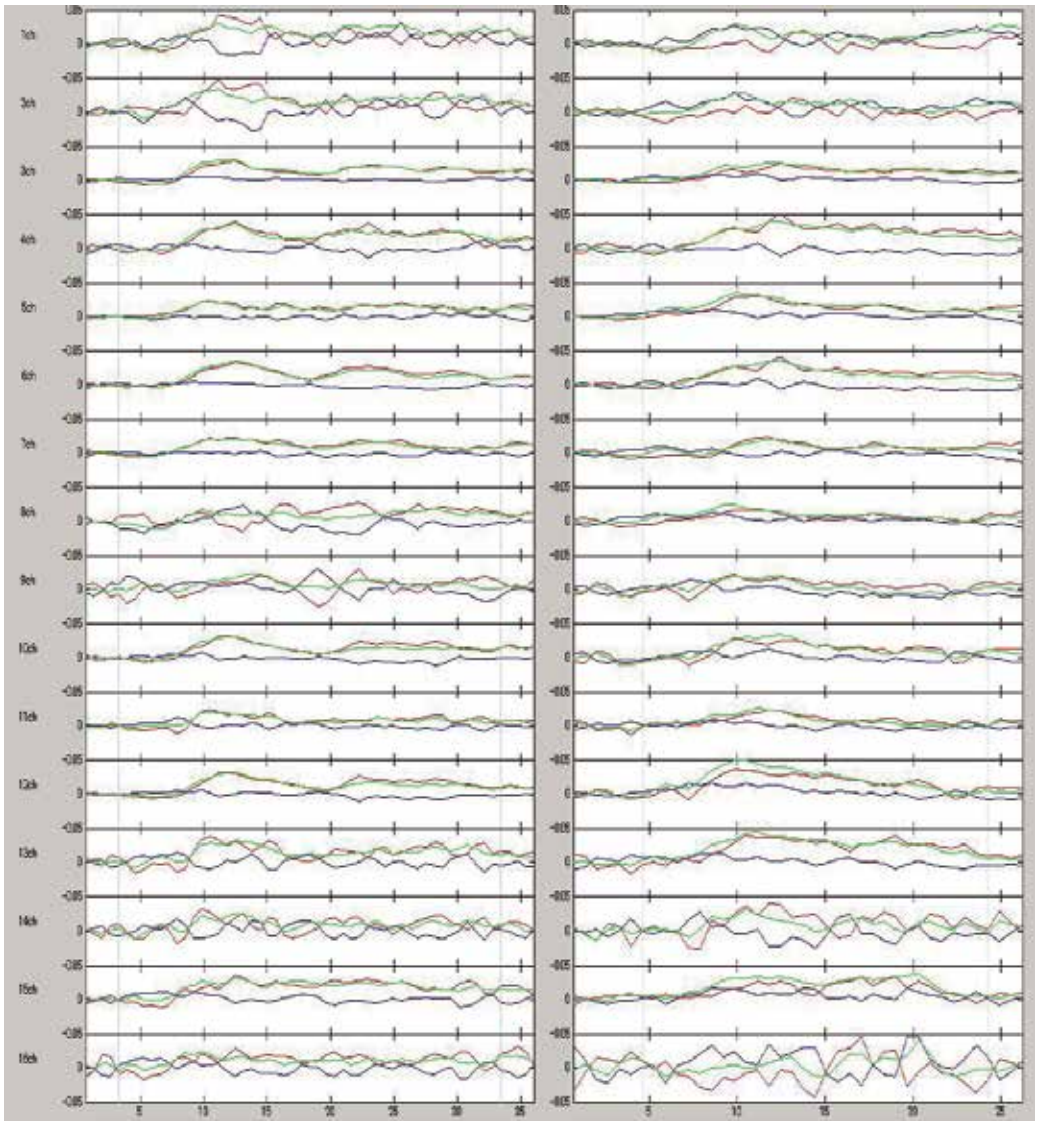

Fig. 8. Comparisons of the grand average waveforms according to dissociative tendency

This demonstrated grand average waveforms of [Hb] changes for all participants according to ADES, in which two samples were divided by the mean scores (the data over the mean is in the left and the data below the mean is on the right side). The red polygonal line indicates [o-Hb], blue indicates [d-Hb], and green indicates the total [Hb] (sum of o-HB and d-HB) relative changes. The vertical axis represents the relative changes in [Hb] (mMmm), and the vertical grey lines represent the start and end of task periods. The numbers on the abscissa indicate measurement time points (seconds). The data of the respective channels was placed according to each number from the top to the bottom.

Comparisons between the baseline and task periods are summarized in Table 1. The respective arbitrary units and t-values for each channel are presented for all, "weak" and "strong" students; significant activations (two-tailed, DF = 32) were obtained on channels 3–15 for all students; on channels 2–7, 10, 12, and 15 for "weak" samples; and on channels 3–8 and 10–15 for the "strong" samples. Comparisons of the activation for the task periods between the "strong" and "weak" samples were calculated; t-values for every channel indicated that they were significantly lower on channels 1**, 2**, and 7* (dorsolateral to the ventral portion) in the right PFC, and higher in channel 13** and lower in channel 16** in the left PFC for "strong" than for "weak" samples (*p < .05, **p < .01, DF = 52) The total ADES scores were negatively correlated with activation in the center prefrontal channel 8 (rostral ventral PFC; r = −.30, p < .05).

	WEAK (n = 27)			STRONG (n = 17)			All 44 Students			Comparisons for task periodes between WEAK and STRONG	
channel	Rest	Task	t	Rest	Task	t	Rest	Task	t	t	p (DF = 52)
1	0.003	0.012	1.37	0	-0.002	-0.56	0.002	0.006	0.88	4.77	0.0002
2	0	0.015	2.36*	0.002	0	-0.61	0.001	0.008	1.44	5.48	0.00001
3	0	0.014	3.13**	0	0.012	4.00**	0	0.013	3.56**	0.51	0.61
4	0	0.018	2.91**	0.002	0.025	3.82**	0	0.022	3.79**	-1.91	0.06
5	0	0.013	4.53**	-0.002	0.014	4.31**	-0.001	0.013	4.90**	-0.40	0.70
6	0	0.016	3.53**	0	0.019	4.38**	0	0.018	4.21**	-0.76	0.45
7	0	0.012	3.42**	-0.002	0.008	2.58*	-0.002	0.010	3.53**	2.45	0.02
8	0	0.011	1.09	-0.002	0.006	3.35**	0	0.008	2.80**	1.08	0.29
9	-0.002	0.005	1.89	-0.001	0.006	1.80	-0.003	0.005	2.16*	-1.09	0.28
10	0	0.015	2.96**	-0.001	0.012	2.44*	0	0.013	3.00**	0.91	0.37
11	0	0.008	2.00	-0.004	0.009	4.18**	-0.003	0.008	3.30**	-0.65	0.52
12	0	0.014	2.76*	0	0.017	3.01**	0	0.015	3.35**	-1.40	0.30
13	0.003	0.014	1.73	-0.005	0.023	4.78**	-0.002	0.018	3.48**	-3.08	0.0031
14	0	0.009	1.30	-0.005	0.013	2.22*	-0.002	0.011	2.20*	-1.40	0.17
15	9	0.018	2.92**	0.005	0.016	2.25*	0.002	0.017	3.20**	0.83	0.41
16	0.005	0.011	1.08	0.010	-0.006	-1.66	0.007	0.003	-0.75	4.00	0.0003

arbitary unit: mMmol *; p < .05, **; p < .01 (DF = 32)
WEAK/STRONG; divided by the mean scores '13.9' of the adolescent dissociative experiences scale (ADES)

Table 1. Comparisons of activations according to dissociative tendency

3.2 Correlation with anger expression

Table 2 shows the descriptive values of the STAXI subscale scores for all participants. Spearman's correlation coefficients were calculated for the relative changes in [o-Hb] for the 16 channels and the STAXI scores. The anger-in STAXI scores were negatively correlated with channel 8 activation (frontal pole of PFC; r = -.31, p < .05). The other scale scores were not significantly correlated with any other channel activation.

	state	trait	AX/In	AX/Out	AX/Con	AX/EX
mean	12.3	20.3	19.2	14.3	22.0	27.5
S.D.	3.5	7.1	4.2	3.7	4.1	7.2

STAXI: State Trait Anger Expression Inventory
AX/In: anger expression in
AX/Out: anger expression out
AX/Con: anger expression control
AX/EX: expression, (AX/In+AX/Out)-Ax/Con

Table 2. Descriptive values of the STAXI

4. Discussion

Some interesting relationships were found between frontal activation and psycho-behavioural variables that can be summarized as follows: 1. Strong dissociative tendencies were generally related to lower PFC activation. In particular, the activation was relatively dominant on the lateral and right sides. 2. Only channel 13 (left inferior frontal gyrus, close to BA46) activation could be directly associated with dissociative reactions with regard to contrast of activations; significant increases in channel 13 and significant decreases in channel 7 (right BA46). 3. Analyses of the correlations revealed that frontal pole (channel 8, close to BA10) dysfunction may be linked to dissociative tendencies. This relationship was paradoxical to anger suppression; the "ANGER-IN" style was correlated with lower activation in this portion (rostral PFC, channel 8).

Similar to the normal control data of many previous NIRS studies, the verbal fluency task provided excellent activation in widespread areas of PFC both in the "strong and "weak" dissociative groups, and this was reasonable, as our sample consisted of healthy students. However, according to ADES, a dissociative tendency might be associated with differences in prefrontal deactivation. In particular, lateral or right side deactivation may influence the dissociative tendency. The findings of the present study also suggest that suppression may be disturbed by over-function in the frontal pole (rostral PFC), and a contradiction could be seen in dissociative experiences. Considering dissociation and repression as coping mechanism to distresses, frontal pole deactivations may induce dissociative defence and the repression of anger expression.

Reviewing related studies, Bell et al. (2010) commented that dissociation is associated with increases in PFC activity and suggested that intervention by the executive system for both automatic and voluntary cognitive processing was common to both hysteria and hypnosis. We found only one study (Amrhein et al., 2008) that has investigated high/low dissociators in subjects without any psychiatric or neurological disorders and without prior trauma experiences. High dissociators show cognitive deficiencies, and a hippocampal and PFC dysfunction was assumed to be the core factor. Although the subjects had clinically disordered post-traumatic stress disorder (PTSD), Lanius et al. (2010) proposed that a dissociative subtype of PTSD is a form of emotion dysregulation that involves emotional overmodulation mediated by midline prefrontal inhibition of the limbic regions. Based on these studies, the results from the present study strongly support involvement of PFC with dissociation. A PET study stated that anger conditions are

associated with increased regional cerebral blood flow (rCBF) in the left inferior PFC and decreased rCBF in the right superior frontal cortex (Kimbrell et al., 1999). An fMRI study indicated that medial PFC activity (mostly identical to BA10 or 9) is related to self-reported rumination and individual differences in displaced aggression (Denson et al., 2009). As "ANGER-IN" means the frequency with which angry feelings are suppressed, rumination appears to be linked to this type of anger expression. Based on these findings and our results, the relationships between anger and bilateral ventral or rostral PFC involvement (dominantly left) can be assumed.

Some limitations of this study should be noted. The data could not be interpreted directly for DD because clinical subjects were strictly excluded. A future study should administer paradigms directly to induce dissociation or present specific stimulation. Similarly, tasks provoking anger such as visual stimuli should be considered. We did not reveal a correlation between frontal activation and state/trait anger, anger-out expression, or anger-control. We should still be conservative when discussing the association between anger suppression and brain function. This study used a frontal-specific methodology that should be complemented with a whole-brain measurement. Considering the importance of the clinical application, relative changes in cerebral [Hb] data as absolute values should be cautiously interpreted. Furthermore, anatomically identifying the measuring points is a major methodological challenge in multichannel NIRS, but the space resolution in NIRS ranges from 2 to 3 cm; therefore, it would not be problematic to discuss functional dynamism within broader frontal connectivity. Rather than being a weakness, high time resolution can contribute to clarifying the network or circuit based on detailed analyses of the time-course and activation patterns. Actually, the OEG-16 has already been applied in a psychological study, and its availability could be introduced (Uehara et al., 2011).

Differences in frontal activation suggest that dissociation might be related to PFC. Activation in the left inferior frontal gyrus could be associated with dissociative reactions in contrast to right side activation. We also suggest that a dissociative tendency and anger suppression could be associated with rostral PFC deactivations. Further study needs to include a clinical application and improve the task paradigm.

5. Acknowledgment

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A summary of this study was presented at the 16th ESCAP in Helsinki on June 2011.

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Part 2

Psychosocial Approach

4

Cognitive Behavioral Analysis System of Psychotherapy (CBASP): A Disorder-Oriented, Theory-Driven Psychotherapy Method from the "Third Generation" of Behavior Therapy Models, Designed for the Treatment of Chronic Depression

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1. Introduction

Major depressive disorder (MDD) is a common disorder which is usually associated with severe and persistent symptoms. The global prevalence of MDD is 1.6% in men and 2.5% in women (Ayuso-Mateos et al., 2000). The lifetime prevalence in the general US population is 16.2% (Kessler et al., 2003). Individuals between 18-29 years have the highest cumulative lifetime prevalence in comparison to all other age-groups. The rate of MDD diagnosis is particularly high in younger females (Wittchen et al., 1992; Kessler et al., 1994; WHO, 2004; Satyanarayana et al., 2009). MDD is the 4th leading cause for "years of healthy life loss" in high- and middle-income countries. The WHO predicts that by 2020 MDD will move upwards to be the 2nd cause (WHO, 2004). The impact of MDD on quality of life is equivalent to that of severe physical illness, such as cancer, diabetes mellitus and chronic obstructive pulmonary disease (Sintonen, 2001; Saarni et al., 2006). In addition, 9-23.0% of individuals with one or more chronic medical conditions suffer of co-morbid depression. Consistently across countries and different demographic characteristics, respondents with depression co-morbid with one or more chronic physical conditions have the worst health scores of all disease states (Moussavi et al., 2007; Trivedi et al., 2009; Satyanarayana et al., 2009). Suicide and chronicity are significant further threats of MDD. Patients with more severe recurrent and/or chronic MDD die up to 15% by suicide (APA, 2000; Wahlbeck and Mäkinen, 2008; Satyanarayana et al., 2009). In one of three cases MDD leads into a chronic course, particularly when antecedent dysthymia is present (Keller et al., 1982; McCullough et al., 1996; Costa and Silver, 1998). A recent Canadian community health survey with inclusion of 36984 individuals aged 15 years and older reports the life-time prevalence of chronic MDD to be 2.7%, representing 26.8% of all individuals affected by MDD (Satyanarayana et al., 2009). The prevalence of dysthymia with or without superimposed major depressive episodes is estimated to be approximately 3%, the lifetime prevalence 6% (American Psychiatric Association, 2000).

1.1 Diagnostic issues of chronic MDD

Chronic depression is defined as unipolar depressive disorder lasting two or more years with less than a two-month period during which the individual reports no symptoms. The rating for chronicity is contingent upon the density of symptoms at the time of assessment, every day in MDD and more days than not in dysthymia. Manic, mixed or hypomanic episodes are listed as exclusion criteria. Coincidences of symptoms with other psychiatric disorders frequently occur (American Psychiatric Association, 2000). In the DSM-IV mood disorders field trial seven chronic course descriptions were reliable differentiable (Klein, 1992; Keller et al., 1995; McCullough et al., 1996). The most common condition is represented by patients with early onset dysthymia that suffer the additional burden of either a more severe and pervasive major depressive episode or recurrent major depressive episodes with or without interepisode recovery (double depression), accounting for up to 75% of the total numbers of affected individuals (Klein et al., 1996). Double depression represents the simultaneous occurrence of two unipolar depressions with distinctive symptom severity and course patterns as well as different age of onset profiles. The antecedent dysthymia is in its origin conceptualized as a "cluster" of intrapersonal and interactional symptoms (Shapiro 1975, Lewinsohn et al., 1978). Dysthymia usually begins with an insidious early onset before the age of 21 (Klein et al., 1996). Affected patients are unlikely to remit over time compared to pure MDD (McCullough, 1988, 1994). The course of the disorder is more frequent than not associated with a repetitious history of self-reported interpersonal disappointments or childhood trauma (Klein et al., 1996). In the context of Keller's and colleagues specificity research it was shown that the probability of both the dysthymia and the major depressive episode remitting following single treatment with either pharmacotherapy or psychotherapy is less than 40% (Keller, 1982, 1984, 1990, 1995; McCullough, 1996). Later studies demonstrated that the combination of psychotherapy and medication was proven to be more effective than medication alone (Keller et al., 1999). However, there are two major reasons that promote chronicity and early relapses of major depressive episodes that lie on the dysthymia side: (1) the interactional components of unmodified dysthymia with the ongoing environment's negative response predisposes the dysthmic patient to stuck in a repetitious state of learned helplessness, a condition that strongly prevents full remission with the consequence of higher relapse rates compared to pure MDD (Keller et al., 1982, 1984, 1988, 1990; McCullough et al., 1991, 1996); (2) the life-long chronic course of untreated double depression places the individual at increased risk for poor general health and associated medical conditions like sleep disorders, anaemia, type-2 diabetes mellitus, hypothyroidism and substance abuse related disorders to name a few (McCullough et al., 1996; Moussavi et al., 2007; Trivedi et al., 2009). In late onset chronic unipolar depression the coincidence of dysthymia is the exception.

1.2 The Sequenced Treatment Alternatives to Relieve Depression study

The Sequenced Treatment Alternatives to Relieve Depression NIHM funded study (STAR*D) was designed to determine which pharmacological treatments and augmentation strategies including cognitive therapy augmentation are most effective following non-remission or intolerance to an initial SSRI or to any of a series of subsequent randomised treatments (Rush et al., 2005). STAR*D` represents the most important current "real world" treatment study ever done on MDD (Rush et al., 2005). Its population consisted of 4041 outpatients aged 18-75 years which were treated in 41 primary and specialty care settings

over a 37-month period. Outpatients with non-psychotic MDD with- and without antecedent dysthymia, and with other co-morbid mental and general medical conditions were included. The evaluable MDD population consisted of 2876 patients (72%) with a mean onset age of 25.3 years. The number of MD-episodes was 6, the length of the current MD-episode was 24.6 month, the length of illness was 15.5 years, and the number of concurrent medical conditions was 3.3. Cognitive therapy was available as either a switch from or augmentation of citalopram in the second step of treatment. Based on the first (n=3671), second (n=1439), third (n=390) and fourth (n=123) treatment steps, the corresponding remission rates were 36.8%, 30.6%, 13.7% and 13.0%, respectively, with an overall cumulative remission rate of 67%. In step-2 remission rates between cognitive therapy and medication in either the switch or augmentation strategies did not differ, although participants in cognitive therapy augmentation had a longer time to remission of 55 days compared to those in medication augmentation with 40 days. Treatment resistance was associated with more concurrent axis I or III co-morbid conditions, socioeconomic disadvantage, chronicity and melancholic or anxious features. With regard to longer-term outcomes a substantial number of patients relapsed. The cumulative proportion of participants without relapse during the naturalistic 12 month follow-up was highest in step 1 remitted patients compared to step 2 remitted patients. In comparison, those patients who were only partially remitted in step-1 and did not enter step-2 treatment had a 50% decreased survival rate compared to patients that remitted at step 1. In general, those patients who required more treatment steps had higher relapse rates during the naturalistic follow-up phase (Rush et. al 2006a, 2006b). The implications of STAR* D are that at present there is a substantial lack of knowledge how to choose among and sequence the different available treatment strategies, how to deliver or implement these treatments, and how to identify which treatments will most benefit particular patients. It is also unknown, whether different strategies or tactics have better outcomes based on different treatment settings (Rush et al., 2009). Future treatment expectations suggest combined outcome criteria that target on complete syndromal remission and complete restoration of social functioning (Nelson et al., 2008). While the increase of the range of medications, biophysical interventions, comprehensive depression-targeted psychotherapies and somatic treatment is encouraging, effective treatment to achieve complete remission and, ultimately, long-term, successful outcomes of social functioning is an unsolved problem and remains an outstanding need in psychiatry, particularly in chronic MDD with antecedent dysthymia (McCullough et al., 1996; Kessler et al., 2003; Schoepf et al., 2007; Nelson et al., 2008).

1.3 Cognitive Behavioral Analysis System of Psychotherapy (CBASP)

In 2006, the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) was officially introduced in Germany for the specific psychotherapeutic treatment of chronically depressed patients. CBASP is developed by James P McCullough Jr (USA) as a specific outpatient protocol that integrates interpersonal and cognitive-emotional strategies. McCullough started his clinical carrier as a "first-wave" operant behavior therapist in the early 70th of the last decade. His work is deeply influenced by Skinner's tradition of radical behaviorism. CBASP addresses directly the specific intrapersonal and interpersonal symptoms of MDD with antecedent dysthymia (double depression). From a perspective of behavior therapy, behavior theory approaches from original and revised models of behavior therapy are incorporated with a strong disengage from the pure cognitive content focus of cognitive therapy. In addition, CBASP uses elements of "third wave" of cognitive behavior therapy methods that

deal with models of self-regulation with respect to motivational and cognitive factors in meta-cognitive processing (Teasdale, 1999) as well as concepts of modern learning theory (Bouton, 2007; McCullough et al., 2010a; McCullough, 2010c). It is important to note that CBASP requires the therapist's personal involvement (McCullough, 2006). Based on Bandura's early behavioral paradigm that psychological functioning involves a reciprocal interaction between behavior and its controlling environment (Bandura, 1969), the CBASP-therapist is viewed as the primary choreographer of behavior change. The therapist, beginning in the first session of therapy, deliberately constructs a qualitatively different interpersonal environment for the individual as well as enacts a disciplined personal involvement role that stands in contrast to the relationships the early-onset chronically depressed patient has experienced with his "Significant Others" (McCullough et al., 2010b). CBASP primarily focuses on the in-session learning process of the patient. In agreement, McCullough's model has been developed through a process of trial and error and over the course of many therapy sessions with various patients into an in-session acquisition learning model (McCullough, 2006). Two types of dependent variables are being distinguished that model the specific learning success, the therapy process and the reduction of symptoms. The first type refers to the learning success and the learning process, i.e., the patient's ability to notice the consequences of his behavior, the patient's ability to apply the "Situational Analysis" independently, the reduction of destructive interpersonal behavior and the patient's ability to confidently draw an emotional distinction between the therapist and his or her "Significant Others". The second type refers to symptom-specific treatment effects, i.e., the reduction of the quality of depression with respect to self perception and the perception of others, the reduction of psycho-social impairment, higher quality of the marital relationship and other factors (McCullough, 2006).

1.3.1 Efficacy of the CBASP and its most important newer applications

CBASP has demonstrated significant effects for treating refractory outpatients with chronic MDD (Keller et al., 2000; Nemeroff et al., 2003; Schramm et al. 2010a), especially in its combination with medication (Keller et al., 2000), developmental trauma (Nemeroff et al., 2003), and double depression (Schramm et al. 2010a). In contrast, in the recently published REVAMP trial (Kocsis et al., 2009) CBASP augmentation with administering of 12.5 hours of psychotherapy (over the intention-to-treat study population) in partially remitted patients with chronic MDD (who had a preference for pharmacotherapy), CBASP was found not to be more effective in reduction of acute symptoms than pharmacological augmentation or augmentation with supportive therapy. However, CBASP (with introducing the technique of "Situational Analysis" in the third session) plus pharmacotherapy was associated with significantly greater improvement in problem solving than Brief Supportive Psychotherapy plus pharmacotherapy; or medication alone (Klein et al., 2011). The implications are (1) that at present it is not clear what treatment dosage level works the best for the CBASP and (2) under which treatment circumstances CBASP is most effective (Schramm et al., 2010b). In addition, it is not clear if the US protocol that introduces the technique of "Situational Analysis" in the third session of therapy has a positive or negative impact on in-session acquisition learning and outcome-measures (Schoepf et al., 2011). A pilot study of a multidisciplinary structured three month German inpatient CBASP program shows promising findings on short- and long-term outcomes as well as on feasibility (Brakemeier et al., 2011). New applications of CBASP represent CBASP in group format in Germany, Canada, and the USA. In Canada, a manual for group CBASP in an inpatient setting that focuses on improvements in perceived functionality shows promising preliminary results (Sayegh, 2010). An ongoing study in the US explores the use of group CBASP with veterans

diagnosed with chronic depression and PTSD. The outcome criteria focus on the reduction in symptoms of avoidance and hyper-arousal present in both, as well as the reduction in depressive symptoms (Favorite, 2010). A further US research line represents the use of CBASP for treating chronically depressed alcoholics in an integrated treatment approach that focuses on simultaneous reductions of depressive symptoms and alcohol intake (Penberthy, 2010). In addition, by the research on the neural mechanisms of chronic depression and the impact of CBASP on behavioural and neural functioning (Schnell et al., 2010), more is learned about the fundamental processes of learning and memory that take place during administering CBASP intervention strategies (Walter et al., 2009; McCullough et al., 2010a).

1.4 Aim of chapter

In the first part important information is summarized about the influence of adaptation on functioning on a formal operational level (Schoepf et al., 2007), learning mechanisms (Schoepf et al., 2007; Neudeck et al., 2010), passive and active ways of stimulus recognition (Schoepf et al., 2007; Neudeck et al., 2010), aetiology and characteristics of double depression (Schoepf et al., 2007; Schoepf et al., 2008a, 2009a, 2009b; Schoepf and Penberthy, 2010), the therapist's function as a reinforcer within the therapeutic relationship (Schoepf et al., 2008b), CBASP`s cutting edges of behaviour change and the principles of intervention, therapeutic goals (Schoepf and McCullough, 2009b), and the treatment strategies and there corresponding mechanisms of action subdivided into "bottom-up" and "top-down" interventions (Schoepf et al., 2007, 2008a). In the second part a multi-step psychotherapy approach is represented that integrates CBASP`s intervention strategies in the therapy of chronic MDD German patients with an inpatient history of therapy-refractory major depressive episodes (Schoepf et al., 2008b).

2. First part

2.1 The influence of childhood adaptation on functioning on a formal operational level

Evolution is defined as a process that allows adaptation between generations. In contrast the term learning is defined as a process that allows environmental adaptation within an organism's lifetime. As organisms behave as if evolution has "prepared" them to associate certain events learning has to be viewed always within its evolutionary context (Bouton, 2007). According to Piaget`s systems-theoretical biological theory, every new organized element of reaction and experience is learned on the stimulus-response level. The application of the element automatically happens in the daily living arena outside the original learning situation (functional and generalizing assimilation). The interaction of accommodation and assimilation creates a dynamic balance on the respective higher cognitive-emotional level as compared to the "specific regulatory factor underlying a biological organization", which he calls adaptation (Piaget, 1973). Successful adaptation leads to the capacity of functioning on a formal operational level with growth of self-efficacy through transitional experiences in the formative period of adolescence. In the crucial period of adolescence the roles of adulthood have to be addressed in almost every dimension of life. A formal operational adolescent is connected to its informing environment and is attached to others, is affected by and changed by the behavior consequences he receives from other interactants. In addition, he is able to recognize the consequences of his behaviors and may develop problem-solving skills, may develop foresight in planning, may develop future orientation, and may have the capacity to directly

confront fearful encounters. Childhood conditions that are likely to produce the development of formal operational thought in the period of adolescence are close relationships with competent and caring adults in the family, the capacity to develop self-regulation abilities, a positive view of self, cognitive motivation to be effective in the environment (i.e., self efficacy and self-determination), friendships, and romantic attachments with pro-social peers (Masten, 2007).

2.1.1 Associative learning of signalling stimuli

A child is biologically prepared to learn to associate signalling stimuli of the environment (cues or incentives) with stimuli that elicit respondent behaviours through the mechanism of classical conditioning. Figure 1 demonstrates the possible relations between signalling stimuli and behavioural tendencies in signal learning.

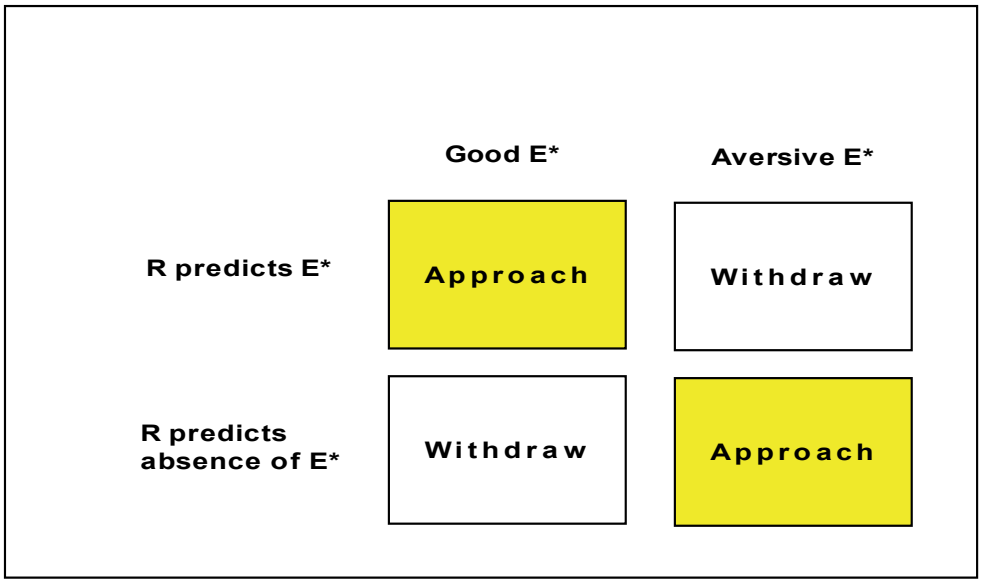

Fig. 1. Associative learning of signalling stimuli. The prediction of a "biologically" important event [E*] causes either approaching tendencies or withdrawing tendencies. S = conditioned stimulus that predicts the presence or absence of E*. Left upper cell: when a signal predicts a good E* animals often begin to approach the signal (positive sign tracking). Right upper cell: when a signal predicts an aversive E* animals tend to withdraw from the signal (negative sign tracking). Left lower cell: when a signal predicts a decrease in the probability of a good E* animals withdraw from it. Right lower cell: when a signal predicts a decrease in the probability of an aversive E* animals tend to approach it (modified according to Bouton, 2007; Schoepf et al., 2007).

Classical conditioning is sensitive to the timing, intensity, and to the novelty of "biological" important events. After classical conditioning has happened a former neutral stimulus elicits a conditional response (interceptive, emotional, and behavioural) that allows the child to prepare as early as possible for the upcoming event as a behavioural phenomenon (signalling stimuli in Pavlovian language). In addition, second- and higher order conditioning, stimulus independent sensory preconditioning, and generalization each provide further ways in which

stimuli that have never been directly associated with an unconditioned stimulus can elicit conditioned responses. Furthermore, the information value of a "biologically" important event is associated with the child's motivational state. The anticipation of a conditioned stimulus that predicts a "good" event causes motivation whereas the anticipation of a conditioned stimulus that predicts an aversive event causes loss of motivation or anxiety.
Associative learning of signalling stimuli may cause implicit shifts of attention in humans. Animal findings show that approaching tendencies towards "good" events and withdrawing tendencies away from "aversive" events are strongly associated with shifts of attention. This general tendency is known as positive and negative sign tracking. Sign tracking is assumed to trigger whole sets of behaviour systems and physiological reactions that may help to ensure that animals continue to make contact with "safe events" and to stay away from "dangerous events". In case that a conditioned stimulus predicts danger either species-specific defence reaction behaviour systems are elicited or more general avoidance reactions can be triggered that aren't species-specific. Species-specific defence reactions describe innate reactions like freezing and fleeing that occur when an organism encounters a predator.

2.1.2 Associative learning of behavioural effects

In contrast, children learn to increase or decrease their contact with "biologically" significant events through instrumental learning. Behaviours that are controlled by there consequences represent instrumentally conditioned behaviours. Instrumental action is always guided by associative learning of signalling stimuli. Four associations are learned in instrumental action:

- associations between behaviours and there perceived effects (conscious level),
- associations between signalling-stimuli of the environment and reflexive behaviours (unconscious level),
- associations between signalling stimuli of the environment and behavioural tendencies (unconscious and conscious level),
- and associations between discriminative (contextual) stimuli and behaviours (unconscious and conscious level).

When instrumental action is controlled by the discriminative stimulus that precedes it the learning mechanism is called stimulus control. Through stimulus control the child learns to discriminate events in which behaviour is reinforced from events were behaviour is not. So called occasion setters simply involve "context cues" that are always present whenever instrumental learning occurs; occasion setters mark the spot where/when the child associates that some behaviour will deliver a reinforcer (discriminative stimulus in Skinnerian language). Reinforcement means strengthening of a specific learning mechanism. Positive reinforcement is defined as a specific situation in which behaviour is followed by a "good" event that represents a positive reinforcer. Negative reinforcement is defined as a specific situation in which behaviour is strengthened because it removes or prevents an aversive event that is a negative reinforcer. Figure two represents the possible relations between behavioural effects and "biologically" significant events in instrumental learning.
Instrumental action may cause implicit shifts of reward and punishment expectations in humans that may help the individual to increase the contact with events that are expected to have "good" outcomes, and to decrease the contact with events that are expected to have "aversive/negative" outcomes.

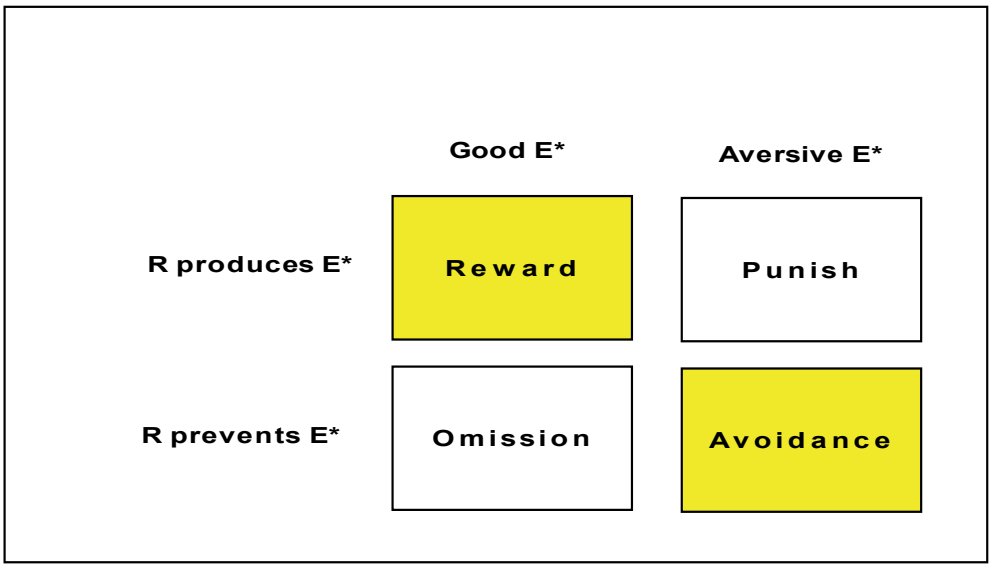

Fig. 2. The law of effect in instrumental action. The effects of behaviours [R] determine the type of learning. Left upper cell: reward learning causes an increase of a behaviour if the behaviour produces a "good" event [E*]. Right upper cell: if behaviour is followed by an aversive E* (punishment) the behaviour typically decreases in strength. Left lower cell: behaviour decreases in strength if it prevents a "good" E* (omission). Right lower cell: if a specific behaviour prevents an aversive E* avoidance or escape learning happens (modified according to Bouton, 2007; Schoepf et al., 2007).

2.1.3 Non-associative learning mechanisms

In contrast, sensitization and habituation represent two forms of non-associative learning since, in order for a response to occur, no association or combination of stimuli is necessary. Both mechanisms are stored as knowledge in the part of the memory system that is called implicit (non-declarative) memory. It is where behavior, skills, and priming processes are stored. Both mechanisms are triggered by a specific cognitive stimulus processing and they originate in certain plastic processes in the nervous system. Sensitization is defined as enhanced perception and increased responsiveness (response readiness) when repeatedly confronted with a certain sensory stimulus. Sensitization represents a mechanism of the central nervous system that plays an important physiological role in everyday life. As a result of the repeated presentation of a specific stimulus, an increase in response occurs. Sensitization therefore represents an induction procedure (caused by specific stimulus properties) and the resulting measurable responsivity. If the induction procedure causes an appropriate response, its perpetual repetition leads to a specific learning process that causes hyper-responsivity. A typical increase in response is an increase of attention with respect to the stimulus cue. Through sensitization, we learn to pay special attention to important stimuli, rather than ignoring them. Sensitization is largely unspecific to the stimulus, which makes it different from habituation. The better known mechanism of habituation describes the opposite, meaning a decrease in response to a stimulus that is repeatedly presented (Neudeck et al., 2010).

2.1.4 Passive and active ways of stimulus recognition

Associative learning of signalling stimuli and instrumental action are present in all learning situations because of the simple cognitive association of what-leads-to-what. The conditioned stimulus represents the "stimulus signal" that runs the situational outcome. In other words, learning on a formal-operative level of functioning is cognitively associating what signal is connected to what upcoming event and how to keep the event coming or removing. Therefore perception and behavior are closely coupled. Perception is defined as the processing of information that is acquired through one of the senses (sight, hearing, smell, taste, touch). This information about the structure of the physical world is used for the adaptive control of behavior. Two different types of processes or ways of stimulus recognition exist: bottom-up and top-down.

- In the case of "bottom-up processing," a specific property of the stimulus is detected; the specific stimulus properties are then combined into more complex forms until final stimulus recognition takes place. This explains why bottom-up processing is sometimes referred to as "passive" (perception). Anatomical correlates to bottom-up processes include the brain stem and the basal forebrain (affect-driven attention).
- By contrast, in "top-down processing," hypotheses about the stimulus as a whole are formed (expectations and prior knowledge); then specific properties are selected and tested and, finally, stimulus recognition occurs. Top-down processing is referred to as "active" (behavior). Top-down processes (given sufficient sensorial stimulation or individually developed goals) can be represented in the dorsolateral or the prefrontal regions as well as the anterior cingulate gyrus and the basal cerebral cortex (Schoepf et al., 2007; Neudeck et al., 2010).

2.2 Aetiological background and characteristics of double depression

Chronic MDD with antecedent dysthymia (double depression) usually begins around 13-14 years of age. McCullough holds that the psychopathology of chronically depressed patients results, to a large degree, from bidirectional interaction between disturbed emotion and stress regulation on the one hand and developmentally inhibiting "person-environment" conditions on the other hand, i.e. in situations where the individual was subject to repetitive experiences of helplessness. The attachment disorder (with a negative attributional style and disturbed behaviours) is perpetuated through generalized avoidance learning, thus accounting for an uncoupling of the person-environment connection (Schoepf et al., 2007, 2008a). It is important to note, that the disorder is as well caused as maintained by global deficits in cognitive-emotional development that involve intrapersonal and interactional domains. The psychological organization is similar to the organization of children during their preoperational stage of development (Schoepf et al., 2008a, 2008b, 2009a). According to a reciprocal model of causation, the decreased cognitive-emotional development results of four contributing factors:

- the genetic contributor represents genetically caused dispositions and personality factors like internalizing or externalizing negative affect,
- the environmental contributor represents early experiences of loss and/or chronic neglect in combination with later adverse life events in the form of failures, hardships, and lack or loss of emotional relationships,
- the cognitive contributor and the behavioral contributor both represent the intrapersonal and interactional effects of recurrent experiences of helplessness when

interacting with the "Significant Others" during childhood (Schoepf et al., 2007, 2008a, 2008b, 2009a; Schoepf and Penberthy, 2010).

2.2.1 Cognitive-emotional level of organization and core pathology

The cognitive-emotional level of organization of the early-onset chronically depressed patient is characterized by preoperational representations in connection with a preoperational thinking style and wishful thinking. This explains why, instead of thinking in an action-oriented and goal-oriented manner, there are deficits in the areas of logical thinking, concept formation, problem solving and reasoning. In addition, affectivity has a powerful impact, causing overwhelming emotions that seem uncontrollable from the patient's subjective point of view. Patients are unable to identify what causes these alterations as their thoughts are constantly revolving around themselves. As a result, the patient does not receive information from his or her environment in an adequate way and is therefore not adequately influenced by relevant environmental incentives

The core pathology is contingent on the disturbed person-environment interaction. The chronically depressed patient experiences the world in dysfunctional ways across different situations and exhibits strikingly maladjusted social behavior. Typical dysfunctional ways of interpreting a situation include: "none will ever be able to forgive me," "it would be best to just die," "I'm a total failure," "I regularly escape into my fantasy world," "whatever I do ends up being wrong," and "everything is always my fault." Social interaction is replaced by interpersonal avoidance behavior in asymmetrical and inflexible ways. Patients typically show hostile-dominant and hostile-submissive personality dimensions. In addition, a chronically low self-esteem value is found as well as feelings of hopelessness that generalize over all interpersonal situations. There are also problems with memory and recalling, poor abilities to observe accurately, diminished self-perception and insufficient processing of new experiences. Due to the weight that McCullough's multidimensional approach puts on the disturbed person-environment-relationship and the resulting deficient ability to act, the patient's core pathology, i.e., the maladjusted way of experiencing the world and the maladjustment with respect to social interaction, becomes the major focus of therapy. McCullough states "I have developed the CBASP to penetrate and change closed perceptual systems of early-onset chronically depressed patients that are closely related to the developmental influence of recurrent experiences of helplessness" (McCullough, 2006; McCullough, 2008; Schoepf et al., 2009a).

2.2.2 The influence of recurrent experiences of helplessness in childhood and adolescence

In general, recurrent (daily) experiences of helplessness have catastrophically psychological ramifications, particularly during childhood development. Seligman's theory of learned helplessness claims in its origin that noncontingent environmental reinforcement responses to a person's behavior reduces the incentive motivation to control the outcome of an event, interferes with further event related outcome learning, and if the outcome is traumatically processed, produces fear as long as the subject is uncertain of the uncontrollability of the outcome, and then produces the state of helplessness and hopelessness (Seligman, 1975; Abramson et al., 1978).

2.2.2.1 Intrapersonal destructiveness of the learned helplessness effect

Table one represents the intrapersonal characteristics of the learned helplessness effect in a severely disturbed female patient with double depression prior to treatment.
The intrapersonal destructiveness of the learned helplessness effect is cognitive-emotional stunting when the child's world becomes so aversive or uncontrollable that mastery of interactional problems is experienced as impossible. The pre-causal and pre-logical child cannot solve the destructive onslaught of its environment and is thrust into an "emotional survival" mode of living. Three negative cognitive effects are implicit within the conceptualisation of learned helplessness:

The destructiveness of the leaned helplessness effect is characterised by ➢ a severely decreased cognitive-learning ability, ➢ a significantly decreased motivation to cope problems, ➢ emotional deregulations, ➢ survival behaviour.
The reward system is biased towards the expectation of punishment ➢ **First expectation:** "less punishment/rejection results from the environment if I react as submissively as I can" ➢ **Second expectation:** "punishment results from the environment if I react in any other different way than submissive" ➢ **Instrumentally learned rule:** "I have to behave totally passively and submissively with the consequence of being shoved around. If I react actively - independently of the way I express my needs (independent of my stimulus value) - I will experience strong responses of punishment and rejection"
The attentional system is biased towards unexpected events ➢ The release of social fear is elicited by fast detection of any verbal- or nonverbal stimulus that predicts uncontrollability or unpredictability

Table 1. Double depression of the adult is usually associated with a refractory cognitive-emotional dilemma. What is observed at the beginning of treatment is an interpersonally avoidant patient with predomination of detached, distant and submissive behaviour. Instrumental avoidance of interpersonal encounter that holds the avoidance of the classical conditioned fear in abeyance is the predominant strategy. As a consequence the environment can not inform the patient (McCullough, 2007).

- generalized retrospective negative causal attributions of failure and success,
- generalized negative outcome expectancies,
- negative cognized goals.

The intrapersonal effects become aware to the child at the point when the child is able to conclude that it doesn't matter what it does with a resulting independent of response expectation. From this time on the child is a prison holder of an ongoing "emotional survival" mode that is strongly coupled with a poor cognitive regulation of motivation. As a consequence the child is (in more cases than not) not able to develop a formal-operative mode of cognitive-emotional functioning in later developmental phases, cognitive-

emotional development is derailed. Uniformity, helplessness and hopelessness become the order of the day. In addition, the ability to recover after situational exposure is reduced and adverse life events are interpreted in pessimistic ways that produce, exacerbate, and prolong acute depressive symptoms (McCullough, 2007).

2.2.2.2 Interactional destructiveness of the learned helplessness effect

Chronically depressed patients create depressing environments (Bandura, 1986). According to McCullough, the cognitive variable in double depression is the mental ability of the adult patient when he was a young child to learn to associate the emotions of fear and terror that accompanied maltreatment with behaviour that subsequently avoided the exacerbation of the negative emotions. From a communication perspective, associative learning of signalling stimuli and instrumentally learned rules mediate verbal and nonverbal responses (messages) that are regularly exchanged between two interactants. A "survival mode" with decreased cognitive regulation of motivation is associated with a severe disturbance of the dynamic person-environment interaction that maintains the learned helplessness effect. Social interaction is experienced as subjectively dissatisfying and is therefore avoided. Necessary adaptation in the period of adolescence and the adversities of later life cannot be dealt with in adequate ways. In addition, the negative socials evaluations and reactions the growing-up adolescence elicits from others provide social validation for a negative outlook on life. Three negative interactional effects are implicit within the conceptualization of learned helplessness.

- Severely disturbed stimulus recognition: the established independent of response expectation results in the child's unawareness of the interactional relatedness to the environment in which it lives. The child becomes oblivious of its stimulus value and does not see why it elicits negative responses on others (McCullough, 1988).
- Loss of social reinforcement: according to a biologically pre-determined person-environment devil circulation the child has not available a sufficient quantity of reinforcing social events in the appropriate motivational state, that are able to accelerate the development of its cognitive-emotional organization. Instead, associative learning processes of stressful encounters with the "Significant Other's" and persistent deviant interpersonal behavior is dominating about adaptive action-outcome learning.
- Deviant behaviours in social encounters: emotional deregulations lead to general interpersonal withdrawal, interpersonal detachment, interpersonal submission and interpersonal passivity. However, in persistent deviant interpersonal behaviour there is a lack of flexibility to use a broader range of interpersonal responses and behaviours which different interpersonal situations warrant. In its extreme form a severely maltreated child (that suffers of impaired development across diverse domains of biological and psychological functioning) has only a narrow range of one or two responses. The child's abnormal behaviour, then, consists of the rigid, constricted, and extreme behaviours that are often performed reflexively, whether they are appropriate to a situational encounter or not. As a consequence, non-corresponding reflexive responses without regard to there consequences often arouse stress and provide the child with an enduring vulnerability factor, placing it at great risk for future environmental maladaptation and psychopathology. The ongoing environment's negative response predisposes the child to stick in a repetitious state of learned helplessness.

2.3 The learned helplessness effect in chronic MDD without antecedent dysthymia

The late-onset form of chronic MDD usually begins during the mid-20s and is associated with a first episode of MDD without antecedent dysthymia. The affected individuals report more often than not conditions without child maltreatment. They hold prison of a persisting "out-of-control" mood state that finally undercuts all of their previous assumptions of controllability. The affected individual therefore is a "hold prisoner" of a later learned helplessness state and "falls back" into a pre-operational mode of cognitive, emotional and behavioural functioning (McCullough, 2008).

2.4 The intentional use of the therapist's function as a reinforcer within the therapeutic relationship

Integrating the concepts of various methods of first and second generation behavior therapists the CBASP is conceptualized in its origin as a single, integrative, and theory-driven third wave behavior therapy model that relies on modern learning theory to guide technique administration (McCullough, 2010c).

With respect to the therapist's basic attitude, it is important that the CBASP therapist is highly aware of the fact that he or she merely helps to give birth to the functional learning processes and insights the patient experiences. In this sense, the therapist has to succeed in letting the patient "think and feel" during the process of becoming aware of proactive interpersonal and health-related behavior in the presence of the therapist. In order to effectively use the interventions of CBASP therapy, the therapist has to be trained and prepared to bring his or her own function as a reinforcer into the therapeutic relationship, and this has to be done in a personal, disciplined and responsible way. During the interaction between the patient and the therapist, the therapist's behavior should, on the one hand, guide and reinforce the patient's gain in knowledge yet, on the other hand, he or she should not interfere with the intrapersonal reinforcement of the patient's stress-induced behavioral patterns. The influence on the patient should not be such that he, due to positive interpersonal reinforcement, tries to present a maximum amount of successful behavior to the therapist, nor should the patient, as a result of positive (add a punisher) or negative (subtract a reinforcer) interactional punishment, avoid the therapist's negative reactions when mentioning dysfunctional behavior (Schoepf et al., 2008b).

2.4.1 The transference hypothesis

One specific transference hypothesis in one of four transference areas that identifies the specific "hot spot" situations should be constructed as early as possible. The transference hypothesis is deduced using the "Significant Other History" (SOH) technique in CBASP (McCullough, 2006, 2008, 2010b; Neudeck et al., 2010). After reconstruction of the course of the depression (in the introductory session of therapy) the patient is asked to name his or her 3-6 " Significant Other's" in the following session and to work through the following three prompts for each "Significant Other" together with the therapist: (1) "What was it like growing up with or being around this person?" (2) Then, "how did he or her causally influence the course of your life in a way that is still present now?" (3) Then, "what is the emotional stamp you take from this relationship that informs who you are today?" In the original US-protocol the time instruction for the SOH-technique was one therapy session (second session). The time instruction was taken back by McCullough in the planning phase of German CBASP-studies (McCullough et al, 2008). According to the modified protocol the emotional reconstruction process in an antecedent-consequent format usually takes two to four sessions of therapy

(Schoepf and McCullough 2009a, Schoepf et al., 2010). The SOH technique is more often than not hurtful for the early-onset patient. The patient has to be informed that negative feelings like fear, pain and sadness may be evoked and that the therapist is blind for "hot spot" situations at this time of therapy (McCullough, 2008; Schoepf and McCullough, 2009a). It is important to note, that a two-step focussing strategy is applied (prompts one and two) before the therapist helps in step three the patient to construct the stamp. The duration of the SOH exercise usually takes at least thirty minutes with respect to one "Significant Other". After the emotional reconstruction process is finished the therapist reviews in the absence of the patient the leading interpersonal theme in which the patient interacted with his "Significant Other's". The interpersonal-emotional theme reflects the early learning history of the patient and is derived from these "stamps" or causal theory conclusions (McCullough et al., 2010b). McCullough (2000, 2006, 2010b) assumes four transference areas of interaction in chronically depressed patients that, from the perspective of developmental psychology, play an important role in the patient's relationship with significant others. His theoretical considerations concerning the transference hypothesis refer to the concept of "tacit knowledge"(Polanyi, 1966) and the idea of "reasoning based on implicit causal theories" (Nisbett and Wilson, 1977). In accordance with these assumptions, learning processes and instrumentally learned interpersonal rules that were developed during "toxic experienced" developmental conditions may have caused implicit shifts of attention and expectation. These shifts may have helped the growing-up child as "emotional surviving strategies" to decrease the contact with interpersonal events in the specific "hot spot area" that are expected to have negative outcomes. Automatic conditioned patterns of interpersonal behavior are elicited and executed regularly in "hot spot" situations. This rigidly ruled behaviour usually does not correspond to the present situation, arouses stress and provides the patient with a social disadvantage.

Specifically, McCullough (2000) describes working with the construct of transference as an exercise in "focused attention." The transference hypothesis differs from Freud's concept of transference since it can be actively acted out in session with the therapist and then processed within the "Interpersonal Discrimination Exercise" (IDE). From a learning theory perspective the transference hypothesis includes the interpersonal content that most likely reflects the patient's expectancy of the therapist's reactions toward the individual (McCullough et al., 2010b). The four transference areas of interpersonal dysfunction in that "hot spots" occur are:

1. in-session moments of intimacy (either felt by the patient or the therapist) that evoke in the patient (Pavlovian) fear of being physically or emotionally abused (intimacy area),
2. in-session events in which the patient discloses emotional needs toward the therapist that evoke in the patient (Pavlovian) fear of being ridiculed or censored (disclosure of need area),
3. in-session events during which the patient makes mistakes towards the therapist (e.g., not doing his or her homework or being unable to solve problems presented during therapy sessions) that evoke in the patient (Pavlovian) fear of severe physical or emotional punishment (mistake and failure area),
4. in-session events in which the patient expresses negative affects towards the therapist that evoke in the patient (Pavlovian) fear of punishment (expression of negative affect area).

Whenever a "hot spot" situation occurs within a therapy session, the transference hypothesis is made explicit through IDE work, i.e. the first way of disciplined personal involvement used in CBASP therapy (McCullough, 2006, 2008). It is important to note for the reader that according to the specific CBASP protocol the patient manual is distributed to

the patient after the emotional reconstruction process is finished (McCullough, 2006, 2008; Schoepf and McCullough 2009a). "Situational Analysis" (SA) is usually introduced during the fifth-to six session. We strongly recommend that working on the functionality teaching and the skill teaching level starts after the CBASP-therapist has worked out the specific transference hypothesis in the absence of the patient. It is our opinion, that the associated IDE technique is the major CBASP technique of "in-session acquisition learning" (Schoepf and McCullough, 2009a). IDE is most effective, if it focuses on "hot spot" events that occur during teaching "Situational Analysis".

2.4.2 The stimulus character of the patient

In addition, in order to use personalized meta-communicative interpersonal techniques (the second way of disciplined personal involvement used in CBASP therapy), it is important to validly measure the hidden emotional, cognitive, and behavioral responses the patient evokes in the therapist (in McCullough words the stimulus character of the patient), using the Kessler's Impact Message Inventory after the first session of therapy (Kiesler, 1983). The technique of "Contingent Personal Responsivity" (CPR) is used in instances where the therapist consequates the behaviour of the patient by disclosing personal responses and feelings produced in the therapist by the behaviour of the patient (McCullough, 2006, 2008; Schoepf and McCullough 2009a).

2.5 CBASP`s cutting edges of behavior change

The application of CBASP requires as well diagnostic skills as supervised practical therapeutic experience. The therapist should become accustomed to the use of motivational strategies through the exactly timed induction and the resolution of cognitive dissonance, as well as the use of creating negative reinforcement situations.

The essential motif of the CBASP method is to focus the patient on what behaviour leads to what outcome (emotionally and interpersonal). In general, "Situational Analysis" (SA) focuses the patient on the consequences of his behaviour and teaches him what he does matters (empowerment), as well teaches him adaptive social skills (functionality teaching and skills teaching dimension of the CBASP). Furthermore, the procedure of SA assists the therapist in identifying and addressing the specific cognitive and behavioural problems of the individual patient that interfere with his effective social management.

In addition, personal involvement techniques are linked both to the functionality teaching- and the skills teaching dimension. A unique type of therapist intervention, called „Disciplined Personal Involvement"(DPI), advocates a non-neutral role for the psychotherapist (interpersonal dimension of the CBASP). The techniques of DPI are based on early concepts of objective counter transference and interpersonal reactions that provide the authorization of the CBASP therapist for using self-disclosures with a maximum impact: to create an interpersonal "safety place" and to transfer the experiences outside the therapy to others, to connect the patient perceptually with his environment, to modify dysfunctional behaviour contingently, and to address/heal developmental trauma arising from negative experiences with maltreating significant other's (Schoepf and McCullough, 2009). Through DPI, the deeply personal nature of the therapist-patient relationship is put into the foreground of therapeutic efficacy as both a moderator variable of in-session acquisition learning and an alternative to therapist neutrality. In comparison to other therapy models the interventions of DPI are deeper and more personal - than sensitive participation in

supportive therapy, - than turning the patient's attention to the analysis of counter transference reactions in psychodynamic orientated approaches, - than the use of meta-communication to modify action-counteraction response patterns in interpersonal therapy, - than the analyses and change of maladaptive behaviour in the awakening effect based behavioural approaches or – than the work of cognitive restructuring processes in cognitive therapy. DPI (especially IDE) basically influences the process of self-update of the patient. Table 2 represents the mayor CBASP technique of behaviour change in outpatients according to the specific protocol, the "Situational Analysis" (SA).

Situational Analysis (SA)

Learning context: the patient usually brings into therapy a completed SA worksheet of either a distressing or pleasant daily living interaction that happened during the last week. The review of the worksheet is usually carried out in two consecutively phases on the flip-chart (some investigators additionally distinguish a learning and transfer phase for didactic reasons).

ELICITATION PHASE

In the first step the interactional (social) event has to be described by the patient from an observational-describing focus. The beginning and the end point have to be clearly addressed.

During the second step the patient's cognitive-emotional attribution is elicited. Relevant and accurate forms represent either self-referring (self-reflecting) emotional or cognitive interpretations, as well as describing (interactional) interpretations and action interpretations.

In the following three steps the verbal and nonverbal interactional responses, the actual outcome (AO) in behavioural terms, and the way the patient wanted to behave in the situation – his desired outcome (DO) - are elicited. In the case of a distressing event a clear discrepancy appears between the patient's AO and DO. At this point a condition of negative-reinforcement is created by the therapist. The induced cognitive dissonance is later reduced by the finding of more adaptive strategies.

The last two steps are important for the patient in order to become aware of the discrepancy between his AO and DO. The patient has first to decide if he got what he wanted by comparing his AO with his DO. Then he is gently asked to explain why he did not behave in the way he wanted to behave.

REMEDIATION PHASE

In this phase, the therapist and patient work on solutions for the patient, to behave in a way that is efficient with respect to his DO.

Shaping of functional interpretations (first step) as well as shaping of missing behavioural aspects of the DO (second step), learning summary (third step), transfer to a future situation and skill training (fourth step) amplifies both the new element of reaction and experience as the conditional relationship between positive efficacy beliefs and positive outcome expectancies.

Transfer is maximized because the target situations come out of the daily living experiences of the patient.

Table 2. Description of the elicitation and remediation phase in SA.

Table 3 represents the major DPI technique of in-session acquisition learning according to the specific protocol in outpatients, the "Interpersonal Discrimination Exercise" (IDE).

Interpersonal Discrimination Exercise (IDE)
Learning context: the therapist directs the patient's focus of attention to the just happened "hot spot"in-session event/moment and writes the"hot spot" behavior on the flip-chart. After this the three phases of IDE are consecutively carried out. **NEGATIVE PHASE** The patient is gently asked to recall a typical past social interaction with one or two of his maltreating "Significant Other's" in a similar situation. In the cognitive form the patient has to describe the behavioral consequences on himself caused by the behavior of his significant other. In particular bad thoughts are evoked through tacit knowledge. In the emotional form the patient is additionally gently asked to re-experience the associated hurtful (refractory) emotions in the presence of the therapist. In particular negative feelings like fear, pain and sadness are evoked. Counter-conditioning according to the principle of reciprocal inhibition takes place by the benevolent therapist's reaction (Schoepf et al., 2007). **POSITIVE PHASE** After the intensity of negative thoughts and emotions is decreased the patient is gently asked to describe his perception of the therapist's reactions. Furthermore, he has to characterize the feelings that have been evoked by the current incident with the therapist. He is then asked to compare the therapist's behavior to the recalled behavior (and the corresponding emotion in the emotional form of IDE) of his significant others in a similar situation. The felt distress of the patient usually decreases at this moment of the exercise. **HEALING PHASE** Sensitive to the timing and the magnitude of the felt decrease of distress in the healing phase of the IDE, the patient is encouraged by the therapist to identify the contrast between the therapist's behavior and the significant other's' behavior. "Automatically" there results a felt increase of the potency of the therapist to specifically reduce interpersonal distress during the experienced "hot spot" situation and a new interpersonal reality of the therapist-patient relationship comes into being meaningful to the patient.

Table 3. Negative phase, positive phase and healing phase in IDE. The starting point is defined by the presence of an in-session "hot-spot" event/moment. In the cognitive form of IDE counter-conditioning of cognitive evoked (Pavlovian) fear is applied in the negative phase. The principle of sensitization is started in the positive phase and is increased in the healing phase (Neudeck et al., 2010). In the emotional form of IDE the principle of counter-conditioning of re-experienced (Pavlovian) fear predominates within all IDE phases. A strong feeling of "safety" within the therapy dyad results that usually elevates the probability of generalizing outside of therapy to the patient's other relationships**.**

The self-disclosures are carefully timed and choreographed by the CBASP-therapist to strategically counteract the patient's destructive interpersonal basic assumptions he has experienced from past negative interactions. In McCullough's words, the job of the therapist is to become "a problem for the patient". That is, patients should experience difficulties integrating the therapist's interpersonal messages of caring and concern into their negative

interpersonal expectations. The sincerity, honesty, genuineness and staying power of the therapist makes it difficult for the patient to escape these interactions by using the old learned distancing strategies like „counterattacking or withdrawing" (Schoepf and McCullough, 2009). Thus, the CBASP-therapist should be systematically prepared to demonstrate his or her own positive or negative feelings that all have message value to the patient within a defined therapeutic situation. This has to be done in a responsible way that is both theory-driven and controlled (McCullough, 2006).

2.5.1 Principles of intervention

The learning CBASP therapist should acquire a thorough understanding of the theoretical foundations of CBASP that are described in the following passage. In addition to G Prouty's pretherapy model for schizophrenic patients and KG Bailey's paleopsychological assumptions (McCullough, 2006), the CBASP therapy model specifically incorporates the following nine theoretical approaches from psychology.

The approaches and the associated interventions are listed in order by publication date of their respective most influential publication, including a brief summary of the relevant therapy strategies and mechanisms of actions used in CBASP.

2.5.1.1 Pavlov's theory of classical conditioning and his concept of transmarginal inhibition and the paradoxical phase

Linked to Pavlov's assumptions (Pavlov, 1941) are the principles of modern learning theory with respect to the signal-reinforcer-relationship in relation to the implicit regulation of attentional control (Bouton, 2007).

In CBASP, associative learning of intrapersonal-interpersonal (Pavlovian) fear through the mechanism of classical conditioning represents the "stimulus input" of the hypothetical construct of double depression as a refractory mood disorder. The construct represents the theoretical basis for: (1) guiding of the patient's attention control in the context of surveying the patient's "emotional learning history" (McCullough et. al., 2010b); (2) counter conditioning (Pavlovian) fear (Schoepf et al., 2008b); and (3) the application of systemic desensitization in order to modify maladjusted and destructive interpersonal types of behavior (Schoepf et al., 2009, 2011).

2.5.1.2 Mowrer's two-factor theory on the generalization and inhibition of fear

Mowrer's theory states in its origin that classical conditioned fear learning allows warning stimuli to evoke conditioned fear that motivates avoidance behavior that provides reinforcement of the instrumental avoidance response through the reduction of fear (Mowrer, 1947).

The principle of avoidance learning is of crucial importance (1) to both the CBASP-therapist and the CBASP-supervisor, defining the course of treatment with respect to the causal direction between the stimulus that reduces fear (provided by the therapist) and the inhibition of the stimulus that was conditioned in relation to the patient's "Significant Other's"; and (2) the specific therapeutic intervention and the possibility to change, inside or outside of therapy (Schoepf et. al., 2009a).

2.5.1.3 Winnicott's concept of objective counter transference

According to Winnicott "objective" counter transference is the constricted feelings, attitudes, and reactions of a therapist induced by a patient (Winnicott, 1949).

Within CBASP, Winnicott's concept constitutes the most important basic assumption, establishing how, with the help of DPI, the patient's resistance that is caused by reactions of negative transference is dealt with and the integration of traumatic learning experiences into his or her self-image is achieved. This implies according to McCullough that the CBASP therapist (1) applies objective counter-transference as a vehicle of in-session change, (2) is able to be oneself with the patient in the therapy, (3) salubriously uses personal responsivity, (4) arranges contingencies so that the patient can learn, (5) makes moment-to-moment decisions with respect to CBASP treatment goals, (6) self-monitors the patient's moment-to-moment verbal- and nonverbal messages, and (7) is focused in supervision on his non-reflected verbal- and nonverbal messages that interfere with CBASP treatment goals.

2.5.1.4 Skinner's radical behaviorist approach to operant conditioning

Closely related to Skinner's basic assumptions (Skinner, 1953), the principles of modern learning theory applied to the behavior-reinforcer-relation with respect to the implicit regulation of situational outcome expectations are crucial to CBASP (Bouton, 2007).
During CBASP-therapy, the principle of operant conditioning and the principles of consequence-based interventions are applied in most therapy situations. This is done in order to (1) activate and modulate executive performance, (2) to systematically practice adaptive goal-directed behavior with the patient, (3) and to improve his or her ability to think and act in formal-operational ways by enhancing perceptive and interpretative performance (Schoepf et al., 2007).

2.5.1.5 Piaget's systems-theoretical biological theory of cognitive-emotional development

Piaget`s theory claims in its origin that a level of formal-operative functioning is achieved through a childhood condition that is associated with competent and caring adults in the family (Piaget, 1973).
In CBASP, the basic assumptions of Piaget's developmental theory play a crucial role in explaining global developmental deficits of cognitive-emotional organization in double depression. Furthermore, Piaget`s theory serves as a theoretical foundation for the systematic construction of new stimulus-response behavior patterns within the therapeutic zone, and for the automatic generalization of a new learned element outside the therapeutic space through the mechanisms of functional and generalizing assimilation (Schoepf et al., 2009a).

2.5.1.6 Seligman's revised theory of learned helplessness and the role of attributional style with respect to cross-situational generalization

Seligman's theoretical idea that organisms exposed to inescapable and unavoidable shocks learn that their actions do not control environmental outcomes (Seligman, 1975; Abramson et al., 1978) formulates the theoretical foundation for the cognitive- and behavioral contributor of the reciprocal model of causation in double depression (Schoepf et al. 2008a; Schoepf and Penberthy, 2010).
In addition, the "independent of response expectation" of the chronically depressed patient justifies (1) the necessity of continuous performed moment to moment related feedback in a personalized form, and (2) discriminatory exercises between stimulus and response as well as response and consequence, using simple situational related contrast techniques (Schoepf et al., 2009a).

2.5.1.7 Kiesler's model of an interpersonal theory

In CBASP, the second important theoretical foundation of DPI form the principles of interpersonal therapy redefined by Kiesler's theory as reciprocal verbal and nonverbal behaviors communicating the encoder-to decoder evoking and decoder-to-encoder impact messages. Kiesler holds that the interaction between a person's interpersonal verbal- and nonverbal behavior and another person's reaction can be understood as a self-sustaining and self-regulatory system that, from the person's point of view, is recurrent in his or her relationships and interferes in the case of social maladjustment, generating appropriate behavior (Kiesler, 1983, 1996).
This holds specifically for the systematic application of personal meta-communicative feedback in the case of a patient's destructive behavior within the therapeutic space (McCullough, 2006; Schoepf et al., 2009).

2.5.1.8 Bandura's reciprocal interaction model and his revised theory of social learning

Bandura's reciprocal interaction model of behavior holds that the type of behavior that a person exhibits partly determines his environmental contingencies, which in turn, influences his behavior (Bandura, 1969). Further elements of his revised theory of social learning are (a) that affiliation patterns, in turn, shape the direction of self-efficacy development, (b) that self-efficacy beliefs contribute to the course of cognitive-emotional development and determine choice of associates and activities, and (c) that under certain conditions, all learning processes can be acquired in a more or less conscious manner via observation and imitation, featuring temporal differentiation of the four sub-processes attention, memory, behavior and motivation (Bandura, 1986).
In CBASP, Bandura's theory forms the theoretical basis to describe a behavioral change process that appears to be interactional by nature. For example, SA represents a top down technique of stimulus recognition that enables the patient to learn in a formal-operative way, how to regulate his environmental interactional process to achieve his own goals. As the patient learns to shape his environment in a more pro-active way in the therapy he is shaped by his environment inside and outside of therapy in a new way. The learning effect to self-administer SA to identify behavioral consequences and to obtain desired interpersonal outcomes is directly associated with positive treatment effects.

2.5.1.9 Bouton's "synthetic approach" to instrumental behavior

Bouton's contemporary synthesis of learning and behavior is important for the conceptualization of early-onset chronic depression as well as the use and development of further learning theory based interventions (Bouton, 2007).

2.6 Therapeutic goals

McCullough has introduced the innovative theoretical concept of "perceived functionality", which he defines as follows: according to him, perceived functionality is an individual's ability to be aware of the effects that one's own behavior has on the other person while being able to draw causal connections between one's own actions and the other person's reactions. The development of the ability of perceived functionality is the ultimate therapeutic goal of CBASP-treatment (McCullough, 2006). The second therapeutic goal of central importance is teaching the patient how he or she can deal with the environment in effective ways. In order to achieve this, CBASP-therapists are systematically teaching the patient, using SA and the strategies of DPI, to change his behavior so that his desired

behavior in a situational event leads to the results he really can obtain. As a result, proactive, goal-directed social behavior and success-oriented thinking in stressful social situations become more probable. Proactive, goal-directed and socially acceptable behavior describes an individual's systematic impact on his or her social and material environment, i.e., conscious, systematic, controlled and socially acceptable. In order to be able to act in such a way, the patient has to experience fear-inhibiting interpersonal reactions within the therapist-patient-relationship, which is achieved through DPI interventions applied by the therapist. This usually leads to the integration of traumatic experiences within former relationships (Schoepf et al., 2007). Success-oriented logical thinking describes an individual's ability to generate relevant, accurate and action-oriented interpretations as well as the generation of goal-directed action reads in a given social situation. Causal reasoning is learned by the individual through confronting situations and acting in them. Thus, development runs from the external to the internal, from the application of SA obeying formal-operational methodology to thinking and experiencing. At the end of the acute therapy phase, the patient has learned to effectively interact with his or her environment and perceived functionality is acquired. Both of these goals have to be further generalized and established during maintenance phase. The therapy and the process of learning represent, at the same time, the result of the acquisition process as well as the method by which it is achieved (Wechsler, 1961; McCullough, 2006).

2.7 Treatment strategies subdivided into bottom-up and top-down interventions

At the beginning of the therapy, the main focus lies on the situational and interpersonal avoidance strategies of the chronically depressed patient. In accordance to its basic assumptions, CBASP assumes that it is necessary to train the patient in actively experiencing his or her problems in life from a "person-environment" perspective before there can be any change. As long as interpersonal avoidance hasn't been overcome, there will be no emotional change of the chronic depressive mood and related modes of experience. Once it has, behavioral changes, personal empowerment and an improvement of dysfunctional regulation of emotions can occur.

Over all, due to its integration of various different methods that stem from various psychological theories, CBASP is a very complex method. For didactic reasons, its therapeutic strategies can be divided into interventions which have "bottom-up" or "top-down" effects on stimulus recognition.

On the one hand, from a bottom-up point of view, a behavioral response to a "person-environment" condition will occur more reflex-like if the psycho-physiological activation of limbic and limbic-cortical structures is strong.

On the other hand, from a top-down point of view, a modulation of the perceptual and mnestic processing gradients that was caused by cortical networks has the effect that the interference of those parts of information that do not match the behavioral response is enhanced, thereby facilitating reflexive behavior once more.

2.7.1 Mechanisms of action of bottom-up strategies

In general bottom-up therapeutic strategies primarily aim at healing the patient from painful experiences early in his or her life, with the help of the therapist using DPI. Here, the patient can experience empathy and practice goal-oriented behavior (for in-depth discussion and further examples, see Schoepf et al., 2007).

The mechanisms of action of bottom-up therapeutic strategies are:

- reciprocal inhibition of maladjusted rule-guided behavior,
- systematic decoupling of behavioral effects and the effort to make these effects conscious,
- systematic counter-conditioning of refractory emotions in the negative phase of the emotional form of IDE,
- and counter-conditioning of fear reactions that occur during the testing of goal-oriented behavior.
- In addition, action-related interpretations and missing behavioral aspects of realistic and desired goal-oriented behavior which aren't present prior to therapy are generated through therapeutic shaping.

2.7.2 Mechanisms of action of top-down strategies

By contrast, top-down therapeutic strategies modulate executive performance and enhance formal-operational thinking and behavior (for in-depth discussion and further examples, see Schoepf et al., 2007).

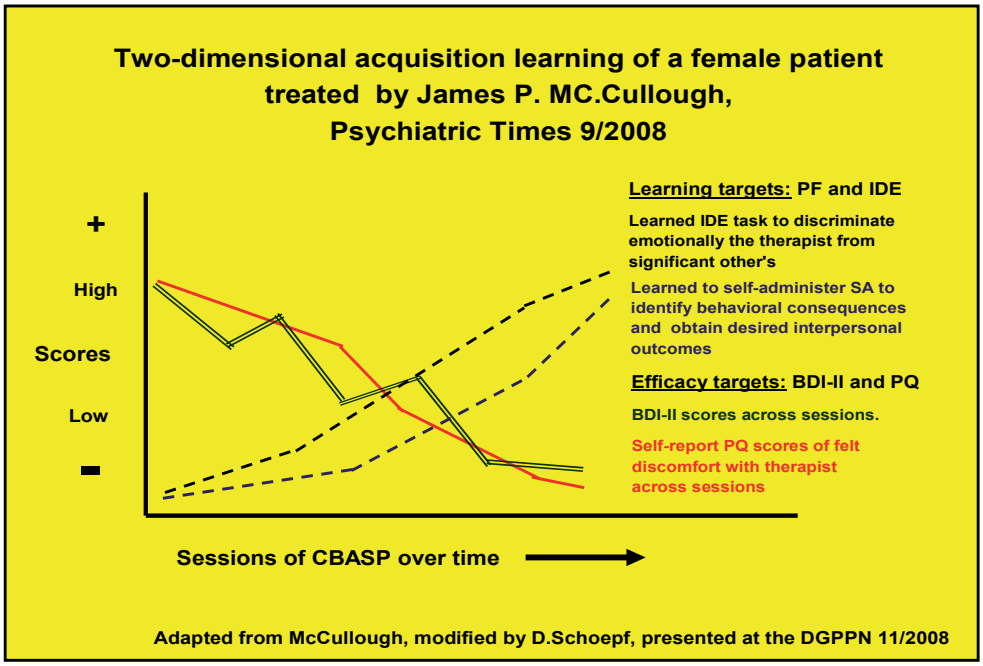

Fig. 3. Example of the learning effects and the effectiveness of "bottom-up" and "top-down" interventions over sessions of CBASP over time within the disorder-oriented and theory-driven CBASP treatment of one of McCullough's patients. Learning targets: PF= perceived functionality. IDE = Interpersonal Discrimination Exercise. IDE represents a typical bottom-up strategy that is based on the principle of counter-conditioning intrapersonal-interpersonal emotional fear. SA=Situational Analysis. SA primarily falls into the category of top-down strategies, stressing the principles of instrumental conditioning, self-efficacy, outcome expectation, exercise of control and PF. Efficacy targets: BDI-II = Beck Depression Inventory. PQ = Personal Questionnaire. High learning scores in IDE and SA are associated with low depression scores and low scores of felt discomfort with the therapist across sessions.

The mechanisms of action of top-down therapeutic strategies are:

- reinforcing and sensitizing the perceptive and interpretative performance by means of attention-focused interventions under aspects of awareness,
- building-up the ability to control and perform with competence in a given situation, by means of contrasting past behavior with the desired goal behavior,
- and shaping mental functions to think and act according to formal operational criteria.

3. Second part

3.1 Multi-step CBASP psychotherapy approach for pre-therapy chronically depressed inpatients

For the treatment of major depressive episodes in chronically depressed patients with antecedent dysthymia considered to be therapy refractory under inpatient conditions, a multi-step psychotherapy approach that integrates McCullough's model, has proven to be successful during 2007-2011 in a small regular ward of the University Hospital Bonn, equipped with a specialized outpatient department. Table four represents the multi-step approach presented 2008 to CBASP-Network and both McCullough and Penberthy (Schoepf et al., 2008b). A clear distinction is drawn between an "inpatient pre-SA treatment phase" that includes two consecutive stages of treatment and care which build on each other, and an "outpatient treatment phase". The approach targets on complete syndromal remission and complete restoration of social function in the acute treatment phase.

Acute treatment phase		
First stage of treatment	**Second stage of treatment**	**Third stage of treatment**
Level of care: inpatient	**Level of care: inpatient or partial hospitalization**	**Level of care: mainly outpatient**
Suggested elements of psychotherapy Mainly basic psycho-therapeutic treatment with an emphasis on supportive elements in order to relieve the patient. Additional "fundamental elements of CBASP therapy".	**Suggested elements of psychotherapy** Mainly basic psycho-therapeutic treatment with an emphasis on problem-oriented elements for the step-by-step increase of the level of stress and the preparation for outpatient treatment. Additional "fundamental and additional elements of CBASP therapy".	**Suggested elements of psychotherapy** CBASP treatment in accordance with the manual in order to attain perceived functionality and a change in world view through fundamental experiences of change with respect to the inter-personal problem area. Situational Analyses and Interpersonal Discrimination Exercises.
Duration: 8 - x weeks, depending on superimposed, psychiatric or somatic diseases and the influence of stressors.		Duration: 12 weeks.
Pre-SA CBASP treatment phase		**CBASP treatment phase**

Table 4. Psychotherapeutic stages of treatment and care in the treatment of chronically depressed patients with an inpatient history of therapy-refractory major depressive episodes.

In the first stage of treatment, fundamental elements of CBASP therapy are applied that use negative reinforcement in the case of pro-active interpersonal behaviour and simple discrimination exercises with respect to health-related behaviour.
In the second stage of treatment, additional CBASP techniques of DPI are used that feature the "deeply personal nature of the therapist patient relationship" in the development and maturation of the patient, as well as additional strategies for the enhancement of executive performance.
The third stage of treatment is considered to be the regular CBASP treatment phase. According to McCullough's manual, situational analyses and interpersonal discrimination exercises, performed in a precise, consecutive order, are central to this phase. In order to guarantee the continuity of the development and the generalization of adaptive stimulus-response behavioural patterns, the CBASP therapist begins the treatment under inpatient conditions and continues therapy under outpatient conditions. Using various examples, the second part of the chapter also looks at the rationale, the definitions and the description of the psychotherapeutic stages of treatment and care, as well as the therapeutic elements specific to CBASP that are being used.

3.2 Fundamental and additional therapeutic elements of the Pre-SA CBASP treatment phase

A pre-therapy patient according to McCullough is an outpatient who cannot learn or benefit from psychotherapy because of the way he behaves with the psychotherapist (McCullough, 2008). McCullough claims that patient learning requires the ability to be verbally controlled by the therapist; and the ability to attend and focus on one thing or stimulus situation (or one task such as SA) at a time.
In the multi-step treatment approach a patient has reached the "Pre-SA CBASP treatment phase" when he or she is able to understand simple relationships between a behavior and its effect with respect to adaptive behavior, and when the patient is able to respond to interpersonal strategies of CBASP with affects that can be clearly defined and specified.
Since, at this stage, the patient's information processing is severely disturbed, the patient has not reached the niveau of a pre-therapy outpatient and is not yet able to conduct a SA with the therapist.

3.2.1 Fundamental therapeutic elements of CBASP in the first stage of treatment and care

During the first stage of treatment and care, the following four basic therapeutic strategies of CBASP should be applied, depending on the therapist's competence and quality of intervention:

3.2.1.1 Negative reinforcement techniques concerning proactive interpersonal patient behavior, with the goal of increasing the frequency of such behavior

Example: The patient talks to the therapist about a certain behavior that he or she has attributed as a "failure": the behavior in question was "not having gone for a walk". The patient expects that his or her behavior of "mentioning the failure" to the therapist will be met with an interpersonal reaction of "some sort of punishment". The fact that the therapist reacts with "non-punishment" leads to an absence of the negative consequences expected by the patient, and thus to stress reduction. Consequently, it becomes more probable that, in a future situation, the patient talks to the therapist about a failure he or she has experienced.

3.2.1.2 The therapist directs the patient's moment-to-moment attention to his or her reported health-related behavior: the patient is made aware of perceived positive effects by pointing to the contrast between before and after, in order to induce intrapersonal, positive reinforcement

Example: The patient mentions a specific health-related behavior to the therapist, for example, the health-related behavior in question may have been that the patient "went for a walk". The patient is expecting a well-meaning, +positive reaction from the therapist (praise) while, at the same time, fearing it. The reaction usually induces a reactance reaction of the patient, e.g., an angry devaluation of the patient's own behavior. Instead of positive reinforcement through praise, the therapist asks the patient about the experience he or she has had during the behavior of "going for a walk". The patient is then asked to compare what it felt like before, during and after "going for a walk". Contrasting these inner states in such a way, the patient usually sees that he or she felt better during and after the walk than before. Thus, the health-related behavior of "going for a walk" becomes more likely for the patient the next time.

3.2.1.3 The extinction of intrusive and destructive behavioral response patterns during social interaction, with the goal of reducing the frequency of such behavior

Example: The patient suddenly devaluates him or herself, without any apparent connection to the context of the interaction, claiming that "everything I do is wrong". The patient is expecting the therapist to respond in a (slightly confused) reassuring way, or by changing the topic of the conversation. Instead, the therapist pauses briefly, sticks to the topic (in a friendly way) and generally remains "undistracted". The behavior of sticking to the topic and not reacting to the patient's destructive, interpersonal behavior leads to a reduction of the frequency of destructive, interpersonal behavior via the mechanism of extinction. It should be noted that this is not a case of negative punishment, since the therapist does not withdraw from the patient.

3.2.1.4 Transformation of the formative influence of "Significant Others" from the patient's past into behavioral terminology about the "here and now", with the goal of determining and making explicit the interpersonal "hot spots" which were shaped by repetitive experiences of helplessness while living together with the "Significant Others"

Example: The patient's mother was experienced as emotionally abusive, repeatedly violating both his personal boundaries and those of his father. Furthermore, the mother is said to have lived a very promiscuous life. For the "here and now", this means that the mother's formative influence on the patient's present life is such that the patient is unable to show affection and trust towards women.

3.2.2 Additional elements of CBASP therapy in the second stage of treatment and care

The patient has acquired the niveau of a pre-therapy patient according to McCullough's definition given in 3.2. The patient has at this stage not learned what CBASP seeks to teach because of problematic interpersonal behaviors that interfere with learning. He is unable to be verbally controlled by the therapist.
Typical interfering behaviors are described by McCullough as follows:

- competitive behavior about the content of conversation,
- changing the subject and behaving like a "moving target",
- refusing eye-contact, instead mind-reading the thoughts of the therapist,
- protesting about his own inadequacy, bringing into therapy crisis,
- highly submissive behaviors and refusing to take any initiative,
- frequently becoming angry with the therapist,
- frequently statements that he is hopeless and cannot be helped.

The CBASP-specific goals of treatment during the second treatment stage have two objectives: reducing the occurrence of strikingly maladaptive behavioral patterns and typical, inadequate social attitudes. Here, "additional elements of CBASP therapy" are given preference, with the primary goal, using the therapist's DPI, to establish an interpersonal context which enables the patient to experience empathy and develop new stimulus-response behavioral patterns. In particular, this includes the following four techniques:

3.2.2.1 Counter-conditioning of interpersonal fear with the goal of modifying strikingly maladaptive interpersonal behavioral patterns and typical, inadequate social attitudes

Example: The typical maladaptive interpersonal behavior of the performance-oriented patient might be characterized by "refusal and withdrawal". The therapist asks the patient about his or her (the therapist's) reaction upon being told that the patient has failed to fully complete the psychological test examination.

Therapist [T]: "What did I do when you told me that you didn't manage to sit through the full examination?"

Patient [P]: "You asked me about the experiences I had during the examination."

T: "What else did I do?"

P: "You asked for details and seemed interested when I told you about the memory exercise."

T: "What else can you remember?"

P: "I don't remember anything else."

T: "In which way did I punish you in that situation?"

P: "You didn't punish me."

T: "How can you tell that I didn't punish you?"

P: "Because you didn't condemn me for not sitting through the entire examination."

T: "Are you trying to tell me that I didn't punish you when you told me that you failed to sit through the examination until the end?"

P: "Yes."

T: "Do you get the feeling of punishment now?"

P: "No."

T: "What are you feeling instead?"

P: "I feel a lot more relaxed than before".

Annotation: The major interpersonal problem of this patient is (Pavlovian) fear that doing a mistake towards the therapist means becoming punished, tacit knowledge to the patient. The therapist is typically pulled to "punish" the patient verbally or nonverbally. Counter-conditioning reduces the fear and helps the patient to interact with the therapist in a more authentic manner including to respond appropriately.

3.2.2.2 Modified IDE (double counter conditioning) with the goal of teaching the patient to reliably discriminate emotionally between the therapist's behavior and the behavior of his "Significant Other's"(for patients with severe and/or refractory disorders, this presupposes that 3.2.2.1 was successful)

Example: Subsequent to counter-conditioning (Example 3.2.2.1), the therapist conducts a modified IDE (double counter-conditioning form):

T: "I'd like to come back to the just happened situation: how did I react when you told me that you didn't manage to sit through the full examination?"
P: "You showed interest and asked me for my reasons."
T: "How did you respond when I showed interest and asked you for your reasons?"
P: "I didn't freeze up and was able to keep talking."
T: "When I asked for more details and seemed interested, how did that effect you emotionally?"
P: "I felt relaxed afterwards."
T: "What would your father have done if you had told him that you hadn't fully completed the examination?"
P: "Oh my God! He would have ranted at me, calling me a loser."
T: "What would have been the effect of your father's condemnation on you, emotionally?"
P: "I would have been very sad and would have developed feelings of guilt."
T: "What's the difference between my behavior and your father's behavior with respect to your own behavior and feelings?"
P: "My father would have called me a loser. I would have frozen up, remained silent, become sad and would have developed feelings of guilt. You didn't condemn me. I was able to talk and I felt relaxed at the end."
T: "What does this mean for our relationship?"
P: "It means that I can open up and that I won't be condemned when I fail to achieve something."

Annotation: Double counter-conditioning has the effect that the therapist usually becomes a safety signal for the patient. It is important to have in mind that the duration of both exercises (3.2.2.1 and 3.2.2.2) usually takes at least thirty minutes.

In addition, the techniques of CBASP are used to strengthen executive performance. Here, the following points seem especially important to us:

3.2.2.3 Practicing how to describe a situation as the basic requirement for being able to differentiate between situations that cause stress and situations that reduce stress

Example: The patient tells the therapist that he has spent a dreadful day with his mother as part of his stress test. The patient learns to identify the precise situation that caused stress, i.e., a fight over dinner, and to describe the situation using behavioral terminology in a successive "what happened next" manner, with a beginning and a clear endpoint and a story that happened in between.

3.2.2.4 Formulating the actual outcome (AO) of a positive experienced encounter using behavioral terminology, and the patient's ability to name the emotional effect of his or her own behaviour (in a self reflective manner). This carefully prepares the patient for the formulation of the AO and the desired outcome (DO) in the context of SA

Example: The above-mentioned patient learns to formulate the AO of an encounter, using behavioral terminology. The situation is taken to be the fight over dinner mentioned above. The patient formulates his AO and the effects his own behaviour has had on him. The AO is: "I told my mother that there's no point in keeping on talking, and then I felt silent". The emotional effect the AO has had on him was: "I felt better".

4. General conclusion

In this chapter, I have given an overview of my theoretical work that I have carried out with a group of colleagues whom I acknowledge at the end of the chapter. The chapter has been coordinated in both parts with James P McCullough and Kim Penberthy (2009) in its first vision, and in the end verbally with Peter Neudeck. Correspondingly, I have chosen Peter Neudeck as co-author. He is an excellent exposure therapist whom I supervise in CBASP since 2009 as I have been supervised by James P McCullough once (McCullough, 2008; Schoepf and McCullough, 2009b). Both of us strongly emphasize the aspects of modern learning theory in CBASP as CBASP therapists. Hopefully, this chapter has persuasively articulated a constructive use of the CBASP related to both chronically depressed outpatients that are able to benefit from CBASP according to the protocol of Jim McCullough (McCullough, 2000) and inpatients with a history of major depressive episodes that are therapy refractory under inpatient conditions (Schoepf et al., 2008b). It is my concern to bring into consciousness that disciplined personal involvement CBASP techniques that are both reliable and valid can only be learned through intensive and supervised training. This is the reason why, to this day, even McCullough himself conducts training for selected learning therapists, using video-supervised case studies. As CBASP-providers, CBASP-supervisors and CBASP-therapists, these therapists are responsible for the distribution and quality control of CBASP in their respective countries (Schoepf et al.

2009a). Further information is available at www.cbasp.org and www.cbasp-network.org. As I was writing the chapter I found myself fueled by hope that this articulation can be of assistance to other psychiatrists and psychotherapists, as well to other mental health practioners who are interested in working with chronically depressed patients in a constructive way to help their patients to get out of their prison of negative thoughts and outcome expectations, as well as to change their destructive interpersonal behaviors. James P McCullough would say: "Dieter, go on teaching your patients to get more what they want". This far, for a number of reasons, I have been inclined to study both the efficacy and the process variables of change of McCullough's model using qualitative methodology. If the success (that is yet not systematically evaluated or published anywhere as the studies are still running) is allowed to stand indication, work with the CBASP would appear to bode well for further applications, for example in a multistep-approach in combination with elements of cognitive processing therapy in PTSD patients and double depression.

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5

Animal-Assisted Interventions; Effects on Human Mental Health - A Theoretical Framework

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1. Introduction

In the Western part of the word the public health challenges have changed dramatically during the last decades. Modern medicine and new technology has reduced mortality rates for most diseases and the life expectancy has increased. However, in the modern society of today, we face new threats to public health, mainly related to life style related diseases and illnesses such as obesity, diabetes, cardiovascular disease, musculoskeletal disorders and mental health problems. The prevalence of mental health problems is high and increasing, and previous epidemiological studies have estimated the lifetime prevalence of mental disorders to be approximately 50 % (Kringlen et al., 2001; Robins & Regier, 1991). Affective disorders are one of the most common mental disorders, and in a WHO survey from sixty countries, one-year prevalence for depressive disorders was 3.2 % (Moussavi et al., 2007). This is slightly lower than in a European survey, which estimated one-year prevalence for major depression to be 3.9 % (Alonso et al., 2004). In different surveys the lifetime prevalence varies from 8 to 18 % (Alonso et al., 2004; Kringlen et al., 2001, 2006). In a Norwegian study the diagnoses with the largest percentage increase in sickness absence the last decade were sleep problems, tiredness, anxiety (Ihlebæk et al., 2007), and today mental health problems account for almost 25% of new disability pension grants in Norway (Mykletun & Knudsen, 2009). In addition to individual suffering, this constitutes a major economical challenge to the society, as a review of Luppa et al. (2007) found that indirect economical costs, mainly due to sick leave and work disability, was twice as high as direct costs. Even though there has been substantial economical effort to develop and strengthen the traditional health care system for these problems, it does not seem to reduce the problem and still many patients do not get the treatment and rehabilitation they need. It is therefore necessarily to investigate other and complementary interventions and therapeutic approaches that might be useful.

According to historical and prehistoric evidence, it is believed that the social symbiotic relationship between man and animal developed without any coercion from the human's side (Odendaal, 2000). During the 20th century the introduction of animals to institutional care settings increased, and the concept of Animal-Assisted Therapy (AAT) was first mentioned by the child psychotherapist Boris Levinson (1962). Levinson described the

benefits of his own dog in counselling sessions with children and youth, and gave numerous examples of ways in which the dog could enhance therapy. A lot of people with mental health disorders have problems in their relationship with other humans. This can be due to several reasons, as rejection, aggressive or sexual assault and other kinds of behavioural problems. Many of these people receive adequate treatment, but for some it may be favourable to use activities related to animals as a means of developing skills in making and maintaining relations with other people to support the ordinary treatment. However, the theoretical foundations for the benefits of interacting with animals are still poorly understood, and the plausible mechanisms are still to be confirmed. The aim of this chapter is to describe different aspects of the human-animal relationship, with emphasis on the positive impact animals may have on human mental health.

2. Defining Animal - Assisted Interventions (AAI)

According to Kruger and Serpell (2010), Animal-Assisted Interventions (AAI) is defined as "any intervention that intentionally includes or incorporates animals as a part of a therapeutic or ameliorative process or milieu". AAI is used as a colloquial term that encompasses both Animal-Assisted Therapy (AAT) and Animal-Assisted Activities (AAA). According to Delta Society (2011), AAT is a goal-directed intervention with animals as an integral part of the treatment process for a particular human client. The process is directed by a therapist who is practicing within the scope of his/her professional expertise. Key features include specific goals and objective for each individual and a standardized evaluation of the progress. AAA provides opportunities for motivational, educational, recreational, and/or therapeutic benefits to enhance quality of life, and is delivered in a variety of environments by specially trained professionals and /or volunteers (Delta Society, 2011). AAA refers to a general category of interventions without a common protocol, and may involve the introduction of one or more animals to an individual in a private or group setting. Related to these definitions, a clear distinction should be made between emotional response to animals and therapy. However, many applications of AAA are designed to benefit individuals by reducing stress and loneliness, and inducing attention to and interaction with the outside word. Several studies designed to evaluate AAT, were evaluating AAA under more current nomenclature (Friedmann et al., 2010). Thus, to meet these somewhat mixed concepts, the term AAI was introduced. This definition provides the flexibility needed to discuss programs that can fit into a medical model, and those of a more quasi-medical nature, which still seek to "affect the course "of people's lives in a positive direction (Kruger & Serpell, 2010).

Despite that some attempts have been made to standardize terminology and procedures, the research on AAIs are still struggling to demonstrate their efficacy and validity. However, some mechanisms and theories have stood the test of time. The first mechanism is related to animals as agents of socialization, the second mechanism is due to the beneficial effects of AAIs on symptoms (mainly anxiety and depression) and physiological indicators of stress/distress, and the third mechanism is related to animals as facilitators to improvement of self-esteem and self-efficacy. The attachment theory is often mentioned as one of the basic theories in the field, although it is not a single mechanism. However, related to the fact that it is one of the explanations of the bond between human and animals, it is described as an important aspect of AAIs. Although most of the available studies concerning AAIs are dealing with the interaction with companion animals, a few studies of AAIs are describing

and measuring the effects of farm animals (including horses) on human mental health. Until now most of these studies are designed in the context of Green care.

2.1 Green care

Green care is an inclusive term for many complex interventions, such as social and therapeutic horticulture, animal-assisted therapy, care farming, green exercise, ecotherapy, wilderness therapy, e.g (Haubenhofer et al., 2010). Although there is much diversity under the umbrella of Green care, the term is grounded on the positive relationship between exposure of nature and human health (Sempik et al., 2010). Care farming (also called *social farming* or *green care farming*) is the use of commercial farms and agricultural landscapes as a base for promoting human mental and physical health, social inclusion and educational benefits through normal farm activity (Sempik, 2008). Most farms are ordinary family-based commercial farms, but also farms connected to health institutions and farms as part of therapeutic communities exist within Green care. Today the estimated number of Green care farms in Norway is 950 (Logstein & Bleksaune, 2010), and other European countries have similar figures (Haubenhofer et al., 2010). There is much variety among care farms, with differences in the extent of farm production or care, and in client groups. These may include patients with defined psychiatric diagnoses, people with learning disabilities, those with a drug history, disaffected youth or elderly people, as well as persons suffering from the effects of work-related stress or obesity. Many care farms offer contact with farm livestock (AAA), while others provide specific Animal-Assisted Therapy (AAT). Typically, the participants take part in the ordinary work tasks, like feeding animals, cleaning animals and the barn, milking cows, and they have the opportunity to pet and interact with the animals as much as they like. Although animal-assisted interventions with farm animals appear to be the most thoroughly studied type of Green care service, the evidence-based research is still scarce.

3. The human-animal relationship

Several authors have highlighted the association between people and animals, and provided some insights to this relationship. Tannenbaum (1995) claimed that the human-animal relationship need to be of a continuous nature and should be bi-directional and voluntary, while Russow (2002) claimed that the relationship must be reciprocal and persistent. She express further that there are no true relationship if the animal don't recognize you. However, it is not obvious that the human and the animal have a similar perception of their interaction. What a human experiences as pleasant, may be unpleasant for the animal. It has been known for many years that dogs and cats that have close contact with humans early in their lives are much friendlier to humans than animals that are exposed later on (Bateson, 1990). The restricted age-range within which such socialization is readily formed is known as the sensitive period for socialization, typically 3-12 weeks of age in dogs and cats. When this period starts, the animal is ready to form an attachment to a wide range of objects, but as it receives experiences with one object, it narrows its preferences to that one object. The consequence is that the animal is no longer able to enable new attachments. If the animal is exposed to several views of the same object while it is still narrowing its preferences, each of those views will be equally effective. Similarly, if the animal is exposed to different animals, including humans, it may form attachments to each of the objects, and the strength of the

attachment will be related to the length of the exposure to the different individuals. When young animals are being exposed to several human individuals, the effect is more a general socialization on humans than attachment to a specific individual. If pet breeders do not give the young animals sufficient experience with humans, the animals will hardly function as pleasant, sociable pets. It is assumed that also farm animals should be socialized on humans in early life to function most effectively in animal-assisted interventions, and to avoid aggressive or fearful behaviour (Berget, 2006). Even without specific work on socialization, farm animals can usually be stroked, people can talk to them, and they may be good transitional beings like pets are.

4. Animals as attachment figures

Katcher (2000) states that animals makes good transitional beings because they show intentional behaviour, they are capable of giving active affection, they can never contradict the attributes projected into them with words, and they can serve as vehicles for projection traits one might find lacking in human beings. According to Triebenbacher (1998) humans have an innate, biologically-based need for social interactions, and this interaction becomes increasingly focused toward specific persons. Behaviours such as following, smiling toward, holding and touching are evident in the relationship between child and attachment figures. Bowlby (1982) defined attachment as a form of behaviour in an individual seeking or maintaining proximity to another that serves as a secure base, and who is perceived as better able to cope with life stressors. Fundamentally this kind of attachment is found between a mother and offspring.

To date theories of attachment used in research on human-animal relationships are based on theories applied on human-human relationships. Katcher and Beck (1989) recorded that a lot of persons appeared to have an attachment to their companion animals similar to that experienced with their friends and family, and Stallones et al. (1988) found that 95 % of elderly respondents regarded their companion animals as friends. In other studies, Cain (1983) and Voith (1985) found that a majority of the subjects regarded the pets as members of the family. Sife (1998) showed that as many as 70 % of people who share their lives with companion animals reported that they consider them as children. A similar study by Wallendorf and Belk (1987) documented that a majority of the respondents answered that their pets were substitutes for children, which may explain the tendency for people to use baby talk when speaking to their pets. Many human personality variables have been identified as being related to pet attachment. For example, people who had pets during childhood or adolescence tended to be more attached to their current pet than first-time caregivers (Kidd & Kidd, 1980), while the single adults tended to be more attached than the married adults. People who indicated a dog as their favourite pet tended to express a stronger attachment than those who reported a cat to be their favourite pet (Johnson et al., 1992).

Crawford et al. (2006) examined if there were some common concepts between traditional attachment theory and human-animal attachment. The authors divided these aspects into among others; emotional bond, secure base, and representational models:

Emotional bond

According to Crawford et al. (2006), emotional bond is associated with closeness, frequency of petting or grooming one's animal, and levels of exercise. Enders-Slegers (2000) related

emotional bond to caressing or holding an animal, or comfort derived from the relationship with the companion animal, while Odendaal (2000) claimed that the success of human-animal interaction is based on a two-way fulfilling of attention needs, and that the more social behaviour an animal exhibits, the more successful the bonding between human and animal can be.

Secure base

As earlier mentioned, the concept of secure base is fundamental in the field of attachment theory (Bowlby, 1988). The emotional security that pet owners report feeling in the relationship with their pets may in some ways parallel physical and emotional security as discussed within attachment theory (Triebenbacher, 1998).

Representation models

One's representational model of attachment often influences one's ability to deal with stressful life events (Bretherton, 1985). Similarly with traditional attachment theory, an individual's relationship with a companion animal may determine how well he or she will cope with stressful life events (Siegel, 1990).
To summarize, attachment implies a long-lasting bond, and correlations between attachment and positive therapeutic outcomes have yet to be convincingly established in relation to human-animal relationship. In the context of AAI, the animal as a transitional object may appear to be more therapeutically desirable than that of an attachment figure (Katcher et al., 2000; Kruger & Serpell, 2006).

5. Animals as agents of socialization

In the late eighteenth century, theories concerning the socializing influence of animals began to apply to the treatment of mentally ill. In the *Description of the Retreat*, Samuel Tuke described how different animals, like rabbits, sea-gulls, hawks and poultry were a part of the milieu at the mental institution. The intention was that the interaction with the animals not only should give a means of innocent pleasure, but also to awaken the social and benevolent feelings (Serpell, 2010).

5.1 Animals as facilitators of social support

According to Cobb (1976) social support is defined as an interpersonal relationship that leads to "the persons believe in being cared for, loved, esteemed, and a member of a network of mutual obligations". Cobb suggested that social support that derives from a social relationship could provide protection from anxiety, depression and other related illnesses. This belief has been supported by research associated to mortality and morbidity of coronary heart disease (Eriksen, 1994), recovery of surgical procedures (Kulik & Mahler, 1989), and psychological well-being under stress (Winefield et al., 1992). The emotional support in initial stages of a severe stressor, like loss of functionality (Glass et al. 1993) and cancer diagnosis (Worthman, 1984), are also shown to be of importance for successfully coping with such stressors. Social support is an important part of mental health interventions as it could preserve feeling of self-esteem and sense of mastery (Milne, 1999).
It is hypothesized that social support acting as a buffer against stress responses or illness can be derived not only from human relationships, but also from a human-animal

relationship. According to McNicholas and Collis (2006) social support from pets may be a replacement for lacking human support, providing a release from relation obligations, enhance reorganization, re-establish routines, and "top up" existing human support. In a review of psychological, social, behavioural and physical benefits from pets with regard to social support, Garrity and Stallones (1998) found that pet association frequently appeared beneficial both directly and as a buffering factor during stressful life circumstances. In a study of horseback riding among children with mental and neuromuscular disabilities, Hart (1992) found that the intervention released joyous human social support as well as the unique sensation and physical challenge of riding a horse. Even the families of the affected children seemed to benefit.

Appraisal support, with affirmation and feedback, is likely to be a part of the contact between the farmer and the participant in Green care. This was also found in the doctoral thesis of Pedersen (2011) on farm animal-assisted interventions for patients with a clinical depression. In addition to the accepting support the animal provided in her study, the participants expressed that they felt the farmer understood their situation and that they could easily express how they felt. Qualitative studies in The Netherlands (Elings & Hassink, 2008) and in Norway (Bjørgen & Johansen, 2007) have also emphasized the farmer contact and the social setting as important aspects for participants with mental health issues. An exploratory study at the Green Chimneys institution among 80 children with behavioural and mental health problems, showed that the children utilized the farm animals as if utilizing the service of a therapist; they visited the animals to feel better, and they learned about nutrition and caring for animals (Mallon, 1994). In a 12-week pilot project on AAI with goats for ten multiply-disabled adults (all deaf), the video registrations showed that the clients expressed joy and decreased withdrawal in contact with the goats. During the intervention the attentiveness and active participation increased. In contrast no such changes were found in a dining room situation on the residential institution for these persons (Scholl et al., 2008).

5.2 Animals as contributors to social contact

A mechanism often mention in the AAI literature is that animals may serve as catalysts or mediators of enhanced communication skills among people. The basis of this mechanism is that animals stimulate conversation by their presence and unscripted behaviour, and by providing a neutral, external subject on which to focus (Fine, 2000; Levinson, 1969). One of the first to evaluate the effects of pets as social catalysts in institutional settings was Corson et al. (1977). They focused on patients who did not respond sufficiently on traditional therapy. However, they failed to find a proper control group, and allowed the experimental group to act as their own controls in an intervention either with a dog in a kennel, on the ward, or at the patients' bedsides. The study showed that the pets and the patients enjoyed much time together, and analyses of videotapes showed that the patients appeared less withdrawn, and communicated more with the therapist. Another study in the early period was the study of Beck et al. (1986) comparing psychiatric inpatients in a room with caged birds with a similar patient group without any animals. The authors concluded that the patients in the room with the birds communicated more, and were more comfortable in communication than the controls. A study by Messent (1983) showed that dog owners walking in a park experienced a significantly higher number of chance conversations with other park users than when walking the same route without the dog. The study also

demonstrated that the conversations were significantly longer when the dog was present. The presence of a dog acted as an ice breaker, providing a neutral and safe opening for conversation. A similar study by McNicholas & Collis (2000) showed that being accompanied by a dog in daily routines such as taking children to school, on public transport, for example, led to an increased number of conversations between people. However, the length of interactions did not increase, and the study demonstrated that the nature of the interaction depended on the relationship between the participants. The effects of the dog as a social catalyst were largest with strangers and smallest with friends. Another study by Bernstein et al. (2000) demonstrated that geriatric persons subjected to AAT were more likely to initiate and participate in longer conversations than a control group getting Non-Animal Therapy (NAT) like arts, crafts and snack bingo. Similar effects were found in a 12-month controlled study of elderly schizophrenic patients where contact with a pet, either a dog or a cat, resulted in significantly improved conversational and social skills in the experimental group compared with the controls (Barak et al., 2001). In a recently randomized controlled trial (RTC) with or without a dog among 24 patients with schizophrenia, Villata-Gil et al. (2009) found significant change in social contact and social relationship in the dog group. However, there were no significant differences in the outcome measures when comparing the two groups. Rosetti & King (2010) found in a review of AAT among a heterogeneous sample of psychiatric patients that AAT can improve socialization. To sum up, positive connections to enhanced social interaction were seen. However, from surveys with pet owners, positive connections to pets as social catalysts are not consistent (Pachana et al., 2005; Parslow et al., 2005).

6. Animals as contributors to reduced arousal, anxiety, and depression

The statement that animals are able to induce and mediate physiologically de-arousing effects, was first forwarded by Edward O. Wilson in his book Biophilia (1984). He defined biophilia as humans' natural tendency to focus on life and lifelike processes. This is not single instinct, but complex learning rules which could form a range of emotions like attraction and peacefulness, but also aversion and anxiety (Wilson, 1993). This tendency gave distinctive advantages in human evolution, and therefore there is partly a genetic basis for this positive responsiveness to nature (Kellert, 1993). This hereditary trait is utilized in different forms of nature-assisted therapy, which is documented to be effective for a diversity of diagnoses, such as obesity, schizophrenia and stress related disorders (Annerstedt & Währborg, 2011). The stress reducing effect of outdoor recreation and natural settings are extensively investigated and Ulrich (1993) emphasizes a probable relationship between nature, reduced stress and health. This stress recovery response is also much used as a potential mechanism of the observed health effects in companion animal research. A decline in blood pressure and heart rate are seen in several studies when people interact and have physical contact with a pet animal. The first published report on effects of companion animals on physical health was made by Erika Friedmann et al. (1980). This report showed a relationship between owning a dog or cat and increased probability of survival one year after heart attacks, myocardial infarctions or severe angina pectoris. While 28 % of non-owners died within one year, only 5.7% of pet owners died. Later research has confirmed this finding (Friedmann & Thomas, 1995). The increased survival could not be related to differences in seriousness of the attack, psychological or social status, or demographic variables. Stress-reducing effects of watching fish in an aquarium have been shown in

several studies (e.g. Katcher et al. 1983). The same parasympathetic effects apply to watching animals of other species that people trust, while the opposite may be found for watching threatening animals. Interaction with a companion animal is also related to increased parasympathetic nervous activity (Matsuura et al., 2007), and increased level of salivary amylase activity which is associated with improvement of the immune function.

Positive physical contact between humans like nursing a baby, or stroking, caressing or massaging between adults, may release the hormone *oxytocin* which is produced in the hypothalamus (Uvnäs-Moberg, 1998). General effects of oxytocin are relaxation and reduced stress level. Oxytocin coordinates both the causes and the effects of positive social interactions, and it can be conditioned to the psychological state or imagery of people. An increase in the beneficial hormone oxytocin is also observed when humans interact with pet animals (Handlin, 2010; Miller et al., 2009; Odendaal & Meintjes, 2003). In the PhD-thesis of Handlin (2010), ten female dog owners and their male Labrador dogs participated together with ten controls. Their levels of oxytocin, cortisol and insulin, as well as their heart rate, were measured. The connection between the quality of the dog-owner relationship and hormone levels was also explored. The short-term interaction between the dogs and their owners resulted in oxytocin release in both species, and the oxytocin levels and positive attitudes regarding the dog-owner relationship were positively correlated. In conclusion the study showed that the interaction with the dog
induced oxytocin release, and promoted oxytocin mediated effects, such as decreasing cortisol levels and blood pressure. Other intervention studies with companion animals have shown a decrease in levels of stress hormones like adrenalin and noradrenalin (Barker et al., 2005; Odendaal, 2000).

Several studies of AAIs with companion animals have examined the connection between changes in physiological measures and reduced state anxiety (Barker et al. 2003a,b; Cole et al., 2007; Hoffmann et al., 2009). There are only a few studies that have examined whether a decrease in anxiety are valid also for interaction with farm animals. However, Berget et al. (2011) found a decline in state anxiety at follow-up six months after the end of a three-month intervention with farm animals for the intervention group of 41 participants with various psychiatric diagnoses (schizophrenia and schizotypal disorders, affective disorders, anxiety and stress-related disorders, and disorders of adult personality and behaviour) compared with the control group, as measured by Spielberger State-Trait Anxiety Inventory (state subscale, STAI-SS). Among the studied diagnoses, beneficial effects on anxiety tended to be higher among the persons with affective disorders. Among clinically depressed persons, Pedersen (2011) found a significant association between a high frequency of complex work tasks with dairy cattle and a decline in state anxiety (STAI-SS) during a 12-week intervention.

Complementary and supplementary treatments are widely used in treatment of depression. More than 50 % of people with depression reported using complementary treatment alone or together with conventional treatment in the US (Kessler et al. 2001). The reasons for this use are several; the side effects of medication are for many people difficult to accept, and a negative view of drug treatment in general could act as an incitement to use complementary treatments. Contact with pet animals is seen to be beneficial for mental health and depression. Souter and Miller (2007) conducted a meta-analysis to determine the effectiveness of AAT and AAA for reducing depressive symptoms in humans. Only five studies, all using dogs, were identified. The mean effect size for the sample of studies was statistically significant, and the findings supported the hypothesis that AAA and AAT are

effective at alleviating depression. A more comprehensive meta-analysis was conducted by Nimer and Lundahl (2007) identifying 49 studies that met the inclusion criteria. The outcomes in the following four areas were studied; medical difficulties, autism-spectrum symptoms, behavioural problems, and emotional well-being. All studies identified moderate effect sizes in the improving outcomes, but research gaps on AAA and AAT were revealed. Previous controlled studies of interaction with pets have shown significant decrease in depression during one week of hospitalisation among 230 psychiatric patients with psychotic and mood disorders (Barker and Dawson, 1998) and after two weeks of intervention with dolphins (Antonioli and Riveley, 2005). In a controlled pilot study on the effect of AAT on anhedonia among 10 schizophrenic patients, the Snaith-Hamilton Pleasure Scale showed significant improvement in the AAT group with a dog compared with the controls (Nathans-Barel et al., 2005). A few studies point to a reduction in depression among persons working with farm animals (Berget et al., 2011; Hine et al., 2008; Ketelaars et al., 2001; Pedersen, 2011). However, for some persons this is only evident during the follow-up period (Berget et al., 2011) or for those that acquire more complex working skills (Pedersen, 2011). Reduction in depression was also found in the control group, although to a lower degree.

7. Animals as facilitators of self-efficacy and self-esteem

Based on social cognitive theory, there is a continuous relationship between a person's cognition, behaviour and environment, and the goal of therapy is to bring about positive changes in a person's self-perception and hence their behaviour by improvements in self-efficacy, self-esteem and locus of control. Perceived self-efficacy is a major determinant of motivation for and choice of activity. It also affects the amount and duration of effort a person will allocate in order to cope in a situation or with a task. According to Albert Bandura (1977) self-efficacy is concerned with judgments of how well one can execute courses of action required to deal with prospective situations. People avoid activities that they believe exceed their coping capacities, but they undertake and perform assuredly those that they judge themselves capable of managing. People with low self-efficacy avoid difficult tasks, they lower their goals, and seek less support from others. Failures make them lose faith in themselves, and in turn contribute to lowered mood and depression (Bandura, 1982, 1986, 1997).

Benefits of AAI is often ascribed as the ability of animals to act as living, interactive tools that can be used to help people see both themselves and the world in new ways, and add new skills and responses to their behavioural repertoires (Nebbe, 2000). Although there is some overlap between these theories and those described in the previous sections, what sets them apart is their emphasis on the formation of a working relation between the client and the animal. Most programs that incorporate equines and animal training and care-taking, draw heavily from these theories. There are to date few long-term follow-up studies of the impact of AAI with companion animals on self-efficacy and self-esteem. However, previous RTC- studies with farm animals for severely diseased psychiatric patients showed an increase in self-efficacy at follow-up six months after the end of a three-month intervention for the treatment group, but not for the controls (Berget et al., 2008a; Pedersen, 2011). The studies indicate that positive effects of animal interventions on self-efficacy among these patient groups may take a long time to develop. However, according to Kruger & Serpell (2010), theories that enhance behaviour changes beyond the context of a working

relationship with an animal are conflicting, and yet no evidence exist that longstanding benefits are derived from participation in such programs.

8. Attitudes to Animal-Assisted Interventions among therapists

There are until now a few studies examining the attitudes of AAIs among different groups of health care personnel. A study of Rice et al. (1973) showed that that the therapists utilized pets as vehicles for cultivating or modelling the positive nature of interpersonal relationship, and most of the 40 respondents pointed out that animals were used to ease the stress of the initial phase of therapy to establish rapport. A qualitative study among 13 psychotherapists using AAT with dogs, found that the majority of the therapists ranked anxiety disorders as one of the diagnoses that profited most on AAT (Mason & Hagan, 1999). Another study by Berget et al. (2008b) examining 60 psychiatric therapists' knowledge, experience and attitudes to Green care and AAT with farm animals for people with psychiatric disorders, showed that most of the therapists thought that AAT with farm animals contributed to increased skills in interactions with other humans. Two-thirds of the therapists believed that AAT with farm animals to a large extent could contribute better to mental health than other types of occupational therapy. However there were no differences in attitudes to AAT between the different professions. A recent survey of beliefs in treatment effects of AAIs for psychiatric patients among 1100 Norwegian practitioners found that the therapists beliefs in treatment effects were most significant for better physical conditions, less symptoms (e.g. anxiety, depression), and a better ability to cope in daily life. The strongest degree of usefulness was reported for mental retardation, while the least significant one was for schizophrenia disorders. Women, more than men, believed in treatment effects and those with a professional experience with AAI more than those without the same experience. Finally, the beliefs in treatment effects from pets were slightly higher than those for farm animals (Berget & Grepperud, 2011). Future evidence-based studies with AAIs in different therapeutic settings will be of importance to develop more professional standards of practise, achieve additional credibility, and become recognized as a legitimate and multidisciplinary speciality. Also studies to investigate effects of AAI's in combination with different rehabilitation programs need to be explored.

9. What kind of species is preferred in AAIs?

Selection of species and type of animal used in AAIs are important in order to obtain the desired outcome. People, who are burdened due to difficult personal circumstances or poor health status, as is common for the elderly, can benefit from choosing a cat that requires less care than a dog or a horse. For people with mental health problems a new branch of AAIs using horses is recently evolving; equine-facilitated psychotherapy (EFP). EFP is an experiential psychotherapy that includes equines, and is facilitated by a licensed credentialed mental health professional together with an appropriately credentialed equine professional. EFP may include handling, grooming, longeing, riding, driving and vaulting (Equine Facilitated Mental Health Association, 2010). Green Chimneys (2010) is an example of a comprehensive residential treatment centre for mentally disturbed children where EFP is one of the important treatment modalities that are available. One difference in using e.g. dogs and horses as complementary treatments is whereas dogs can be available 24 hours a day to provide companionship and comfort, EFP requires a significant infrastructure and

human organization in order to provide treatment. Previous studies have demonstrated that EFP is uniquely effective in motivating psychiatric patients and facilitating treatment (Bizub et al., 2003; Burgon, 2003; Fitzpatrick & Tebay, 1997). Similar findings are also shown in studies with traditionally farm animal species (dairy cattle, beef cattle, sheep and goats) (Berget et al., 2007; Scholl et al., 2008, Pedersen et al., in press). However, Cawley et al. (1994) did not reveal any benefits from an eight-week intervention with a horseback-riding programme on self-conception among adolescents with special educational needs. To sum up, a variety of animal species can be used in AAIs, but it is recommended to restrict them to domesticated species, partly by considerations of the safety of the participants, and partly in order to ensure adequate animal welfare. The most feasible species are therefore companion animals, horses and farm animals.

10. Summary and conclusions

The prevalence of mental health problems is high and increasing. Many patients experience that they might not receive satisfactory treatment and rehabilitation in the traditional health care system, and it is therefore necessarily to investigate other and complementary interventions and therapeutic approaches. One such complementary intervention is AAI, with growing evidence of beneficial effects. The relationship between people and animals is complex, and should always be bi-directional and voluntary. Processes of human-animal interactions may partly be explained by a number of different models or theories, and most of these are based on theories developed for human-human relationships which are applied for human-animal relationships. These theories are not mutually exclusive; and probably there will be large individual differences in which theoretical framework that are most useful and adequate. There are several common concepts between Bowlby's traditional attachment theory and human-animal attachment, and it is hypothesized that animals could play an important role in creating emotional bonds, provide a secure base, and to assist in building representational models. Another theory is social support, and pets may offer a substitute for lacking human support, and thereby acting as a buffer against stress responses or illness. Furthermore, studies show that pets often acts as catalysts facilitating social contact between humans. The theory of biophilia emphasizes that humans through evolution have a natural tendency to focus on nature and life, and as a consequence there are beneficial relationship between nature, reduced stress and health. A release of the hormone oxytocin and decline in blood pressure and heart rate, are seen in several studies when people interact and have physical contact with a pet animal, and this might explain the reduced arousal, anxiety, and depression reported in several studies on AAI. Yet another relevant theoretical framework is Bandura's model of self-efficacy, and animals can be seen as living, interactive tools that can be used to help people add new skills and develop coping abilities. Even though several theories have been proposed, the theoretical framework of AAI is still insufficient. New theories should be developed that generate testable predictions of specific effects of human-animal interactions.

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6

Institutional Therapeutic Alliance in Multi-Professional Treatments with Severely Disturbed Patients

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1. Introduction

In this paper I would like to show some relevant issues to consider in the alliance assessment of severely disturbed patients treated in institutional contexts by a multi disciplinary staff. I will start with a brief review of a few relevant researches about the therapeutic alliance in such settings and I will introduce the need to distinguish the classical psychotherapeutic one-to-one alliance, from the alliance between the patient and the staff conceived as a whole. After that I propose a methodology to assess it and finally, I will show some evidence that supports this distinction and suggests its clinical relevance.

The therapeutic alliance with severely disturbed patients has two main particular complexities that must be taken into account if we want to explore and understand it: on the one hand, these patients show important difficulties to establish a significant one-to-one relationship with another. And on the other, the treatment of these patients involves many professionals from different disciplines, whom are very relevant for the patient not only because of their technical expertise, but because of their personal engagement with the patient and his/her healing process. While the first complexity has been studied in many different ways, the second one has been almost neglected, at least from an empirical research point of view.

In the fifties and sixties some authors used the social and relational psychoanalysis theorization to reflect and propose new forms of treatment. Balint, Rapoport, Laing and Maxwell Jones are some of the most relevant example of this Anglo-Saxon movement that developed various therapeutic interventions based on an interpersonal conception of psychiatric diseases. According to these authors, since a major portion of psychic suffering comes from problems related to human relationships and social interaction processes, treatment must consist, in the first place, in living again experiences of social interaction in a new relationship characterized by its therapeutic and re-educative nature. Initially, only psychotherapists or analysts were called to enter this role, but quickly authors like Rapoport (1960) showed that other figures, with which the patient establishes meaningful interactions, could accomplish the same function. In the same direction, the pioneer Peplau (1952/1991) - from nursing field - has developed in the early fifties the Interpersonal Relationship Nursing Theory. According her, the nurse-patient relationship is the essence of the psychiatric nursing work and constitutes a significant factor for patient's insight and change.

Following these points of view, nurses, social workers, occupational therapists and also other patients, contribute to the "relational" and "social" healing process of the patient. Actually, there is empirical evidence that confirms these clinical observations. The first one is a study of Ferguson and Carney (1970), which demonstrated that in therapeutic settings, where informal and spontaneous interaction is possible and frequent, the patient potentially develops significant and therapeutic relationships not only with the doctors, but also with nurses and social workers. And more recently, Gallop et al. (1994) have reached a very similar conclusion exploring an in-patient eating disorder unit, in which the patients established equivalents levels of alliance with the various members of the therapeutic staff, no matter their professional role.

Thus from a clinical and empirical perspective, seriously disturbed patients treated in institutional settings by an interdisciplinary staff, can establish significant relationships not only with the psychiatrist or the psychotherapist, usually considered as the most relevant figure, but also with every member of the therapeutic staff. These are very interesting findings if we consider the crucial and so well documented role of the Therapeutic Alliance in psychotherapy outcomes. In other words, can we consider the multiple significant relationships available for the patient in terms of multiple potentially therapeutic alliances? And, is this distinction relevant for clinical practice and research? If yes, the patient establishes the alliance with only one professional, with many of them, with the staff as a whole? A few authors have inquired these questions and, as we will see, they have proposed many different methodologies to study them.

2. Alliance assessment within the institution

The first two researches that explore the Alliance in a psychiatric inpatient setting were done in the mid-eighties. In 1985, Allen and his colleagues (1985) conducted a longitudinal study to observe the relationship between Therapeutic Alliance and outcomes of 37 inpatients, almost all psychotics or personality disorder patients. They find a positive correlation between psychological improvement and a growing of the alliance perceived by the therapists, so they conclude that therapeutic alliance and therapeutic changes are concomitant and interdependent processes. Two years latter, Clarkin and his collaborators (1987), using a quite similar design, study 96 psychiatric inpatients, finding that better alliance at the end of the hospitalization is positively associated with the patient's better global functioning. Both research have many methodological limitations, but beyond that, they are among the firsts examples in which the alliance was assessed using every member of the staff as a source of observation; in fact, both conceive the alliance as the patient's collaboration and active engage in the treatment and assesses it by calculating a mean of the therapist's perception of patients' behavior related with their healing process.

3. Patient and case-manager alliance

Other groups of researches explore the relevance of a positive alliance between the patient and his/her case manager. There are three interesting studies from the nineties that highlight the need to consider the alliance in institutional settings as an interpersonal phenomenon instead of the patient's collaboration with the treatment. Using a more relational definition of the alliance, all of them show that a good alliance between patient and case manager helps considerably the patient's therapeutic course and process.

Nonetheless, these authors have used different constructs of the alliance. On the one hand, in Germany Priebe and Gruyters (1993), assess the alliance perception of 100 out-patients, almost all psychotics, based on Lester Lubosrky's Helping Alliance model; while from the other one, in Australia two studies use the Working Alliance proposed by Bordin to measure the relationships of several case manager-patient couples respectively (Solomon, Draine & Delaney, 1995); Neale & Rosenhec, 1995). Neglecting many methodological limitations of these studies, they report interesting relationships among better patient-case manager alliance and quality of life improvements, pharmacological compliance, treatment satisfaction and symptoms reduction.

4. The alliance between the patient and all the staff members

Another interesting research in terms of its methodological innovation is the study conducted by Priebe and Gruyters (1994). They examine many variables that influence the course of the treatment in 30 day hospital psychiatric inpatients, and they find a predictive value of the Therapeutic Rapport established with the patient form the staff's perspective. As we can see, this is another conception of the alliance that involves an additional way to assess it: the staff's vision agreed by all its members.

In the same direction, the work of Mona Eklund (1996) in Sweden are probably the first empirical studies in which there is an accurate reflection on the enormous complexity and multiple dimensions and levels of the rapport that patients and therapists establish in this kind of treatment. She proposes a novel method to compare the alliances that the patient establishes with a reference or main therapist in contrast with two other secondary co-therapists engaged in the treatment. The study explores the relationship between the alliance and many outcomes indexes in 20 patients of a psychiatric day-care unit based on occupational therapy. The results suggest that the more the patient becomes attached to his/her main therapist instead of his/her co-therapists, the more he/she experiments improvement in his/her global mental health and occupational functioning (like motor and interpersonal skills, will and habits).

5. Steps towards an alliance with the institution

Finally, there are a few types of researches that inquire how the ward atmosphere and the characteristics of the staff influence the treatment success. Various authors from the seventies related mostly to Ocupational Therapy, suggest the patient's perception of several emotional and organizational dimensions of the therapeutic staff and milieu, are associated with therapeutic process and outcome.

In this context, the study of Eklund and Hansson (1997) constitutes one of the first research that explores these variables with a longitudinal design. They assess the ward atmosphere perception of 20 patients in a psychiatric day-care and find that two aspects of these variables are consistent and early predictors of therapeutic success: after one month of treatment, low levels of anger and aggression and of staff control intensity, both perceived by patients, are positively associated with symptom improvement.

It is quite interesting to understand this result as an adequate bond between the patient and the therapeutic staff. But not an optimal bond among the patient and the various figures involved in the treatment, like the alliance with the main or the co therapists, but between the patient and the staff perceived as a whole, as a cohesive and unitary therapeutic system.

In fact, recently Johansson and Eklund (2004) offer support for this thesis correlating some dimensions of ward atmosphere and the helping alliance perceived by the patient. In this sense, ward atmosphere and therapeutic alliance can be two different ways to understand the same phenomenon. Psychological tradition, mostly influenced by psychoanalysis, has described it in terms of working, collaborative and faithful rapport, or as the therapeutic alliance; Occupational Therapy tradition, more used to work and deal with an interdisciplinary staff, conceives it as the milieu of emotional and organizational atmosphere. Both perspectives ignore some aspects: the first one, doesn't take into account the group dimension of the alliance that develops in institutional multidisciplinary settings and centers itself exclusively in the singular relationships between patient and therapists; the second one, neglects the reciprocal and relational nature of the phenomenon since the atmosphere is mainly understood as a characteristic of the institutional functioning itself and not as result of the inter-subjective encounter among specific staff and patients.

6. Therapeutic alliance with the institution

This brief and non exhaustive review of the main empirical research in the field of Therapeutic Alliance in institutional settings with seriously disturbed patients shows us the complexity of the phenomenon and the need to distinguish it from the alliance that occurs in the psychotherapy setting. However, conceptual and operational definition of the alliance and the source of assessment are very heterogeneous from one research to the other: in fact, sometimes the alliance has been understood simply as the patient's collaboration with the treatment, other times as the quality of the patient and therapist's bond; occasionally the source of measurement has been the staff as a whole and at times each therapist separately; from time to time authors have assessed it using one generic question and other times with a well validated scale derived from the psychotherapeutic field.

As we can see in table 1, almost all of these researches have conceived the alliance as a one-to-one rapport between a therapist and a patient. Nevertheless, and considering ward atmosphere studies, it becomes quite interesting to inquire, other than the alliances "within" the institution, the alliance "with" the institution. That requires a reflection on a new assessment focus: the patient-staff relationship or the therapeutic alliance established between a single patient and a therapeutic staff understood as a whole.

In a recent paper, along with my colleagues from Bologna University, I have proposed the term of "institutional therapeutic alliance" (ITA) as a way to distinguish the alliance developed among a patient and the whole staff involved in his/her treatment, from the classical alliance established between a patient and a single therapist (Pulido, Monari, Rossi, 2006). Paraphrasing Bordin's formulation (1994), the ITA could be defined as a mutual understanding and agreement about goals and the necessary task of moving toward these goals along with the establishment of bonds to maintain the collaborative work between the patient and the therapeutic staff as a whole. As you can see, the definition emphasizes the relational and reciprocal character of the phenomenon and implicates that patient and staff have to negotiate and renegotiate many aspects of the treatment, from expectations, specifics therapies and therapeutic strategies, to interpersonal distance, setting issues and the rules and norms of the institution (Monari et al., 2005).

In fact, many mental health units, like day-hospitals, day care units, therapeutic communities, etc., instead of imposing a regular treatment they try to propose treatment programs adequate to the patient reality, for example, by structuring the patient's daily

schedule and his/her specific activities according to his/her personal characteristics and concrete possibilities. Probably an institution that is able to be flexible to the patient's needs and at the same time maintain its own organization and identity, has better chances to establish positive therapeutic alliances with his clients. In contrast, more rigid institutions may have difficulties to establish adequate levels of Alliances, since in such places patients are treated in a very standardized way and the therapeutic tasks and goals are decided unilaterally by the staff or even only by a head doctor.

The concept of ITA does not constitute a theoretical reformulation of Bordin's model, but rather a clinical extension to treatments in which two or more therapists are engaged at the same time in the patient's therapeutic process. As we described elsewhere, the notion presuppose that "*the whole staff, on the one hand, can represent itself as a unitary object to the patient, and on the other, that can operate and rapport with the patient as a cohesive unity*" (Pulido, Monari & Rossi, 2008, p. 278).

There are many clinical observations that support this hypothesis. Authors from the psychoanalytic field have explored the way in which the patient interacts with the staff and vice versa, and suggest that many times the staff rapports with the patient as an organic whole and appears in the patient's mind as a cohesive unitary object. In other words, in institutional multi-professional treatment, many times a bi-directional relationship emerges between a subject (the patient) and a group (the staff) that operates and moves itself as a compact whole.

For example, Correale (1991) and Enriquez (1988), two of the most important European authors on institutional psychoanalysis, account for interesting examples that show the relationship between a patient and a staff as a whole. The first one describes clinical examples in which a single patient modifies in a very significant way the normal functioning of the therapeutic staff, and the second one analyzes different situations in which the internal conflicts within the staff influence considerably and negatively the patient's symptomatic condition.

Another good example is the concept of institutional transference. This phenomenon – described for the first time by Rider (1953), and further developed by Martin (1989) – is a well known paradigm about how some seriously disturbed patients tend to defend themselves from establishing significant one-to-one relationships, investing an impersonal, more permanent, predictable and stable object such as an institution or an institutional staff. Just as the transference and counter-transference phenomenon, that within the psychoanalytical framework were first considered as obstacles to the analytical process and second, as central aspects of the treatment, the institutional transference phenomenon, historically conceived as a patient's resistance to engage into an analytical relationship, can be viewed as a treatment resource instead of a defensive process.

According to Zetzel (1956) and Bordin (1994), severely disturbed patients have so many problems to enter a one-to-one close relationship that the sole development of a therapeutic alliance in a dyadic rapport could be a positive and primary outcome index and most of the time, when it happens, it is the result of a very "*critical, extended and painful process*" (Bordin, 1994, p 27.) for almost every psychotic, schizophrenic, and borderline patient. That is the case for the classical psychoanalytical or psychotherapeutic work, but when this process occurs together with other co-therapeutic processes and involving more than one or two professionals in the global treatment that the patient feels interrelated and coherently connected, the patient has a chance to form a positive alliance with the staff as a whole, which supports and holds a potential establishing of one-to-one close relationships in a lower anxious and painful way for the patient. In this sense there is a very stimulating phenomenological study coming form the

field of psychiatric nursing research, that shows that many patients have difficulties to distinguish nurses or other figures from other operators and tend to refer to the "*staff in the aggregate*" (Thomas, Shattell & Martin, 2002, p. 104).

Source / *Construct*	*Patient*	*Therapist*	*Therapeutic Staff as a whole*	*Each Therapist individually*
Patient's collaboration				Clarkin et al. 1987 (psychiatric in-patient; n=96) Allen et al . 1985 (psychiatric in-patient; n=37)
Therapeutic bond	Priebe & Gruyters 1994 (psychiatric day hospital; n=30)		Priebe & Gruyters 1994 (psychiatric day hospital; n=30)	
Helping Alliance (patinet-therapipst)	Solomon et al. 1995 (patient and case manager; n=90) Neale & Rosenheck 1995 (patient and case manager; n=143)	Solomon et al. 1995 (patient and case manager; n=90) Neale & Rosenheck 1995 (patient and case manager; n=143)		
Working Alliance (patient-therapist)	Eklund 1996 (psychiatric day-care unit based on occupational therapy; n=20) Priebe & Gruyters 1993 (patient and case manager; n=100) Johanson & Eklund 2004 (psychiatric in-patient n=61)	Priebe & Gruyters 1993 (patient and case manager; n=100)	-	Eklund 1996 (psychiatric day-care unit based on occupational therapy; n=20)
Ward Atmosphere	Eklund & Hansson 1997 (psychiatric day-care unit based on occupational therapy; n=20) Johanson & Eklund 2004 (psychiatric in-patient n=61)			

Table 1. Therapeutic Alliance assessment in institutional settings

Nonetheless, this notion of the patient-staff relationship does not preclude the establishment of significant rapport among the patient and single therapists, but rather suggests that in institutional multi-professional settings we can verify two different levels of alliance. In fact, not always do the patient and staff produce a clear subject-group relationship. Occasionally, the patient develops a significant bond with some therapist and perceives the other therapists of the staff as forming a "nebulous group" of operators. Other times, the staff appears mostly as a group of singular and separate therapists with whom the patient interacts in different and specific ways and level of intimacy, establishing, for instance, a positive relationships with someone(s) and negative interactions with other(s) (Pulido, Monari, Rossi, 2008). Precisely, regarding this aspect, Correale (1991) observes that "*the investment of the institution, together with or instead of the investment of the single therapist, is a very usual evidence, for some extent inevitable, and always significant*" in the institutional work (pp. 172). Thus, regularly the patient engages at one with the single(s) therapist(s) and at another level with the institution including the staff as whole. Figure 1 represents the way in which these two levels appear in the interaction between a patient and a single therapist. The rapport established among them is conditioned by their mental representation about the staff and the patient-staff relationship. At the same time, these two-levels could be dissociated or fused, coexist in contradiction or in harmony and forming a synergic or a conflictive rapport among each other.

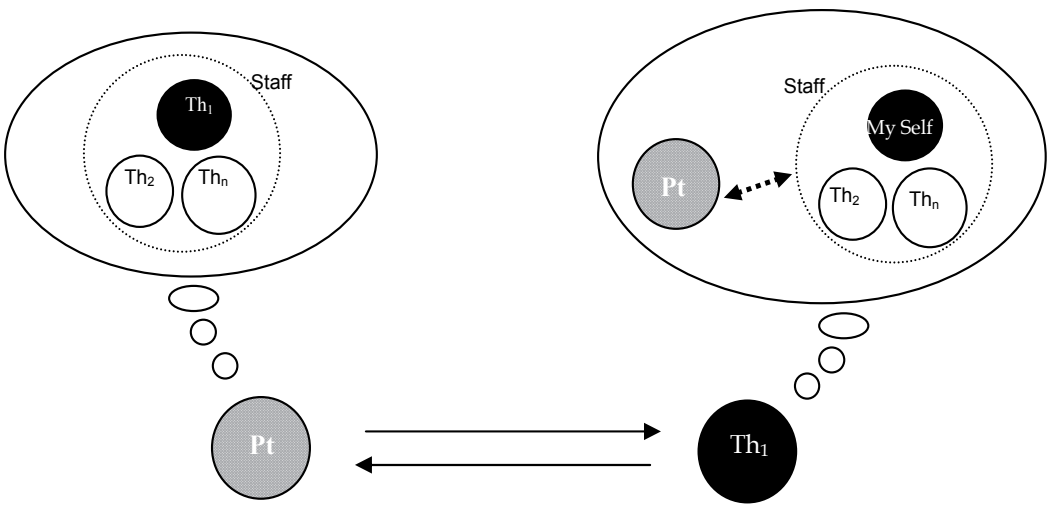


Fig. 1. Two relational levels within the patient-therapist interaction (*Note:* Pt = patient; Th = therapist)

7. Institutional therapeutic alliance assessment

We have collected some preliminary data that empirically sustain these hypotheses. We studied psychiatric patients from two day hospitals in Bologna, Italy, most of them with diagnosis of schizophrenia or personality disorder. Each therapeutic staff was conformed more or less by a head psychiatrist, four to six psychiatric nurses, a social worker, and a few postgraduate psychology students. They all maintained a direct, daily and continuous relationship with the patients. The institutions admit a maximum of 12 to 15 patients at the

same time and the length of the hospitalizations is around 6 weeks. The treatment consisted of pharmacotherapy and does not include any kind of psychotherapy. During the day, patients took their medicines and engaged in activities more or less organized, such as patients-staff meetings, socio-recreational activities and clinical interviews.

To assess the ITA we developed the Institutional Working Alliance Inventory – or IWAI – which has three main parts for patients and therapists:

1. The first part determines the presence of the two alliance levels (one-to-one and one-to-group) and the relationship between them. The patient answers the following general question: *In this staff there is a therapist (can be a doctor, a nurse, an occupational therapist, etc.) which is very close to me?* The patient answers YES or NO and then responds four items located under the YES or NO options. These four items explore the extent in which the presence or absence of a "close relationship" with one therapist coexists or does not coexist with a feeling that the rest of the staff is significant too. Total scores go from -4 to 4. Negatives values indicate absence or negative patient-staff alliance independently if there is or no an alliance with one particular therapist.

   In a pilot study with 39 patients (Pulido, 2010), we find that most part of the sample (54%) establishes high bonding with a single therapist and at the same time a positive relationship with the staff. Patients were consulted at discharge and as you can see in the table 2, only 10% does not perceive the staff as a source of contention and support, and many of the 90% that conceives it in a positive way does not establish a singular rapport with one of the therapists (14/35). This result suggests that we can describe three main patterns of therapeutic alliance within the institution: a) Alliance with one/therapist and the staff at the same time (64%); b) Alliance just with the staff (36%); and c) Alliance just with one-therapist (10%). And it seems that the first case is the most frequent, at least in our sample of day hospital psychiatric patient treated by a multidisciplinary staff.

Patient establish an…		… alliance with the staff as a whole?		
		Yes	***No***	***Total***
… alliance with one therapist?	***Yes***	21 (54%)	4 (10%)	25 (64%)
	No	14 (36%)	0 (0%)	4 (10%)
	Total	35 (90%)	4 (10%)	39 (100%)

Table 2. Two levels of therapeutic alliance (*Note. N=39)*

2. The second part assesses the quality of the therapeutic alliance with the focus on the patient-staff relationship. This part is an adaptation of the short form of the well-known Working Alliance Inventory developed by Horvath and Greenberg (1987). We transformed the original items in a way that they can account for a patient-staff relationship instead of a patient-single therapist rapport. There are 12 self-report parallel items for patients and therapists that they answer by using a 7-point Likert scale. It yields three 4-item added subscale scores – Task, Goal and Bond – as well as one overall score. Relative to the staff version, each therapist answers for himself. Then, overall and subscale scores correspond to the average of the staff members' values. In addition, a further index – the average of the item SD – indicates the internal agreement level of the staff's members, where lower scores indicate higher level of agreement. The

following is an example of an item in the patient and therapists version: *"I am confident in the staff's ability to help me"; "we are confident in the staff's ability to help (name of the patient) "*.

We tested the psychometric properties of the scale in a sample of 94 patients and two therapeutics staff (Pulido et al., 2010). Internal consistency and inter-rater reliability (for the staff version) reached adequate values: patient version shows an excellent reliability with a Cronbach's Alpha of .915, whereas the staff version shows adequate and significant reliability index between arbiters (ICC between .61 and .87; $p<.05$ in almost every item, except for two) and an ICC averages of .69 and .60 for each therapeutic staff. We also explored its factorial structure, and as many other authors, we did not confirm the classical three Working Alliance's dimensions of tasks, goals and bond. Instead of that, we found only one generic factor for the staff version which accounts for 79.8% of the variance, and three factors - one generic plus two secondary - for the patient form that account for 75% of the overall variance. The generic factor includes items about the quality of the professional relationships and the level of agreement with the treatment's goals and tasks, while the two secondary dimensions of the patient version refer, respectively, to negatives and meta-perceptive, or meta-communicative, aspects of the patient-staff relationships.

3. The third part verifies to what extent the patient answers the items of the II part thinking primarily at the staff as a whole, thinking in this or that therapist depending of the item, or having in mind just one specific therapist in almost all sentences. Our data shows that 78% of a total of 94 assessed patients at the end of the treatment, answered the scale actually considering the staff as a unitary and cohesive object and just few cases answered in the other two ways (Pulido, 2010).

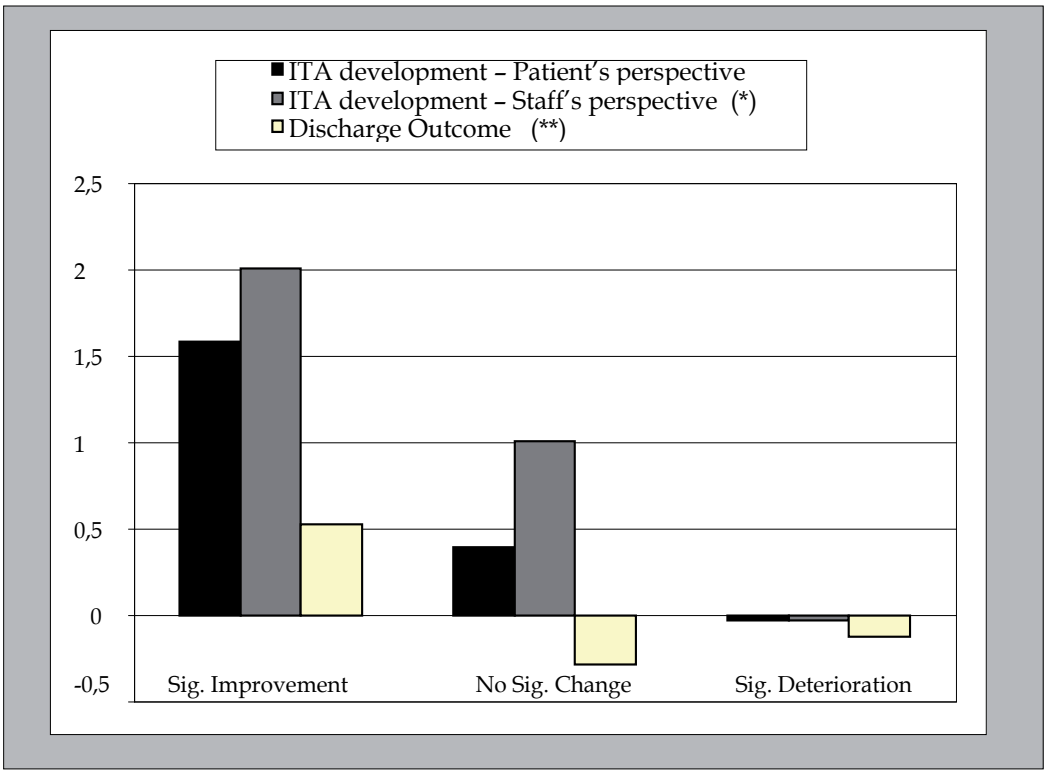
8. A longitudinal study

We conducted a longitudinal study to explore many aspects of the Institutional Therapeutic Alliance, like factors that influence its early formation and development, and its relationship with treatment outcomes (Pulido, Monari & Rossi, 2008). We assessed many variables in 55 patients in different steps of the partial hospitalization: admission, after one week, discharge and after 3-month from the end of the treatment. We found that initial ITA is not a good predictor of treatment success and that it is strongly influenced by the patient's feelings, expectations and attitudes toward several aspects of the treatment at admission. In fact, patients who began the treatment with a higher positive approach towards the treatment – that is more hope/trust and less fear/pessimism – in general report a higher perception of the alliance's quality with the staff after the first week of hospitalization ($r = .54$, $p < .01$).

The result suggests that early alliance would be strongly conditioned by several internal aspects of the patient that can obstruct the emergence of a real inter-subjective matching with the staff. In this sense, with severely disturbed patients the early alliance could be a sort of expectancy index toward the therapist(s) and the treatment, rather than an actual measure of the ITA. It is quite possible – considering the psychiatric severity of our sample and the complex dynamics of groups and institutions – that patients need more than one week of treatment to form a realistic image of the staff and to establish a relationship with its members.

In contrast with the low predictive value of the early ITA, we found that its positive growing during the treatment is a significant factor for therapeutic success and recidivism

prevention. Based on follow-up data of 31 patents, we formed 3 follow-up groups. 1) Patient with significant improvement; 2) patient with no significant change; and 3) patients who were re-hospitalized or presented significant deterioration after three month form discharge. As we can see in the graph 1, patients of the *significant deterioration* group, although they finished the treatment achieving symptomatic improvement similar to those of the *no significant change* group, show a poorer development of the alliance, which is statistically significant in the staff perspective.



Note. N=31. $^{**}p < .01$; $^{*}p < .05$. Numbers of the axis are Residual Gain Scores with pre-tests (symptoms and ITA) as baseline and post-test (symptoms and ITA) as dependent variable.

Graph 1. Discharge outcome and Variation of ITA in the 3-month follow-up groups (Pulido, Monari, & Rossi, 2008).

From a clinical point of view, this evidence suggests that the staff should consider its own perceptions of the in-treatment variations of the ITA and not exclusively the patient's symptomatic condition, in order to judge if the patient should be discharged or not. Usually, the alliance has been considered as a process variable that influences the treatment outcome, but it seems that in the case of severely disturbed patients – at least when they are treated in institutional settings – it would be important to consider it as an outcome variable by itself. The results, confirm some aspects of Peplau's intuition that what help to the patient recovery, more than an adequate early or initial patient-psychiatric nurse relationship, is the capacity to move form an orientation to a resolution phase of the relationship (Stockmann, 2005).

All together, this evidence shows us the relevance of studying the therapeutic alliance in institutional contexts and the need to differentiate it from the dyadic alliance studied in psychotherapy settings. The studies I just have presented have many methodological limitations like the heterogeneity of the sample and the outcome assessment (we used only a self-report measure from patient's perspective), but constitute the first empirical data to support the idea of two different levels of the alliance in multi-professional settings and the importance of the level of the patient-staff relationship, that we call Institutional Alliance, to reach good outcomes and to prevent re-hospitalization or deterioration of discharged severely disturbed patient.

9. Questions for further research

There are so many questions still open that need further empirical inquiry. First of all, we need to understand better the relationship between the two levels of alliance and the way in which they relate with treatment process and outcome. Are they independent processes? If they are, how they influence each other? At the same time, we should continue the developing process of the Institutional Working Alliance Inventory, using bigger samples to confirm its psychometric properties and generalize it to other settings and cultural contexts other than Italian day hospitals. And last, but not least, there is a very important issue, almost unexplored empirically, regarding the characteristics and dynamics of therapeutic staff that relate positively and negatively with fruitful negotiating institutional alliance processes. For example, in clinical practice we can distinguish different kinds of therapeutic staff that probably influence both of the alliance levels we are talking about: from pseudo-staffs in which the professionals are not bonded to each other in a collaborative, complementary and interrelated fashion to help the patient; to mature staffs in which the different professionals feel a relevant part of the therapeutic system and constantly reflect about their practice to become adaptable and flexible to the patients' needs without renouncing to the staff's own identity and coherence.
In synthesis, there are so many hypotheses to verify, methodological issues to improve and conceptual distinctions to do, but one thing is quite sure: the therapeutic staff is more than a sum of multi professionals' expertise and could become a significant therapeutic tool for the severely disturbed patient's healing process.

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Quality of Life in Mentally Ill People

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1. Introduction

It is much easier to measure any of biological parameters than to describe any of them. Medical science is more „evidence based" when can be expressed by parameters represented by amount of numbers describing functions in a body. Unfortunately, thanks to statistical approach to the medical science, philosophical or psychological dimensions disappear when considering the human life and its pathologies.
Quality of life seems to be a good example of controversy seen in medical science of nowadays. On one hand, quality of life in medicine seems to be too vague to be defined by conventional, measuring loving approach, and in this way it is postponed just as an additional parameter standing in a rest, on the other hand, quality of life represents integral feature which refers to complex evalutation of our therapy from patients point of view.

2. Quality of life – evolution in understanding the term

It is troublesome to define what is the quality of life. Everyone has individual and unique experience with every day life bringing both positive and negative aspects. Our evaluation of (our) quality of life is surely influenced by many individual aspects that can refer only to our experience. But can we generalize this individual experience to experience of the others? If so, what is relevant and what is irrelevant in evaluating one´s life from external or expert position?
Althought many difficulties, scientists tried to develop more precised concepts of understanding quality of life. These concepts have been influenced by evolution in understanding other important terms, such as health, disease and determinants of health.
The modern concept of the quality of life has been developed for more than 90 years. Soon after World War II, mainly material and economic conditions were considered to have an influence on the perceived quality of life. At that time, employment and good living conditions were the main prerequisite for having a good quality of life. Later, with the development of medicine and the society, new factors influencing the quality of life emerged, such as social, political, psychological, environmental and spiritual aspects, accompanied by the concept of new lifestyle demands.
In the 21st century, medicine (and psychiatry as well) is facing new challenges, different from those in previous centuries. The prevalence of non-communicable diseases, such as obesity, hypertension, diabetes mellitus, musculoskeletal disorders and other conditions,

reached the level of new pandemics replacing the earlier pandemics of infectious disease (tuberculosis, poliomyelitis etc.), having both economic and ethical impacts. Demographic changes in the population have postponed morbidity to an older age as people live longer now. This is related to comorbidities in the elderly, growing in number and exceeding the population of children and adolescents. Generally, the economic and social impacts of this demographic shift are expected to occur in most of the developed world.
The shifts in morbidity and mortality are well observed and recognized, with people dying at an older age and with more diseases. The most common cause of death are cardiovascular diseases followed by cancer. This situation is in the Czech Republic, too. As many of these conditions cannot be cured completely, they considerably influence the health-related quality of life the elderly patients. An approach to treatment with respect to the biopsychosocial concept of a human being may be an important way to improve the quality of life of the elderly and dying patients.

2.1 Human and human´s needs

Historically, the oldest concept was based on identifying first parameters of human satisfaction – human needs. First, material conditions were taken into account – living in poverty implied low quality of life and vice versa. This idea was close to policy makers who were interested in social and material indicators of well being.
Later, other conditions were studied – material, social, cultural, psychological and spiritual ones. The most complexed theory of human needs was presented by american psychologist Abraham Maslow. Maslow has ranged human needs into hierarchy according to their importace. First of importace are basic (or physiological) needs – they allow us to survive – and they are the first essential step to achieve *higher*, more developped needs. When these *lower* needs were fulfilled then it was an elementary precondition for a man to be satisfied – no shortcoming in considered need limited expected satisfaction. Graphically, hierarchy of human needs is represented as a pyramid where the more basic needs are situated at the bottom. (see fig. 1). Maslow theory of human needs promoted further thinking what is the quality of life and what are the influencing indicators of quality of life.

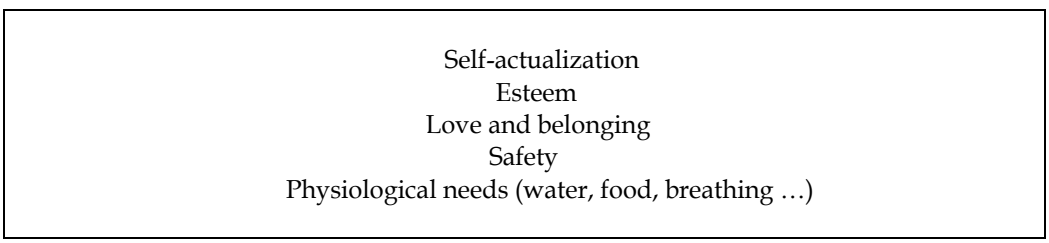

Fig. 1. Maslow´s hierarchy of needs

2.2 From spiritual and philosophical concepts to the concept of Health Related Quality of Life (HR-QoL)

Theory of human needs seemed to be essential when considering quality of life. It showed people need more than good functionning of all body systems – they need feel to live in safety, to be accepted by a community of other people, to feel good self-esteem, to have individual perspective reflecting one´s wishes and dreams. Later then, medical point of view has been accompanied by psychological, spiritual, social and spiritual dimensions

intersecting in one term – quality of life. Despite diversity in some of aspects mentionned above, simplified concept of health related quality of life showed its importance.
Health related concepts of quality of life seemed to be much better understood and much better accepted by health care professionals, especially when evaluating outcomes of therapy or any other intervention, with special attention to therapy which seems to be is expensive or troublesome (typically in oncology or intensive care). The Karnofsky Performance Scale (measured by the decimal Karnofsky score, where 100% represents ideal or perfect health status and 0% represents death, see fig. 2)isused in oncology to evaluate patient´s fitness before starting and during oncological treatment, or the APACHE II. evaluation system (Acute Physiological and Chronic Health Evaluation Systém, with total score from 0 to 71, where higher score means more serious condition with higher risk of death) used to evaluate patient´s fitness in intensive care could be good examples. (see fig. 3)

100% – normal, no complaints, no signs of disease
90% – capable of normal activity, few symptoms or signs of disease
80% – normal activity with some difficulty, some symptoms or signs
70% – caring for self, not capable of normal activity or work
60% – requiring some help, can take care of most personal requirements
50% – requires help often, requires frequent medical care
40% – disabled, requires special care and help
30% – severely disabled, hospital admission indicated but no risk of death
20% – very ill, urgently requiring admission, requires supportive measures or treatment
10% – moribund, rapidly progressive fatal disease processes
0% – death

Fig. 2. The Karnofsky Performance Scale

1. Age
2. Hematocrit
3. White Blood Count
4. Rectal temperature
5. Middle arterial pressure
6. Heart rate
7. Respiratory rate
8. Serum sodium level
9. Serum potassium level
10. Level of oxygenation
11. Arterial pH
12. Serum Creatinine level
13. History of severe organ insufficiency
14. Glasgow Coma Scale score

Fig. 3. The APACHE II. evaluation system - issues (calculator for obtaining the total score is needed)

2.3 Multidimensional concept of quality of life – more than just medical approach

Multidimensional concepts are the most developped and the most complexed concepts dealing with quality of life. These concepts combine traditional material and health-related approach with further dimensions, such as spirituality, self esteem, well-being, autonomy and competences, or acceptance by community and usefullness of an individual in community. They reflect global fitness of an individual when living in everyday society. Thence, ecclectical approach is typical in multidimensional concepts of quality of life. WHO Model of quality of life could be an example of such koncept (see chapter bellow).

Despite its intended complexity, they cant define entirely what quality of life is in general. Any interpretation of one´s quality of life or any comparison of quality of life among individuals will cause methodological difficulties.

3. How to evaluate quality of life?

As mentionned above, quality of life is a complex category comprising many aspects: physical and mental condition, social networks, and environmental, educational, economic and cultural aspects of an individual. The quality of life is highly subjective and its evaluation is problematic. It can be evaluated on different levels – individual level, group level (e.g. group of patients with a disease) or population level.

Two different methodological approaches can be used – qualitative and quantitative approach.

3.1 Qualitative approach in research of quality of life

Qualitative approach in research of quality of life requires more intense contact with individuals evaluating quality of life. This approach seems to be less exact for further statistical analysis because of using less standardized procedures even though it can reveal many important, individually specific aspects of quality of life.

The most common techniques of qualitative research of quality of life are inspection, interview, focus groups, content analysis of texts or documents.

3.2 Quantitative approach in research of quality of life

Quantitative approach in research of quality of life refers to measuring different aspects and parameters of quality of life. It uses more standardized procedures which can be perceived as more exact and more accessible to statistical analysis of data. Neverthless, t here is a risk of neglecting some of individually specific aspects of quality of life and thence of misleadings.

When studying the quality of life, questionnaires are most frequently used. Nowadays, there are hundreds of questionnaires available that can be found in the ProQolid database of psychometric instruments. This database comprises, among others, tools for assessing the quality of life, divided according to the research aim into generic instruments (used for the whole populations, both healthy and ill), disease-specific instruments (related to certain diseases, such as HIV or cancer) and target-population instruments (related to target populations, such as children or senior citizens).

The most common techniques of quantitative research of quality of life are questionnaires, studying of medical records, statistical surveys, structurized inspection.

Questionnaires of quality of life are a very popular tool – they are easy to be used in clinical practice, despite having limits (reduction of information, statistical trstiny of hypotheses, problems with generalization of results and interpretation of summarized results).

ProQolid database (Patient Reported Outcome Quality of Life Instruments Database) is collecting many of questionnaires used in research of quality of life – they are devided into generic instruments, disease-specific instruments and instruments used for targeted population.
Generic instruments can be used for any group of patients or healthy individuals. They can be used for a population research of quality of life as well. Thein disadvantage can be perceived in lower sensitivity in detection of any of strong influencing phenomenon (such as a disease). Some examples of generic instruments in ProQolid database are attached bellow:

AQoL Assessment of Quality of Life
CSQ Client Satisfaction Questionnaire
EQ-5D Euroqol EQ-5D
GQoL Global Quality of Life Scale
HAQ Health Assessment Questionnaire
PedQL tm Pediatric Quality of Life Inventory™
PLC Quality of Life Profile for the Chronically Ill
PQoL Perceived Quality of Life scale
QL-Index Spitzer's Quality of Life Index
QALYs Quality Adjusted Life Years
QLI Ferrans and Powers Quality of Life Index
QLQ-E Quality of Life Questionnaire-Evans
QLSI Quality of Life Systemic Inventory
QODD Quality of Dying and Death
QOLI Quality of Life Inventory®
QOLS Flanagan's Quality of Life Scale
QUEST Quality of End-of-life care and Satisfaction with Treatment scale
QWB Quality of Well Being scale
QWB-SA Quality of Well-Being scale Self-Administered
SAS-SR Social Adjustment Scale - Self Report
SEIQoL Schedule for the Evaluation of Individual Quality of Life
SF 12 SF-12® Health Survey and SF-12v2™ Health Survey
SF 36 SF-36® Health Survey and SF-36v2™ Health Survey
SQLP Subjective Quality of Life Profile
SWED-QUAL Swedish Health-Related Quality of Life Survey
TAAQoL TNO-AZL TNO-AZL Questionnaire for Adult's Health-related Quality of Life
TACQoL TNO-AZL TNO AZL Children's Quality of Life
TAPQoL TNO-AZL TNO-AZL Preschool children Quality of Life questionnaire
TEAQV Tableau d'Evaluation Assistée de la Qualité de Vie
TedQL Quality of Life measure for children aged 3-8 years
WANQ Wyke's Assessment of Need Questionnaire
WHOQoL World Health Organization Quality of Life assessment instrument
WLQ Work Limitations Questionnaire
YQoL tm Youth Quality of Life Instrument

According to ProQolid Database

Fig. 4. Generic Instruments – Examples (ProQolid Database)

Disease-specific instruments are used for group of patients suffering from studied disease. They monitore impacts of a disease on patient´s common life. Some examples of disease-specific instruments in ProQolid database are attached bellow:

Q-LES-Q Quality of Life Enjoyment and Satisfaction Questionnaire
PTQL Pictorial Thai Quality of Life
QLQ-IR/QLQ-SR Oregon Quality of Life Questionnaire Interviewer Rating version / Respondent Self-Report version
W-QLI Wisconsin Quality of Life Index
ACQLI Alzheimer's Carer's Quality of Life Instrument
ADRQL Alzheimer's Disease-Related Quality of Life
QoL-AD Quality of Life in Alzheimer's Disease
QUALID Quality of Life in Late-Stage Dementia Scale
CBS Cornell-Brown Scale for Quality of Life in Dementia
D-QoL Dementia Quality of Life Instrument
DEMQoL Measurement of health-related quality of life for people with dementia
QOLAS Quality of Life Assessment Schedule
QLDS Quality of Life in Depression Scale
SLQQ Sexual Life Quality Questionnaire
ILSS Independent Living Skills Survey
LQOLP Lancashire Quality of Life Profile
QLQ/CEQ Quality of Life Questionnaire or Client Experiences Questionnaire
QLS Quality of Life Scale
ONYCHO Onychomycosis Quality of Life questionnaire
APQLQ Angina Pectoris Quality of Life Questionnaire
MILQ Multidimensional Index of Life Quality
CHAL Quality of Life Questionnaire for Arterial hypertension
MINICHAL Short form of Quality of Life Questionnaire for Arterial hypertension
MacNew MacNew Heart Disease Health-related Quality of Life Questionnaire
LVQoL Low Vision Quality-of-Life Questionnaire
GlauQoL Glaucoma Quality of Life Questionnaire
NEI-RQL-42 National Eye Institute - Refractive Error Quality of Life Instrument – 42

According to ProQolid Database

Fig. 5. Disease-Specific Instruments – Examples (ProQolid Database)

Instruments for targeted population are used for studying quality of life of specific population, such as children, adolescents, adult men, war veterans etc. They depict characteristic feature of such population. Some examples of instruments for targeted population in ProQolid database are attached bellow:

Children **(SCLQI-**Children's Dermatology Life Quality Index, **COHQoL**- Child Oral Health Quality of Life Questionnaire apod).

Adolescents **(JAQQ-**Juvenile Arthritis Quality of Life Questionnaire, **Stoma-QOL**-Stoma-QOL)

Caregivers **(PSQI-**Pittsburgh Sleep Quality Index, **MCSI**- Multidimensional Caregiver Strain Index)

Terminally ill patients **(HQLI -** Hospice Quality of Life Index apod.)

Adult men (**N-QoL** Nocturia Quality of Life Questionnaire, **PC-QoL** Prostate Cancer Quality of Life scale)

According to ProQolid Database

Fig. 6. Targeted Population Instruments – Examples (ProQolid Database)

3.3 WHO model of quality of life

The WHO has been trying to define and evaluate the quality of life since its first definition of health in 1946. From that time on, health-related aspects of the quality of life have prevailed. For its assessment, numerous methodological tools were developed: the performance status, APACHE scoring system, quality of life indices (with the Karnofsky score being the best known), self-rated quality of life scales, quality of life questionnaires (with the EuroQol, SQUALA or WHOQOL questionnaires being the most widely used), individual interviews or focus groups. Any of the above-mentioned tools for measuring the quality of life can be used at different levels: an individual level – evaluating the quality of life in individuals, a group level – assessing the quality of life in groups of patients or people, and a population level – measuring the quality of life in populations of patients suffering from certain diseases or undergoing some therapeutic modalities.

The WHO model of the quality of life and WHO questionnaires are highly appreciated for their complex and practical approach to the quality of life. The WHO model describes the quality of life as a very heterogeneous, specific, individual and sophisticated category which can only be understood in its complexity. The WHO formed working groups for developing psychometric instruments measuring the quality of life and this painstaking research and work aimed at designing questionnaires lasted for more than 15 years before these could be used in practice.

The WHO questionnaires have good psychometric characteristics and are highly recommended for research into the quality of life.

Traditionally, research into the quality of life has been the domain of somatic medicine (the quality of life in patients with HIV, cancer, rheumatological conditions, after transplantations or undergoing some therapeutic modalities). However, the first studies concerned with the quality of life in psychiatric patients, such as those with mood disorders or schizophrenia, have been carried out in many countries all over the world. Unfortunatelly, research into the quality of life of the elderly patients with psychiatric morbidity in institutional care is rare up to now.

Some of the WHO Quality of life questionnaires are listed bellow:

- WHOQoL 100- 100-items WHO questionnaire of quality of life – general population
- WHOQoL BREF–26-items WHO questionnaire of quality of life – general population
- WHOQoL OLD – 33-items WHO questionnaire of quality of life – suitable for seniors
- WHOQoL-HIV-WHO questionnaire of quality of life for patients with HIV positivity
- WHOQoL Children – WHO questionnaire of quality of life for children population
- DIS-QoL – WHO questionnaire of quality of life for people with disabilities

Fig. 7. WHO Quality of Life Questionnaires – Examples

4. Quality of life in psychiatric disorders

4.1 Organic disorders

Dementia is one of the most common psychiatric condition in senior population. Its prevalence estimation is about 5% of population at the age of 65, with further exponential increase in association with age. Etiology of dementia is represented by more than 60 various cause, the most common is atrophic – degenerative cluster (dementia of Alzheimer´s type, Lewy body disease, frontotemporal dementia, subcortical dementia etc.) followed by cluster of symptomatic dementia (vascular dementia and other symptomatic dementia).

According to research, patients with dementia generally experience worse quality of life compared to seniors without dementia (Hoe et al, 2006). Seniors with dementia living in community tend to retain higher autonomy compared to seniors hospitalized because of any of mental disorders (Hoe et al., 2009, Spector and Orrel, 2006).

In Czech republic, we have designed a unique, cross sectional study. We have chosen Kromeriz region to compare quality of life of seniors living in community without dementia, then of seniors without dementia hospitalized in geriatric wards because of somatic disease and finally of seniors with dementia hospitalized in inpatient psychogeriatric ward. The last group of seniors had significantly the worst quality of life, compared to formel groups of seniors. Seniors who were hospitalized in psychogeriatric ward experienced significantly the highest risk of social exclusion, loneliness, refusal of patient families, loss of autonomy with dependence on health care professionals in performing activities of daily living and last, these seniors had the highest risk of long term hospitalization. Mentally ill seniors hospitalized in psychogeriatric ward were at highest risk of developing major depression and further acceleration of dementia (cognitive decline and decline in non-cognitive symptoms). Positive correlation between decline in cognitive functions (measured by Mini-Mental state examination, MMSE) and lowered quality of life in seniors was found (see fig. 8). Deterioration in functionning (represented by activities of daily living, ADL) and worsening of the quality of life in seniors with dementia correlates significantly (see fig. 9). Guardianship in relation to quality of life in seniors was studied by Jurickova (Jurickova et al, 2011).

As for gender in our research, women formed more vulnerable group of seniors compared to men (Luzny, 2009).

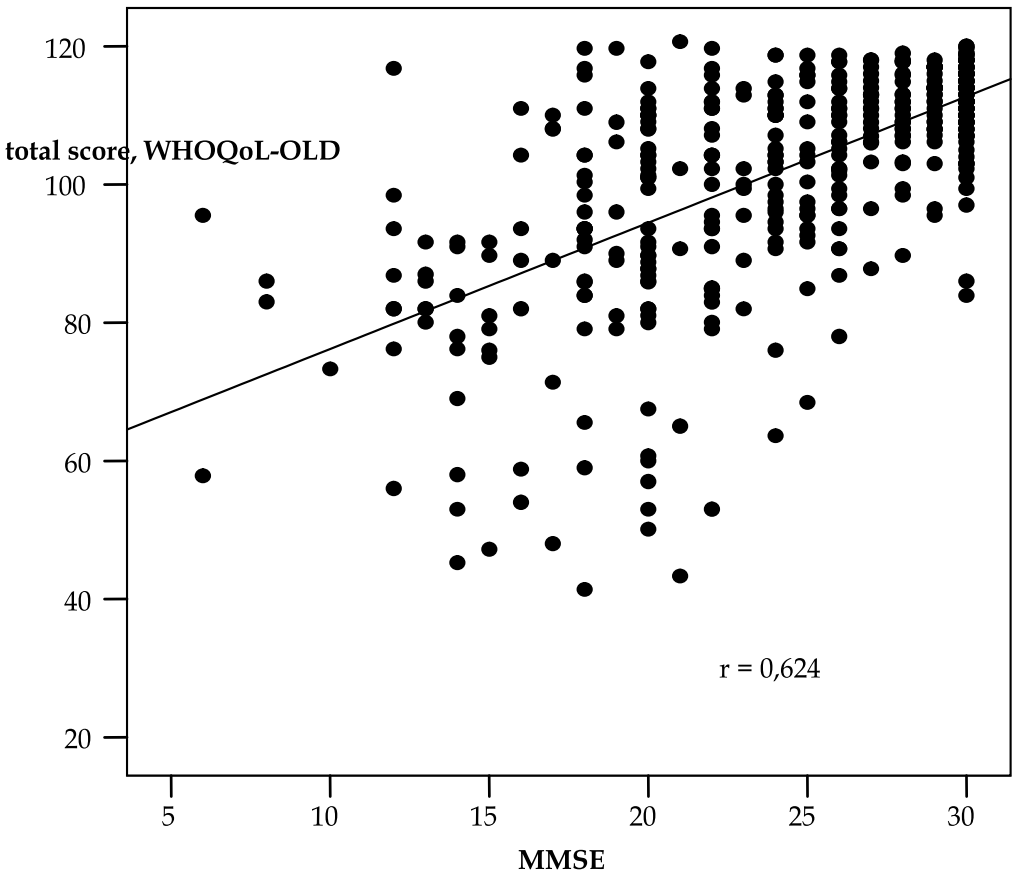

Fig. 8. Correlation between decline in cognitive functions and lowered quality of life in seniors with dementi

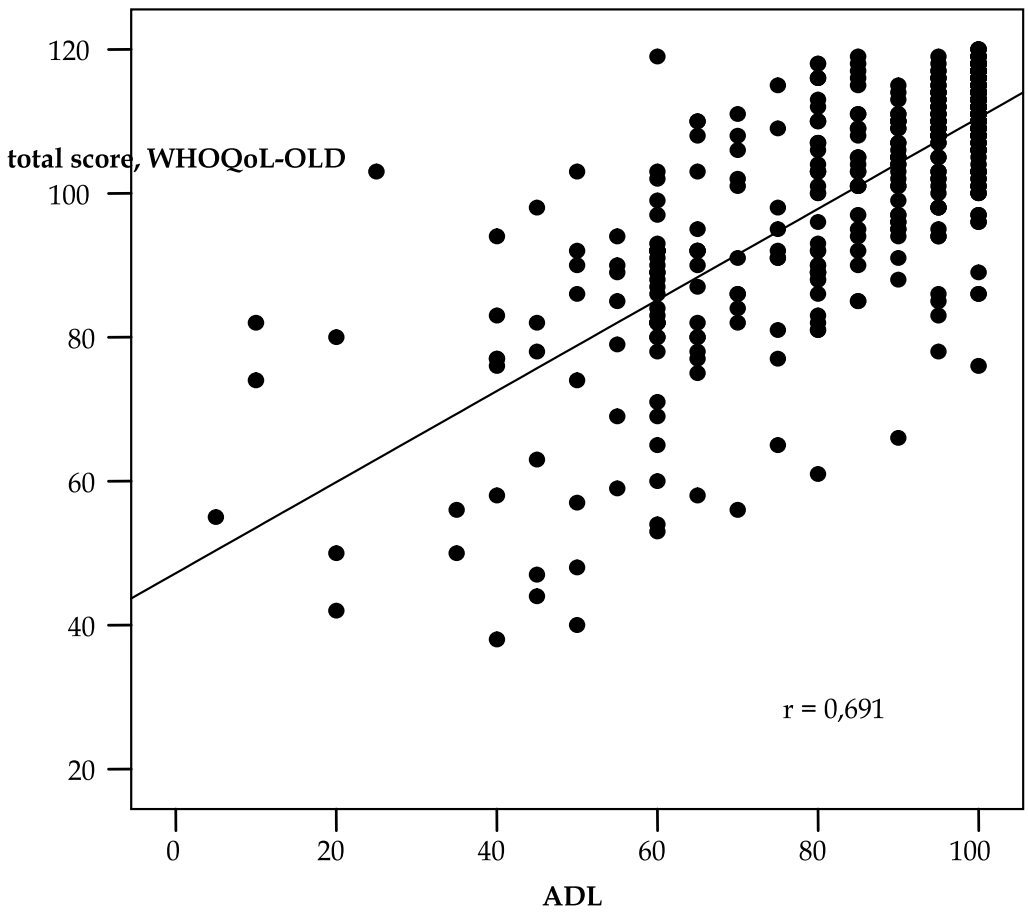

Fig. 9. Correlation between deterioration in functionning (activities of daily living, ADL) and quality of life (total score WHOQoL OLD) in seniors with dementia

4.2 Substance abuse disorders

Psychoactive substances attracted human attention from all times through history. Prevalence of experience with psychoactive substance in general adult population ranges from 25% of population as for smoking to 90% of population as for experience with drinking alcohol. 33% of population has lifetime experience of at least one illegal drug (Semple et al, 2005).

Abuse disorders cause many of social, economic and health related problems - unemployment, homelessness, divorces and high rate of criminality are on top of the problems. Researchers showed significantly worse quality of life of patients with substance abuse disorders compared to healthy control groups. On contrary, treatment of substance abuse disorders improved level of social functionning of addicted patients with secondary increase in perceived quality of life of these patients. Social and psychological conditions influencing quality of life in substance addicted patients were studied by Czech researcher Donkova (Donkova, 2009).

4.3 Schizophrenias

Schizophrenia is severe long-lasting psychiatric disorder changing thinking, perception or altering behaviour towards the others in acute phase of this disorder, in chronic phase of disorder, self-esteem, self-confidence, functionning in community or autonomy is usually altered too. Treating schizophrenia usually requires life-long adherence in therapy, what cause problems and leads to relapse of a disease (Staring et al, 2009). Schizophrenia is typical psychiatric disorder which is stigmatizing an individua and worsening his or her positron in community. All aspects mentionned above are worsening quality of life in patients with schizophrenia (Chromy, 1995).

4.4 Affective disorders

Affective disorders include broad spectrum of disorders characterized by pathological mood. Depression is one of the most common conditions in this cathegory (unipolar, bipolar or recurrent type). Anhedonia is worsening quality of life of depressed patients, together with apathy, abulia and dyssomnia (Ay-Woan et al, 2006). Positive correlation between depressivity in seniors (measured by Geratric Depression Scale, GDS) and low quality of their lives was found by Luzny (Luzny, 2009) – see fig. 10.

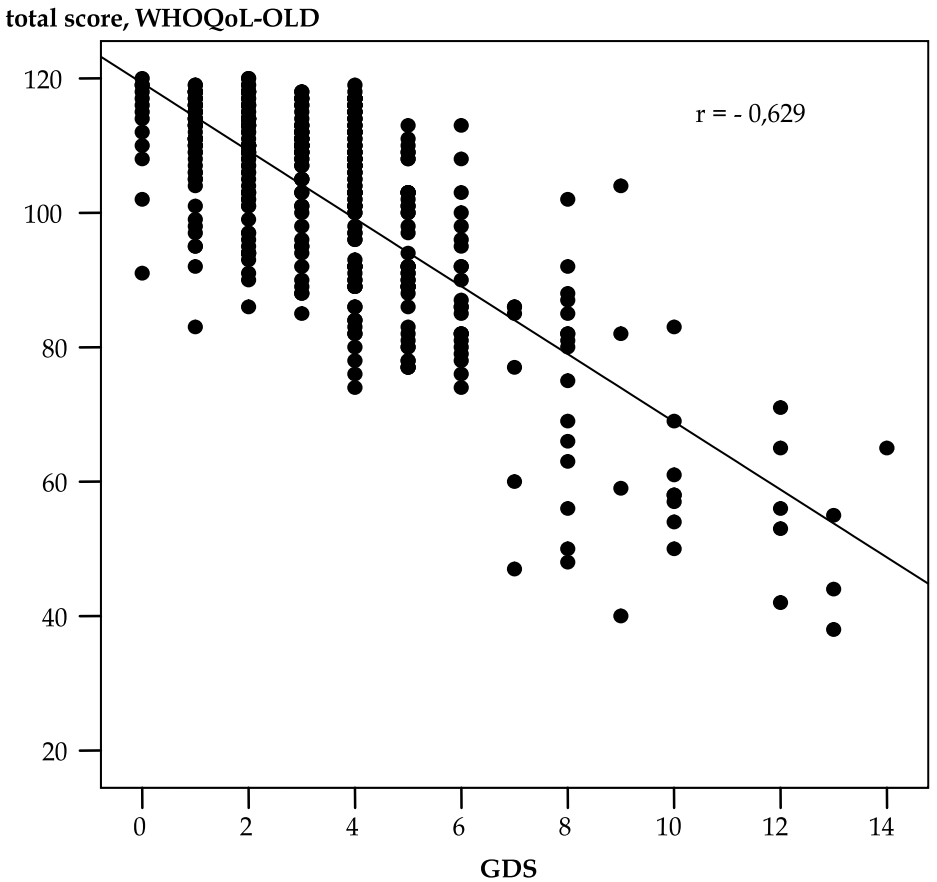

Fig. 10. Correlation between depressivity ald quality of life in seniors

4.5 Anxiety and stress-related disorders

Stress-Related disorders are one of the most common conditions in psychiatry. In developped countries, the prevalence of this cluster of mental disorders in general population is about 8.9% (Semple et al, 2005). Althought these disorders, formely called neuroses, don´t alter seriously essential parts of human psyche, they affect satisfaction with life and lead to worsening of quality of life (low self-confidence, low self-esteem, feelings of exhaustion, feelings of worsening in labour and daily life activities). Beard et al. have studied health related quality of life across the anxiety disorders and have described such correlations (Beard et al, 2010).

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Part 3

Physical Aspects

8

Interaction Between Inflammatory State and Neurochemical Changes in Major Psychiatric Disorders

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1. Introduction

Inflammation is the immunological mechanism to react against danger signal. In old days, inflammation is characterized by heat, redness, pain, swelling and loss of function in gross appearance and inflammatory cells infiltration to the affected area in microscopical appearance. Even though it is not always possible to demonstrate the inflammatory cells infiltration in certain part of brain area in patients with psychiatric disorders, there are evidences such as enhanced production of inflammatory mediators that indicated the reaction of the immune system. It is generally considered that immune reactions occur in response to a danger signal such as abnormal cell death. With time, scientists in both immunology and neuroscience fields realized that the danger signals occur not only due to microorganisms, foreign bodies or tissue injury but also some noxious situations such as psychological or emotional stress.

The involvement of immune system in psychiatric disorders is, in fact, recognized since 1927 by Wagner-Jauregg, the only psychiatrist who ever awarded Noble prize for his work on malaria inoculation in treatment of dementia paralytica (Raju, 1998) which was the treatment of psychosis by inducing fever, known as 'pyrotherapy'. That evidence indicated that the immune activation induced by infection could cure the psychotic symptoms since fever is associated to immune activation. On the other hand meningitis induced toxic psychosis without fever was reported by Fischer, 1963. Taken together, in the field of Medicine, the relation between infection, inflammation, fever and psychotic symptoms became of interest since early 20th Century. Around similar period, in the field of Biology, Selye (Selye, 1954) has reported that the neurogenic stress situation induced by forcible immobilization could effectively inhibit inflammation in the experimental granuloma-pouch under the dorsal skin of rat after chronic irritation with cotton wool and that reaction was abolished in adrenalectomized rats. That finding indicated that the anti-phlogistic effect or suppression of immune activation was largely dependent on secretion of anti-phlogistic corticoids from the adrenal glands. That was the earliest starting point indicating the effect of stress on the immune system although it was difficult to conclude if the immobilization is

physical or emotional stress, in other words, if that suppression of immune activation induced by external agent came centrally.

In 1975, Ader and Cohen reported that immune suppression could be induced by behavioural condition (Ader and Cohen, 1975). That was the clear demonstration that peripheral immune system could be influenced by emotion or behavioural manipulation. In the following years, the body and brain crosstalk through immune system became of interest in pathophysiology of psychiatric disorders. In 1987, the low natural killer cell activity in patients with depression was reported (Irwin et al., 1987). In early 1990s "sickness behaviour" was proposed as peripheral immune activation induced depressive like behaviour based on the fact that injection of bacterial toxin, lipopolysaccharide, peripherally could induce depressive like behaviour (Bluthe et al., 1992). They also reported that sickness behaviour induced by peripheral immune activation was reversed by administering the antagonist of interleukin-1 (IL1) receptor. While sickness behaviour is, unlike major depressive disorders, a short term syndrome, the symptoms of sickness behaviour such as lack of interest, inability to concentrate, loss of appetite, disturbance of sleep and social anhedonia are the similar symptoms as in depression. Thus, immune activation in the periphery was considered as part of the pathophysiological mechanisms of major depression and anti inflammatory medication or manipulation of immune system became of new therapeutic interest.

The first theory on the immune activation in psychiatric disorders proposed was "macrophage theory of depression" (Smith, 1991) in which the association between cytokine secreted from macrophage and hypothalamus activity were proposed as pathophysiological mechanism of major depressive disorder. This theory has highlighted the interaction between immune system and endocrine system which could influence the emotion and higher function of the human brain. Based on the finding related to the connection between lymphocyte function, hypothalamo-hypophysial-adrenal axis and depression which indicated the impaired lymphocyte response to mitogen stimulation (Maes et al., 1989), the macrophage theory of depression was extended to monocyte-lymphocyte hypothesis of depression (Maes et al., 1995). The same authors have also extended the hypothesis to another major psychiatric disorder, schizophrenia (Smith and Maes, 1995). It was discussed that the cytokines, such as, IL1 and IL2 in low concentration could enhance the dopaminergic neurotransmission whereas high IL2 could suppress it. Around this period, the impairment of neutrophil and macrophage phagocytoses in depressed patients was also reported (McAdams and Leonard, 1993). Changes in immunoglobulin, complement and acute phase protein levels were also reported in patients with depression (Song et al., 1994). Also in late 1080s, Nishino and colleagues has first demonstrated the prostaglandin E2 (PGE2), an enzyme involved in inflammatory process is increased in the saliva of depressed patients (Nishino et al., 1989).

Based on the different subtypes of immune cells, some studies explore the ratios between different subsets of T-lymphocytes and demonstrated the higher T-helper/T-suppressor cytotoxic cell ratio in depressed patients (Maes et al., 1992). The enhanced T-helper type 1 immune response which is associated with development of inflammation was proposed in major depressive disorders. Similar development in research related to inflammatory response and schizophrenia also occur around this later 20th Century and the beginning of 21st Century. The increased T-helper type 2 cells in the blood of patients with schizophrenia were reported and the dominance of T-helper type 2 reaction was suggested (Sperner-

Unterweger et al., 1999). Based on this finding "Th-2 hypothesis of schizophrenia" was proposed (Schwarz et al., 2001). Around the same period in the beginning of 21st Century, the tryptophan degradation induced by the indoleamine 2,3-dioxygenase (IDO) enzyme in the presence of inflammatory state became of interest as a link between immune function and serotonergic abnormalities due to reduced tryptophan availability (Capuron et al., 2002; Maes et al., 2002). A year later, the possible involvement of downstream tryptophan metabolites in terms of neurotoxic changes in major depressive disorders and further immune system and NMDA-glutermatergic neurotransmission interaction were proposed in "neurodegeneration hypothesis of depression" (Myint and Kim, 2003).
Several therapeutic strategies have been studied in the area of immune activation and psychiatric disorders. The antagonist of pro-inflammatory cytokine such as tumour necrosis factor-α (TNFα), eternacept, and n3 fatty acids are those studied and given some promising results. Recently, add-on therapy with inhibitor of cyclooxygenase-2 (COX-2) enzyme, celecoxib which was originally an anti-inflammatory medication was reported to enhance the response to both anti-depressant therapy and anti-psychotic therapy. Moreover, the possible use of inflammatory based biomarkers in diagnosis and choice of medication in major psychiatric disorders are considered.
In this chapter, brief basic immunology on inflammation, findings and mechanisms related to inflammatory state in psychiatric disorders, the immune-endocrine interaction, immune-endocrine-tryptophan metabolism interaction and inflammation-tryptophan metabolism-neurochemicals interaction network were explained and discussed.

2. Inflammatory state

2.1 A short survey of the body's defence system

The body's defense system is a complex arrangement of physical, chemical, biochemical, and cellular barriers. Here we will focus on immunity, which is the result of the interplay between two "immune" systems: the innate immune system, which is phylogenetically older, and the adaptive immune system of T and B cells (Medzhitov and Janeway-CA, 1998). The innate immune system functions in an antigen-nonspecific way, while antigen-specific mechanisms are mediated by the adaptive one. Characteristic cells of the innate immune system are e.g. granulocytes, natural killer (NK) cells, monocytes/macrophages, or dendritic cells. The innate immune system is the first line of defense against infection and it provides signals for the activation of the adaptive immune system. Innate responses serve to regulate the onset, duration, magnitude, and character of the antibody- and cell-mediated adaptive response. In contrast to the adaptive immune system, the innate immune system is not able to confer long-lasting memory, i.e. immunity against a specific pathogen.
In the late 1980s, Janeway proposed the model of the antigen-presenting cells, which are able to recognize and differentiate distinct groups of microbes by special receptors, the so-called pattern-recognition receptors (Janeway, Jr., 1989). The identification of pathogen-associated molecular patterns or microbe-associated molecular patterns by the innate immune system allows the body's defense system to discriminate between "infectious non-self" and "non-infectious self". This concept was expanded by Matzinger's hypothesis of danger signals as inducers of the body's defense system (Matzinger, 1994). According to this new concept, immunological phenomena like autoimmunity, sterile inflammation, or the acceptance of the fetus, who is immunologically 50% non-self, by the mother's immune system can be explained. Matzinger proposed that antigen presenting cells are not activated

by an infectious non-self signal, but by danger signals from injured host cells, damaged tissues, or metabolic stress. According to the term "pathogen-associated molecular patterns", she introduced the term "damage-associated molecular patterns" for these endogenous danger signals.

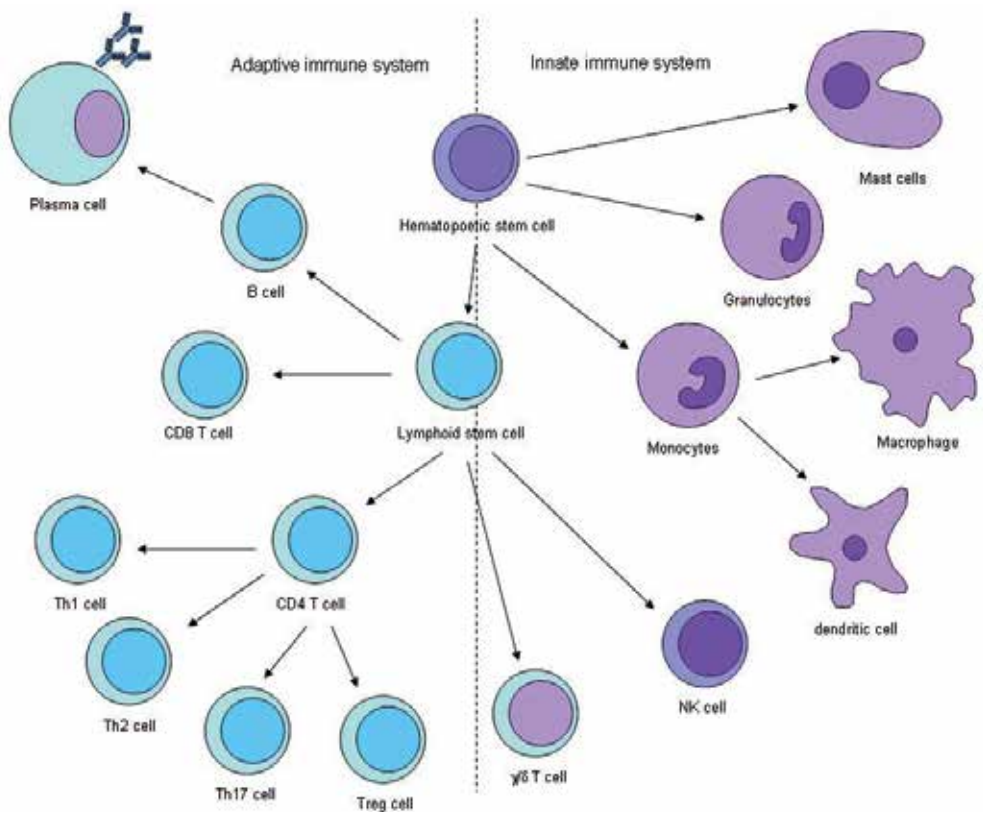

Fig. 1. Both arms of the cellular immune system (adapted from Drexhage et al., 2010).

The innate immune system provides a broad array of different receptors for the identification of both kinds of molecular patterns. The best known group of receptors is the family of Toll-like receptors (TLRs), which are able to recognize both, exogenous and endogenous molecular patterns (Medzhitov, 2009). TLR4 for example recognizes the pathogen-associated molecular pattern of bacterial lipopolysaccharide as well as the damage-associated molecular patterns of endogenous heat-shock proteins, while TLR3 is an intracellular recognition receptor of both, viral and self double-stranded DNA (Sirisinha, 2011). To limit an overshooting immune response to the minimum necessary tissue damage, the innate immune system is down-regulated by several negative regulators such as soluble decoy TLRs and intracellular TLR regulators like suppressors of cytokine signals (SOCS) and the enzyme A20 (Sirisinha, 2011).

The cells of the adaptive immune system are T cells (bearing the α/β T cell receptor) and B cells. The adaptive immune system induces T cells to change from a naive phenotype to either an effector functional type or a memory phenotype. The T cells are principally subdivided into CD4 and CD8 T cells, according to their surface receptors with affinity to

either the major histocompatibility complex II (CD4) or I (CD8). CD4, or helper T cells, are specialized to activate other cells and fall into distinct functional classes. More than twenty years ago, the dichotomy of Th1 and Th2 cells was introduced. The main function of Th1 cells (sometimes known as inflammatory T cells) is to fight against intracellular pathogens and to activate macrophages to kill the pathogens they harbor, while Th2 cells activate B cells to produce antibodies against extracellular pathogens (Janeway et al., 2001). More recently, other T helper cell subsets have been identified with Th17 cells being the most prominent ones. Th17 cells are specialized in clearing pathogens that cannot be handled by Th1 or Th2 cells including some bacteria and fungi (Jager and Kuchroo, 2010). In addition to these effector cells, CD4 T cells can also have regulatory properties; the most prominent are the regulatory T cells (Treg) cells, who are responsible for the downregulation of the T helper cell-mediated immune response. Their major function is therefore to maintain self-tolerance and immune homeostasis.
The function of CD8 T cells is to identify infected cells via the interaction of their surface protein CD8 with the antigen bearing MHC I receptor and to kill these cells by destructing their membrane. In analogy to the T helper subsets, CD8 cells can also form subsets like Tc2 and Tc17. The phylogenetically old form of T cells, characterized by the gamma/delta T cell receptor ('γ/δT-cells') is not easily subsumed to either the adaptive or the innate immune system, since it combines some characteristics of CD4 T cells, CD8 T cells, and NK cells. Cytokines and chemokines, the transmitters/hormones of the immune system, help to determine the particular type of adaptive response and the expression of costimulatory cell surface molecules that are required for efficient immune cell activation. T helper cell subsets are characterised by their respective cytokine profile. Typical Th1-like cytokines are Interferon-γ (IFN-γ), Interleukin-2 (IL-2), and IL-12, typical Th2 cytokines are IL-4, IL-10 (in the mouse, not in humans), IL-13 and others (Del Prete, 1992). IL-23 induces the subset of Th17 cells, which are characterized by the production of the partly redundant cytokines IL-17A and IL-17F; both cytokines promote tissue inflammation via induction of the production of pro-inflammatory cytokines like IL-1, IL-6, TNF and pro-inflammatory chemokines like CXCL1 and IL-8 (Jager and Kuchroo, 2010). However, the cytokines and chemokines are orchestrated in an extremely complex way and most of the effects are dependent on the simultaneous production of different cytokines. The generation of the aggressive Th17 cells, for example, requires the presence of the anti-inflammatory cytokine TGF-b together with the multifunctional cytokine IL-6, while TGF-b alone induces the development of immunosuppressive Treg cells (Jager and Kuchroo, 2010).
Besides the cellular components of the two immune systems, the humoral (i.e. soluble) components are the complement system and the acute phase proteins within the innate system and the antibodies, produced by activated B cells within the adaptive system.

2.2 The immune-brain connection

There is a strong relationship between the cytokine system and the neurotransmitter system. In vitro- and in vivo studies showed the modulating effect of interferons on the production of prolactin (Vankelecom et al., 1997) and – particularly interesting with regard to psychopathology – on the catecholaminergic, dopaminergic, serotonergic und glutamatergic neurotransmitter systems, e.g. the induction of transcriptional activity of the serotonin transporter (Kamata et al., 2000; Morikawa et al., 1998; Shuto et al., 1997; Katafuchi et al., 1995). TNF-α regulates the secretion of norepinephrine in the brain (Nickola et al., 2001).

Peripheral administration of TNF-α induces the cerebral tryptophan content (Ando and Dunn, 1999) and the synthesis of serotonin and dopamine (Hayley et al., 2002). There is experimental evidence that IL-1 can activate the serotonin transporter thereby increasing the reuptake of serotonin from the synaptic cleft (Ramamoorthy et al., 1995). Furthermore, IL-1 activates the serotonergic system (Gemma et al., 1997). The considerable overlap in biological activities of IL-1 and 5-HT indicates that the interactions between these two systems may be involved in the modulation of behaviour.
IL-2 can affect gene expression, neuronal activity and neurotransmitter release in brain regions, subserving sleep, memory and cognition, locomotion, and neuroendocrine function. IL-2 modulates neurotranmission of acetylcholine, dopamine, and norepinephrine in a biphasic manner (Petitto et al., 1997). It appears to be a potent and specific regulator of neurotransmission in frontal cortex, hippocampus, striatum, and hypothalamus (Hanisch and Quirion, 1995).
IL-6 is produced by neurons, astrocytes and microglia (Van Wagoner and Benveniste, 1999). This cytokine promotes neuronal differentiation and survival (Gadient and Otten, 1997) and modulates the above summarized neurotransmitter systems (Song et al., 1999; Qiu et al., 1995; Qiu et al., 1998). Several studies have investigated the influence of IL-6 on the production, release, and metabolism of 5-HT. Peripherally administered IL-6 increases the concentrations of tryptophan and the serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) in the brain (Wang and Dunn, 1999; Wang and Dunn, 1998; Zalcman et al., 1994) and it has been proposed that the interaction between IL-6 and brain serotonin is a complex process (Barkhudaryan and Dunn, 1999).

2.3 Stress and CNS immune system

The effect of chronic stress on the peripheral immune system and its relevance for MD has extensively been discussed (O'brien et al., 2004). Recent in vivo evidence now suggests that stress-induced elevation of glucocorticoids also enhances immune function within the CNS through microglia activation and proliferation and with a loss in the number and volume of astrocytes (Czeh et al., 2005). Animal studies show that stress induces an enhanced expression of proinflammatory factors such as IL-1β (Pugh et al., 1999; Nguyen et al., 1998), macrophage migration inhibitory factor (MIF) (Bacher et al., 1998; Niino et al., 2000; Suzuki et al., 2000) and cyclooxygenase-2 (COX-2) (Madrigal et al., 2003) in the brain. Elevation of these proinflammatory factors is accompanied by dendritic atrophy and neuronal death within the hippocampus (Sapolsky, 1985; Woolley et al., 1990), which are also found in brains of subjects with MD. These detrimental effects of glucocorticoids in the CNS are mediated by a rise in extracellular glutamate (Moghaddam et al., 1994; Stein-Behrens et al., 1994) and subsequent over-stimulation of the NMDA receptor. Such an over-stimulation of the NMDA receptor results in excitotoxic neuronal damage (Takahashi et al., 2002). Nair and Bonneau could demonstrate that restraint-induced psychological stress stimulates proliferation of microglia, which was prevented by blockade either of corticosterone synthesis, of the glucocorticoid receptor, or of the NMDA receptor (Nair and Bonneau, 2006). These data show that stress-induced microglia proliferation is mediated by corticosterone-induced and NMDA receptor-mediated activation within the CNS. Moreover, NMDA receptor activation during stress leads again to increased expression of the enzyme COX-2 and its product prostaglandin E2 (PGE2), which in turn is able to stimulate microglia activation. Therefore, a vicious circle may be induced, if the stress response is not limited, as it is discussed in MD.

2.4 Inflammatory state in major psychiatric disorders

2.4.1 Schizophrenia

Several epidemiologic studies give strong evidence for urbanicity at birth and upbringing to be a major risk factor for schizophrenia (Pedersen and Mortensen, 2001; Mortensen et al., 1999; Lewis et al., 1992). Another well replicated aspect is the seasonality of birth with a 5-8% excess of winter and spring births for individuals who later develop schizophrenia (Torrey et al., 1997). Both, urbanicity and saisonality, support the idea of a pre- or perinatal exposure to a viral infection as being a risk factor for developing schizophrenia (Franzek and Beckmann, 1996; Yolken and Torrey, 1995). In recent years, accumulating data showed the significant association between maternal infection during pregnancy with a higher risk for the offspring to develop schizophrenia (Brown and Patterson, 2011). Thus, a neurodevelopmental insult resulting from a prenatal viral infection, or a latent postnatal (viral?) infection may be associated with a chronic immune activation, possibly leading to a kind of mild autoimmune reaction, or a chronic, latent 'mild encephalitis' (Bechter, 2001). Recent animal experiments strongly support this concept (Vuillermot et al., 2010).

There are several lines of evidence for a mild activation of the immune system in schizophrenia. Some investigators dealt with antibody titres, some with cellular markers and others with cytokine measurements in serum, CSF, or in vitro from stimulated peripheral immune cells. Different hypotheses have been published according to the findings, e.g. the hypothesis of dopamine receptor activating autoantibodies (Knight, 1982), activated monocytes (Smith, 1992), a predominance of the Th2 system (Schwarz et al., 2001), or a deficiency of autoimmune T cells (Kipnis et al., 2006) playing a key role in the pathophysiology of schizophrenia.

A considerable number of reports show elevated antibody titers against several antigens in schizophrenic patients. The first report on antibodies against brain tissue in cerebrospinal fluid (CSF) of schizophrenic patients was published in the 1930ies by Lehmann-Facius (Lehmann-Facius, 1937). Others followed, describing anti-neuronal and non-CNS-specific auto-antibodies, or anti-viral antibodies in schizophrenia (e.g. (Heath et al., 1989; Schwarz et al., 1999; Torrey et al., 1982), for review see (Gaughran, 2002)). Some data suggest a role for endogenous retroviruses that may be activated by endocrine changes during adolescence and early adulthood – the main age at onset – or during an exogenous virus infection (Karlsson et al., 2001; Leweke et al., 2002).

However, no disease-specific pathogen could be identified up to now. The situation is comparable with the field of Multiple Sclerosis research, where strong evidence points to an infectious/autoimmune pathogenesis, but where the causative pathogen is still unknown. Regarding the cytokine profile, Potvin and coworkers (Potvin et al., 2007) reported in their systematic review of changes in seven cytokines in patients with schizophrenia that the IL-1 receptor antagonist (IL-1RA), soluble IL-2r and IL-6 were increased in the serum of schizophrenia patients while in vitro IL-2 synthesis was decreased. IL-1 is a potent pro-inflammatory mediator, inducing febrile response, production of acute phase proteins and activating e.g. T cells, B cells; its soluble receptor antagonist blocks these effects und is therefore acting as an anti-inflammatory agent (Gabay et al., 2010). The soluble IL-2 receptor is shed from the surface of activated immune cells and blocks the pro-inflammatory action of IL-2 (Nelson and Willerford, 1998). In contrast, IL-6 is a pluripotent cytokine, which exerts not only pro-inflammatory activity, but also regulates the balance between Th17 and Treg cells (Neurath and Finotto, 2011). Since it has a broad array of functions, it is difficult to interpret its role in the presence of elevated IL-1RA and sIL-2R levels. It is important to keep

in mind that immune measures, especially measurement of cytokines, in schizophrenic patients are limited by confounding factors. Factors influencing peripheral cytokine levels are e.g. smoking, gender, age, diet, weight, physical activity, sleep disturbance, alcohol consumption, smoking and last but not least antipsychotic and other medication (Irwin, 2002; Kronfol, 2002; Hinze-Selch and Pollmacher, 2001). Thus, immunological findings based on cytokine measurements in schizophrenic patients have to be interpreted with care. An increased B cellular immune response accompanied by a reduced T cellular immunity was repeatedly described in acute schizophrenia (Maino et al., 2007; Steiner et al., 2010). Based on the currently available data, the T cell immunity cannot clearly be associated with the Th1, Th2, Th17 or the Treg subset (Drexhage et al., 2010). However, increasing evidence points to an activation of circulating monocytes in schizophrenia (Drexhage et al., 2010; Drexhage et al., 2011).

2.4.2 Depression

The so-called sickness behaviour is the non-specific reaction to infection and inflammation. Sickness behaviour is characterised by weakness, malaise, listlessness, inability to concentrate, lethargy, decreased interest in the surrounding, and reduced food intake – all of which are depression-like symptoms. Thus, sickness behaviour was proposed to be a model of major depression (Dantzer, 2001). The sickness-related psychopathological symptomatology during infection and inflammation is mediated by cytokines such as IL-1, IL-6, TNF-α, and IFNg. Their active pathway from the peripheral immune system to the brain is via afferent neurons and through direct targeting at amygdala and other brain regions after diffusion at the circumventricular organs and choroid plexus (Dantzer, 2001). Clinical evidence also shows that the changes in cognition and mood that are an integral part of major depression are also caused by these cytokines (Capuron et al., 1999). Important lessons regarding the involvement of elevated pro-inflammatory cytokines in the pathophysiology of depression can be learned from IFN-a administration in patients suffering from malignant melanoma or hepatitis C (Myint et al., 2009). Another important impact comes from rheumatoid arthritis research, where a complex pro-inflammatory immune state is frequently accompanied with depressed mood (Bruce, 2008). To underline the functional relationship between an inflammatory process and depression, several studies have demonstrated the anti-depressant effect of anti-inflammatory drugs (Tyring et al., 2006; Uguz et al., 2009). These findings resulted in clinical trials demonstrating the efficacy of non-steroidal anti-inflammatory drugs as add-on treatment of major depression (Müller et al., 2006; Akhondzadeh et al., 2009). On the other hand, antidepressants have significant anti-inflammatory effects, as recently reviewed by Janssen and colleagues (Janssen et al., 2010); they normalize elevated levels of circulating proinflammatory cytokines like IL-6, TNF-a, IFN-g, and IL-1, again indicating that the activation of the immune system may be directly involved in the pathophysiology of depression. Recent even demonstrate the possible usefulness of antidepressants to treat rheumatoid arthritis (Sacre et al., 2010).

Beside these indirect lines of evidence for the involvement of an immune process in the pathophysiology of depression, there is a large body of findings of an activation of the immune system in depressed patients. The most frequently investigated immune parameters in patients suffering from major depression is IL-6. Most of the publications report a marked increase of in-vitro IL-6 production or serum IL-6 levels in depressed

patients. Since IL-6 is a prominent marker of monocyte activity, a predominant activation of the monocyte/macrophage system in major depression was hypothesised (Smith and Maes, 1995). Recent meta-analyses have clearly pointed out the evidence for elevated IL-6 levels in patients suffering from depression (Howren et al., 2009; Dowlati et al., 2010). Regarding the elevation of the inflammatory markers C-reactive protein (CRP), IL-1, IL-1RA and TNF-a, the two meta-analyses came to diverging results.
IL-6 may be involved in the modulation of the HPA axis (Plata-Salaman, 1991). Activation of the HPA axis is one of the best-documented changes in major depression (Roy et al., 1987). Furthermore, the relationship between psychological or physical stress and an enhanced IL-6 secretion in the peripheral immune system seems to be well established (Salas et al., 1990; LeMay et al., 1990; Zhou et al., 1993; Miyahara et al., 2000). An impaired ability of stress coping is often observed in depressed patients. Thus, the high number of data showing elevated peripheral IL-6 levels in MD patients may be partly related to psychological stress.
However, it should be recognized that an inherent heterogeneity exists in the aetiology of depression and different neurotransmitter systems may be disturbed. Based on the commonly accepted idea of major depression as heterogeneous group of disease entities, the group of Arolt investigated the difference between melancholic and non-melancholic major depression regarding their cytokine expression patterns (Rothermundt et al., 2001). They detected profound differences between these diagnostic subgroups: Non-melancholic patients showed increased counts of leukocytes, lymphocytes and NK-cells in the acute stage of disease and after several weeks of treatment, while their in vitro production of the cytokines was unchanged. Melancholic patients on the other hand had normal cell counts but a decreased in vitro production of IL-2, IFN-γ, and IL-10 during the acute stage of disease. Following clinical improvement, the cytokine production patterns normalised in these patients.

3. Inflammation-endocrinology and metabolism interaction

Apart from all the mechanisms discussed above regarding how inflammation itself could be detrimental to the brain and how inflammatory response system (IRS) is involved in psychiatric disorders, the interaction between IRS and endocrine system and metabolism could induce greater degree of damage to the brain. Among the different endocrine systems, this chapter will be focused on the stress hormones system which is the most involved in inflammatory reaction. In the same manner, among the different metabolic pathways, the tryptophan metabolism and glycolysis pathways will be mainly discussed in this chapter due to their significant involvement in neurochemical changes related to psychiatric disorders.

3.1 Inflammation and stress hormones interaction

Hypothalamo-pituitary-adrenal (HPA) axis is the key stress hormone axis which has interaction with immune activation and inflammation. Investigations of the role of the HPA axis in the psychopathology of depression commenced over 40 years ago when it was reported that depressed patients have a higher circulating plasma cortisol concentration than those that are not depressed (Board et al., 1957; Sachar et al., 1970). It was discovered that this synthetic glucocorticoid would normally suppress the secretion of cortisol by activating hypothalamic and pituitary glucocorticoid receptors thereby suppressing the

secretion of corticotrophin releasing factor (CRF) and adrenocorticotrophic hormone (ACTH), which in turn, reduced the activation of the adrenal cortex and the release of cortisol. The mechanism whereby these changes occurred was explained in terms of a negative feed-back loop whereby the raised plasma glucocorticoid concentration controls the further release of the steroid. However, it soon became apparent that in patients with major depression, the negative feed-back loop ceased to function due to the desensitization of the central glucocorticoid receptors. The negative dexamethasone suppression test thereby became a diagnostic marker of melancholic depression (Carroll et al., 1968a, b). As in major depression, it was reported in a systematic review that the evidence for elevated basal cortisol was consistently observed in first-episode, drug-naïve schizophrenia patients (Bradley and Dinan, 2010) although some studies reported negative finding (Strous et al., 2004).

It is frequently assumed that the synthetic glucocorticoids such as dexamethasone, act on glucocorticoid receptors in an identical manner to the natural glucocorticoids such as cortisol. This may not be the case. Dexamethasone acts primarily on the glucocorticoid receptors in the anterior pituitary, does not readily enter the brain and therefore differs substantially from natural glucocorticoids that activate both mineralocorticoid and glucocorticoid receptors (Trapp and Holsboer, 1996). There is also evidence that while dexamethasone may reduce the release of CRF, it does not suppress the release of arginine vasopressin (AVP). There is evidence that AVP, not CRF, is the main activator of the HPA axis due to chronic stress and major depression (Scott and Dinan, 1998). Although very little has been studied on CRF in schizophrenia, there are reports regarding increase AVP in schizophrenia (de Leon et al., 1994; Raskind et al., 1975). The increased action of AVP is further exacerbated by the action of IL-1β and IL-6; chronic immune activation is related more to AVP than CRF in the activation of the anterior pituitary (Raber and Bloom, 1994). In this way, chronic immune activation could induce abnormal HPA axis in both depression and schizophrenia.

On the other hand, recent in vivo evidence suggests that stress-induced elevation of glucocorticoids also enhances immune function within the central nervous system (CNS) through microglia activation and proliferation and with a loss in the number and volume of astrocytes (Czeh et al., 2006). Animal studies show that stress induces an enhanced expression of proinflammatory factors such as IL-1β (Pugh et al., 1999), macrophage migration inhibitory factor (MIF) (Bacher et al., 1998; Niino et al., 2000; Suzuki et al., 2000) and COX-2 (Madrigal et al., 2003) in the brain. Elevation of these proinflammatory factors is accompanied by dendritic atrophy and neuronal death within the hippocampus (Sapolsky, 1985; Woolley et al., 1990), which are also found in brains of subjects with major depression. These detrimental effects of glucocorticoids in the CNS are mediated by a rise in extracellular glutamate (Aucott, 1994; Stein-Behrens et al., 1994) and subsequent over-stimulation of the NMDA (N-methyl-D-aspartate) receptor. Such an over-stimulation of the NMDA receptor results in excitotoxic neuronal damage (Takahashi et al., 2002). Nair and Bonneau could demonstrate that restraint-induced psychological stress stimulates proliferation of microglia, which was prevented by blockade either of corticosterone synthesis, of the glucocorticoid receptor, or of the NMDA receptor (Nair and Bonneau, 2006). These data show that stress-induced microglia proliferation is mediated by corticosterone-induced and NMDA receptor-mediated activation within the CNS. Moreover, NMDA receptor activation during stress leads again to increased expression of

COX-2 and PGE2. Both, COX-2 and PGE2 per se are able to stimulate microglia activation. Therefore, a vicious circle may be induced, if the stress response is not limited, as in most of the psychiatric disorders.

3.2 Inflammation-stress hormones-tryptophan metabolism interaction

Not only the interaction between inflammation and stress hormones but also their further interaction with tryptophan metabolism brings the whole complex pathway to attention in psychiatric disorders. Tryptophan is an essential amino acid which has indole ring structure and is obtained from the dietary source approximately 20 nmol/day. The reference value of plasma tryptophan ranges from 45 to 60 nmol/l (Eynard et al., 1993). Of those, 50 to 85% are bound to albumin in unstable manner (Yuwiler et al., 1977). Serotonin is synthesized from about 1% of the available tryptophan in the body. Main serotonin synthesis occurred in the enterochromaffin cells in the gut and 10 to 20% occurred in the brain after crossing blood brain barrier (BBB). The central availability of tryptophan mainly depends on the competition by the large amino acids at the transport across BBB and partially depends on the cerebral demand (Fernstrom, 1977). About 99% of tryptophan is metabolized in the liver by the tryptophan 2,3-dioxygenase (TDO) (Watanabe et al., 1980). The TDO activity is mainly controlled by the tryptophan level itself and therefore, its activity is generally stable.

After tryptophan is catabolised into kynurenine (KYN), it is further catabolised into 3-hydroxy-kynurenine (3HK) by kynurenine-3-monooxygenase (KMO) enzyme. After 3HK, further degradation continues to 3-hydroxyanthranilic acid (HAA) through the action of kynureninase. After that, the catabolism proceed either into complete oxidation pathway and forms adenosine triphosphate (ATP) which occurs mainly in the liver, or into quinolinic acid (QUIN) which is finally degraded into nicotinamide adenine dinucleotide (NAD). From the complete oxidation pathway, picolinic acid (PIC) is also formed in small quantity. In physiological condition, the catabolism goes mainly to ATP formation and only minor portion goes to NAD formation (Leklem, 1971). KYN can also be catabolised by the kynurenine aminotransferases (KATs) into kynurenic acid (KYNA) (Figure-2). This metabolism in the liver is more or less stable and age and gender has influence on this metabolism (Leklem, 1971) especially in terms of excretion of the metabolites of further downward KYN pathway. The formation of tryptophan to nicotinic acid and its derivatives is important and the impaired condition could result in the disease pellagra. Moreover, since ATP formation in the cells is dependent on NAD, depletion of NAD is fatal to the cells especially if the cell is under stress. In normal state, to get normal NAD requirement, QUIN synthesis occurs only transiently in the liver and QUIN does not accumulate in the hepatocytes (Bender, 1989).

Since KYN itself could be transported across the blood brain barrier, on top of the kynurenine formed in the brain by tryptophan breakdown, extra KYN is available from the periphery for further kynurenine metabolism in the brain. Sixty percent of brain KYN was contributed from the periphery (Gal and Sherman, 1980). In the brain, tryptophan catabolism occurs mainly in the astrocytes and microglia (Grant and Kapoor, 1998; Grant et al., 2000; Heyes et al., 1996). Although some neurons also posses indoleamine 2,3-dioxygenase (IDO) and/or TDO2 (Miller et al., 2004), neurons are not the main sites of kynurenine pathway in the brain. While the human astrocytes are shown to produce mainly KYNA because of lack of KMO enzyme, microglia and macrophages produce mainly QUIN (Guillemin et al., 2001; Guillemin et al., 2000; Guillemin et al., 2005a). The astrocytes

metabolize QUIN produced by the neighbouring microglia (Guillemin et al., 2001). In the brain, in physiological condition without immune challenge, as in the liver, this kynurenine pathway may serve mainly for glycogen storage and synthesis of small amount of NAD required for the central nervous system (Leklem, 1971).

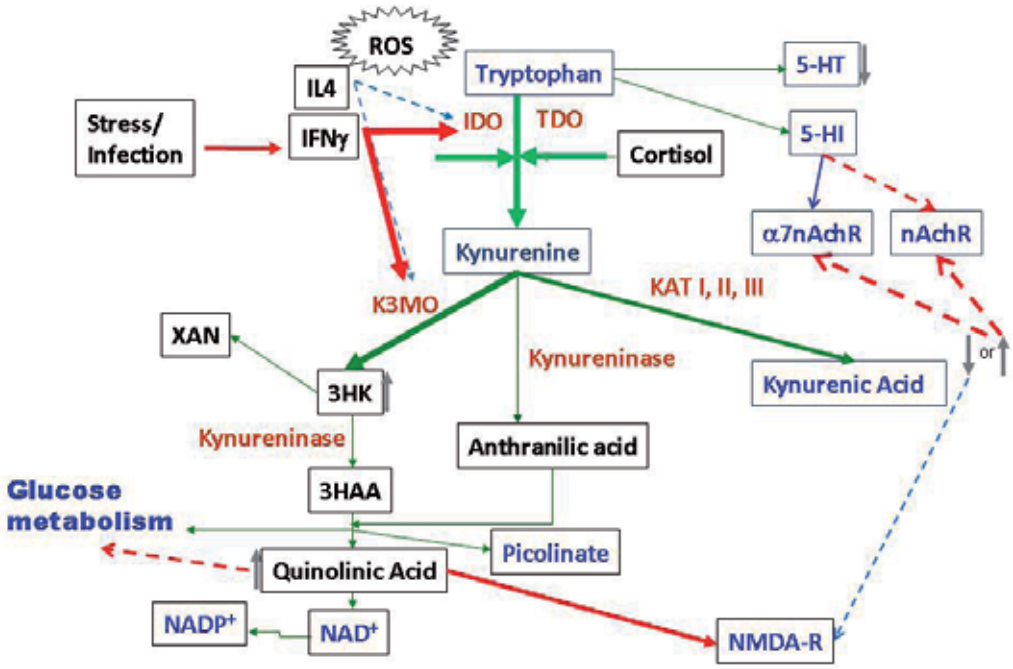

Fig. 2. Immune-NeuroEndocrine-Tryptophan Interaction (adapted from Myint et al, 2009)

In case of inflammation, infection or oxidative stress which activates the enzyme IDO in the extrahepatic tissues, such as, lungs, placenta, kidneys, spleen, blood and the brain (Heyes et al., 1993; Mellor and Munn, 1999), the extrahepatic tryptophan metabolism shifts the tryptophan metabolism away from the liver (Moffett et al., 1998). In this case, tryptophan breakdown through KYN pathway occurs mainly in the blood and lymphoid tissues (Moffett and Namboodiri, 2003). The IDO activity is enhanced by pro-inflammatory cytokines such as interferon-γ (IFNγ) (Carlin et al., 1987; Yasui et al., 1986), and inhibited by the anti-inflammatory cytokine IL4 (Musso et al., 1994). As discussed above, in case of stress or related conditions, such as inflammation, HPA axis activity will be enhanced and glococorticoid secretion is increased. In this situation, TDO activity is further enhanced by glucocorticoids (Knox, 1951; Salter and Pogson, 1985). Although not many studies have been carried out on the interaction between stress hormones or glucocorticoids and TDO, some studies have demonstrated that hepatic TDO activity can be enhanced via glucocorticoid mediated transcriptional activation (Nakamura et al., 1987), although hepatic heme is the essential requirement in this activation (Ren and Correia, 2000). This activation of TDO by stress hormone will induce further increase in tryptophan breakdown, and as a result, the KYN formation becomes much higher than physiological condition. Since the liver cell uptake of KYN is not efficient for extrahepatic KYN, the further KYN pathway mainly occurs extrahepatically. The activity of KMO is also enhanced by pro-inflammatory

cytokines (Mellor and Munn, 1999). Therefore, in case of inflammation, the formation of 3HK becomes enhanced much faster than KYNA formation and the balance between formation of 3HK and KYNA shifted to 3HK side. In the presence of inflammation, activated monocytes are found to be the robust producers of QUIN (Chiarugi et al., 2001). During inflammation, QUIN production persists till the inflammatory process is completed (Heyes and Lackner, 1990). Since some of the KYN metabolites activate inflammatory reaction, this could further prolong the QUIN synthesis (Melillo et al., 1993), whereas some of the metabolites inhibit the proliferation of T cells and NK cells (Frumento et al., 2002) and inhibit the further inflammatory process and stop further QUIN formation. In this way, immune tolerance is achieved through tryptophan depletion and homeostasis in KYN pathway is maintained.

Therefore, in case of acute inflammation, the transient disturbances in the tryptophan metabolism will take place through; (1) effect of inflammatory mediators on IDO activity and (2) interaction between glucocorticoid and TDO activity. This might be one of the reasons that could induce sickness behaviour during acute inflammation. In fact, all those changes are some how necessary for the body homeostatic mechanism to regulate the inflammatory response and to generate the energy that the body requires during acute inflammation.

4. Inflammation-tryptophan metabolism-neurochemicals interaction

The frontiers in the field of interaction between tryptophan metabolism and neurochemicals proposed that the tryptophan shunted away from the serotonin synthesis towards degradation into kynurenine as a mechanism involved in the psychiatric disorders (Lapin and Oxenkrug, 1969; Mangoni, 1974). Based on this mechanism several studies have been carried out in tryptophan and kynurenine changes in depressive disorders. One very early study on plasma kynurenine levels in depressed patients and controls demonstrated lack of significant difference between the groups (Wood et al., 1978), whereas, another study on plasma neutral amino acids and tryptophan in mania and depressed patients demonstrated reduced tryptophan availability in the patients compared to healthy controls (Moller and Amdisen, 1979). At the same time, a post mortem study was carried out on tryptophan metabolism and schizophrenia. The investigators reported the increased tryptophan and kynurenine in the brain of schizophrenia without evidence of generalized deficit in serotonin (Jospeh et al., 1979).

After the discovery of the effect of pro-inflammatory cytokines on IDO enzyme activity (Carlin et al., 1987; Yasui et al., 1986) and the interaction between glucocorticoids and TDO activity (Knox, 1951; Nakamura et al., 1987; Salter and Pogson, 1985), the link between inflammatory state, tryptophan metabolism and serotonergic neurotransmission became of interest in the field of psychoneuroimmunology. Somehow, the report of a study on QUIN and kynurenine pathway metabolism in different inflammatory and non-inflammatory neurological diseases brought this field forward although it failed to show the significant association between metabolites in the CSF and psychiatric disorder such as depression (Heyes et al., 1992). Since that time many research groups focussed on tryptophan breakdown and psychiatric disorders such as depression, anxiety disorders and schizophrenia.

4.1 Interaction with serotonergic neurotransmission

As discussed above, in the brain, the inflammatory state enhanced tryptophan breakdown and that in turn induces low availability of tryptophan for serotonin synthesis (Lapin and Oxenkrug, 1969; Mangoni, 1974). Unlike TDO, the enzyme IDO is not specific to tryptophan alone but degrades any compound with indole ring. Therefore, in case of inflammation and IDO activation, serotonin is degraded not only by monoamine oxidase (MAO) into 5-hydroxyindole acetic acid (5HIAA), but also by IDO into formyl-5-hydroxykynuramine (f5OHKYM) (Pertz and Back, 1988). This further reduces the serotonin availability for optimal serotonergic neurotransmission.

The earliest study on interaction between pro-inflammatory cytokines, tryptophan degradation and depression was carried out on patients with chronic active hepatitis C who were treated with IFNα which is a pro-inflammatory cytokine (Maes et al., 2001) . The investigators have demonstrated the association between increased in serum IL-8, serum kynurenine to tryptophan ratio that indicates increased tryptophan breakdown and depression rating scales. Unfortunately, there was no data on serotonergic neurotransmission. However, another study on IFNα therapy but in melanoma patients, also demonstrated that, in antidepressant-free patients under IFNα treatment, the decreases in serum tryptophan correlated with depressive, anxious, and cognitive symptoms, but not neurovegetative or somatic symptoms (Capuron et al., 2003). The author stated that those associations were not observed in those treated with paroxetine, a selective serotonin reuptake inhibitor (SSRI). At least, this study indirectly indicated that the development of symptoms in association with serum tryptophan level was related to insufficient serotonergic neurotransmission since paroxetine treated patients showed lack of those associations.

The occurrence of depression during pregnancy or post-partum period was also considered to be associated with inflammatory state (Maes et al., 2000) and serotonergic neurotransmission (Gu et al., 2003). A study demonstrated that the tryptophan breakdown was increased in pregnant women than non-pregnant women and the difference was more pronounced in those with anxiety and depression (Maes et al., 2002). Another study also demonstrated that low mood in post-partum period was associated with continuously low serum tryptophan after the delivery due to increased degradation into kynurenine (Kohl et al., 2005). Taken altogether, there is again, another circumstantial evidence of relationship between inflammatory state, tryptophan degradation and serotonergic neurotransmission.

There is only one study which investigated on association between complete triad of inflammation, kynurenine level and serotonin in the blood of the patients with pure major depression (Mackay et al., 2009). This study demonstrated the association between kynurenine levels and degree of depression in the patients treated with SSRI fluoxetine. Here again, there is no proof of direct association between inflammation, tryptophan degradation and serotonergic abnormalities in depression. Regarding the association between tryptophan degradation and serotonergic neurotransmission in schizophrenia, only one post-mortem study (Jospeh et al., 1979) and one CSF analyses study were carried out (Issa et al., 1994). Although the post-mortem study could show the increased tryptophan and kynurenine in the brain of the patients, and CSF study could demonstrate the reduced tryptophan level in the schizophrenia group, both studies failed to demonstrate the association with serotonergic neurotransmission.

Although there is no experimental study showing the direct relationship between increased IDO activity, tryptophan breakdown and reduced serotonergic neurotransmission, the circumstantial evidences from human studies in depression indicated the association between pro-inflammatory states, increased tryptophan breakdown and impaired serotonergic neurotransmission.

4.2 Interaction with glutamatergic and dopaminergic neurotransmission

The disturbance in glutamatergic neurotransmission is one of the common pathways involved in the pathophysiology of depression and schizophrenia. The first findings indicating the involvement of glutamatergic neurotransmission in mood disorders based on the preclinical data with N-methyl-D-aspartate receptor (NMDA-R) antagonist, ketamine (Silvestre et al., 1997). The antidepressant effect of NMDA-R antagonist, ketamine, was also reported in depressed patients (Berman et al., 2000). The hypofunctioning of glutamatergic neurotransmission as part of the pathophysiology of schizophrenia was proposed based on the finding of low glutamate concentrations the CSF of schizophrenia patients (Kim et al., 1980). Unlike in depression, NMDA-R antagonist, ketamine could enhance the neurochemical reaction of amphetamine-induced dopamine release in healthy controls mimicking the neurochemical reaction in schizophrenia patients (Kegeles et al., 2000).

As explained before, during inflammation and enhanced tryptophan breakdown, extra amount of peripheral KYN becomes available for the further KYN metabolism in the brain, since KYN can be transported across BBB. In case of pro-inflammatory state in the brain, the KYN metabolism in the astrocytes and microglia might also be enhanced. Therefore, the kynurenine pathway is highly activated in the brain. The KYN metabolites contribute directly to the neuroprotective-neuro-degenerative changes in the brain through direct effects on several neurotransmissions. The QUIN is a NMDA-R agonist (Bender and McCreanor, 1985) and accumulation of QUIN could result in excitotoxicity. It was reported in an in-vitro study that the metabolite QUIN could induce selective apoptosis to astrocytes (Guillemin et al., 2005b). 3HK causes neuronal apoptosis (Okuda et al., 1998) while QUIN causes excitotoxic neurodegenerative changes (Schwarcz et al., 1983). However, KYNA is the NMDA-R antagonist (Perkins and Stone, 1982) and is protective against excitotoxicity of QUIN (Kim and Choi, 1987).

Therefore, the pro-inflammatory status in major depression would activate not only IDO (Carlin et al., 1987; Yasui et al., 1986) but also KMO enzyme activities (Mellor and Munn, 1999) and this might in turn shift the KYN metabolism to the 3HK and QUIN arm with possible reduction in KYNA (Figure-2). The changes in NMDA-R agonist and antagonist, QUIN and KYNA might have impact on glutamatergic neurotransmission. Moreover, it was proposed that the increased in those toxic metabolites imbalanced to formation of KYNA might prime the astrocytes-microglia-neuronal network to be vulnerable to environmental factors such as stress. It was also proposed that, the imbalanced KYN pathway induced impaired glial-neuronal network might contribute to the recurrent and chronic nature of major depression (Myint and Kim, 2003). The neurotoxic metabolites might induce astrocytes apoptosis and certain neuronal apoptosis which would bring the glial-neuronal network weaker and reduction in syntheses of neurotrophic factors and prime the system to be vulnerable to stress and get psychiatric consequences. The loss of astrocytes might further induce glutermatergic abnormalities also through disturbance in glutamate-glutamine metabolism.

In patients with major depression who are drug naïve or medication free for at least 4 months, an imbalance between those neuroprotective and neurotoxic pathways with lower protective metabolite has been and demonstrated (Myint et al., 2007b). The ratio between KYNA and KYN (KYNA/KYN) which indicated how much of KYN would be degraded into KYNA was significantly lower in depressed patients than healthy controls. Moreover, 6-week medication with currently available antidepressants, mainly, selective serotonin reuptake inhibitors (SSRIs) could not reverse the metabolic imbalance in KYN pathway back to normal. We have hypothesized that such an uncorrected imbalance with higher 3HK and QUIN to KYNA ratios, in the long term, might induce further loss of astrocytes and neurodegenerative changes that in turn induces the chronicity, treatment resistance and progression of the disease. In major depression, there are evidences of neurodegenerative changes and loss of astrocytes (Rajkowska et al., 1999). In addition, the decreased glutamate and glutamine levels in pregenual anterior cingulate cortex of depressed patients with associated severity of clinical symptoms have been reported (Auer et al., 2000; Rosenberg et al., 2005).

Not only in adult depression but also in adolescent depression, the kynurenines seem to play a role. A recent study reported that in magnetic resonance (MR) spectroscopy in melancholic depressed adolescents, the choline levels which indicated the turnover of cells showed positive correlation with serum KYN and HAA/KYN ratio (Gabbay et al.). This study also demonstrated that the serum KYN and HAA/KYN ratios were significantly increased in those adolescents with melancholic depression than non-melancholic depression. Moreover, it was reported in this study that the serum KYN and HAA/KYN were positively correlated with depression scores. It could be concluded that the shift in KYN pathway more to the arm of 3HK, HAA and QUIN is involved also in adolescent melancholic depression.

In case of cytokine therapy induced depression, such as, IFNα therapy induced depression, increase in IL-6 and decrease in KYNA or increased in KYN/KYNA showed significant association with development of depressive symptoms (Wichers et al., 2005). However, another study showed that both KYNA and QUIN were increased in IFNα treated patients (Raison et al.), although the ratio between metabolites from these two arms was not reported. Nevertheless, both studies indicated the enhanced TRP degradation and change of KYN metabolites after immune challenge with IFNα and the depressive episodes were the consequences.

Further evidences also arise from animal experiments regarding the association between inflammation, tryptophan metabolic pathway abnormalities and depression. O'Connor and group demonstrated that lipopolysaccharide induced depressive behaviour through the action of enhanced IDO enzyme activity (O'Connor et al., 2009c). This group also demonstrated in the bacille Calmette-Guérin (BCG) mouse model of depression (O'Connor et al., 2009b) that immune activation using BCG could induce depressive behaviour and activation of IDO enzyme activity followed by activation 3-hydroxyanthranillic acid oxidase (HAAO) enzyme which enhance degradation of HAA and that in turn enhances the formation of neurotoxic QUIN. Moreover, blockade of IDO was demonstrated to prevent the depressive behaviour. In another study, IFNγ knock-out mice did not show the depressive behaviour when challenged with BCG since IFNγ is the inducer of IDO enzyme (O'Connor et al., 2009a). These evidences indicate that manipulating the KYN pathway could be a novel therapeutic strategy for counteracting depression.

Regarding bipolar mania, increased expression of TDO2 in anterior cingulate gyrus of post-mortem brain tissues from bipolar patients was reported (Miller et al., 2006). There is only one study reported on kynurenines changes in the plasma of bipolar mania patients (Myint et al., 2007a). It was reported that in bipolar mania patients, there was no significant reduction in KYNA, even though a trend of decrease was observed. Moreover, it was reported in that study that 6-week treatment with currently available mood stabilizers did not show any changes. Although the pro-inflammatory state in bipolar disorder was not clearly stated, there are some reports on pro-inflammatory state in bipolar disorders (Kim et al., 2007). The pro-inflammatory state induced kynurenines imbalance may also be involved in the pathophysiological mechanism of bipolar disorders. Further more detailed studies are still necessary to find out the interaction between immune status, tryptophan metabolism and neurotransmitter function in bipolar disorders.

In case of schizophrenia, a study in post-mortem brain tissue in different cortical regions revealed increased KYNA levels in schizophrenic samples compared to a control sample, particularly in the prefrontal cortex (Schwarcz et al., 2001). Another investigation in the amygdala, a small and nonsignificant increase of KYNA in medicated schizophrenics was observed (Miller et al., 2006). Those studies raised a question as to whether the increase in KYNA might be associated with antipsychotic medication. However, the increased levels of KYNA was also observed in the CSF of schizophrenic patients (Erhardt et al., 2001). Since most of the patients in this study were drug-naive first-episode patients, this increase could not be caused by antipsychotic treatment. It was hypothesized that accumulation of KYNA may lead to schizophrenic symptoms (Erhardt et al., 2003). An experiment in rat demonstrated that KYNA concentration significantly reduced in hippocampus, striatum and prefrontal cortex after one month treatment with antipsychotics, haloperidol, clozapine and raclopride (Ceresoli-Borroni et al., 2006). This study also demonstrated that one year treatment with haloperidol still continue reduction in KYNA concentration in the interstitial fluid of the rat brain.

Since prefrontal cortex area is involved in the pathophysiology of schizophrenia (Andreasen et al., 1992) the increase in KYNA might be involved in pathophysiological mechanism. Since KYNA is the NMDA-R antagonist, it could be concluded that the development of psychotic symptoms are associated NMDA-R antagonism. KYNA is the antagonist of all three ionotropic excitatory amino acid receptors (Perkins and Stone, 1982). Even though KYNA is generally considered as protective metabolite against QUIN, its abnormal accumulation beyond physiological level could induce glutamatergic hypo-functioning and might disturb cognitive function (Olney et al., 1991). Moreover, while one of tryptophan metabolites 5-hydroxy indole (5HI) activates the α7-nicotinic acetylcholine receptor (α7nAchR) and induces glutamate release (Mannaioni et al., 2003; Zwart et al., 2002), KYNA is an antagonist of α7nAchR (Hilmas et al., 2001). Since KYNA down-regulate the permissive role of 5HI activation on α7nAchR, the accumulation of KYNA could suppress α7nAchR function and induce disruption of auditory sensory gating (Shepard et al., 2003). In addition, it was reported that KYNA inversely regulates the dopaminergic tone (Wu et al., 2007). In this context, 5HI and KYNA exert synergistic action on dopaminergic neurotransmission. These interactions of KYNA with other neurotransmitters such as 5HI could contribute to some behavioural or cognitive consequences such as psychosis and cognitive impairment other than neurodegenerative changes.

Not only the positive symptoms but also the negative symptoms are part of the psychopathology of schizophrenia. There are also considerable evidences of loss of brain volume in schizophrenia (Takahashi et al., 2009). Unfortunately, the tryptophan research in schizophrenia most of the studies concentrated only on KYNA. There is only one group reported on 3HK (Condray et al., 2011; Yao et al.) although no clear change was demonstrated and no balance between potentially neuroprotective metabolite, KYNA, and neurotoxic metabolites such 3HK was investigated. Nevertheless, this group has demonstrated the association between 3HK and (1) total symptoms score at the time of recruitment, and (2) response of positive symptoms to 4-week neuroleptic treatment in first episode neuroleptic naïve schizophrenia patients. The associations between negative symptoms, brain volume changes and potentially neurotoxic metabolites in the pathophysiology have been ignored in schizophrenia research. Most of the therapeutic possibilities proposed are to manipulate KYNA (Erhardt et al., 2009). Without knowledge of interaction between different potentially neuroprotective and potentially neurotoxic metabolites, manipulation of just one metabolite would raise an issue regarding the potential untoward neurotoxic effects in the patients. Our recent finding in medication naive schizophrenia patients indicated increased 3HK and decreased KYNA in the plasma compared to healthy controls (Myint et al., 2011) and it was reversed by 6 weeks antipsychotic treatment. This would be the indirect indicator of accumulation of 3HK due to enhanced KMO activity induced by pro-inflammatory statues in schizophrenia. As discussed in depressive disorders, this might further lead to increase NMDA-R agonist QUIN in certain brain areas and excitotoxicity. To answer the question on clear interaction of inflammation, tryptophan breakdown and glutamatergic neurotransmission is more complicated.

4.3 Interaction with cholinergic and adrenergic neurotransmission

In pro-inflammatory state, although the balance between 3HK and KYNA might generally shift to 3HK arm, because of the general increase of KYN the formation of KYNA may also be higher than normal state. Since it is NMDA-R antagonist, well balanced increase may counteract the negative effects of QUIN through NMDA-R and the homeostasis will be maintained. As mentioned before, in schizophrenia, there is considerable evidence of increase formation of KYNA observed both in CSF (Erhardt et al., 2001) and at certain areas of the brain (Schwarcz et al., 2001). Also a study on IFNα treated patients show increase of both KYNA and QUIN in the CSF (Raison et al., 2010). In those cases, consequences of increase KYNA may induce negative impact on other neurotransmissions.

Apart from the interaction with α7nAchR, the metabolites 5HI and KYNA also have interaction with non-α7nAchR. The metabolite 5HI was reported to inhibit non-α7nAchR mediated release of noradrenaline (NA), dopamine (DA) and acetylcholine (Ach) (Grilli et al., 2006). Similarly, KYNA inhibit the function of the non-α7nAchR by reducing the expression of those receptors (Hilmas et al., 2001). Therefore, inhibition of non-α7nAchR by increased KYNA could also disturb cholinergic and noradrenergic neurotransmission.

Therefore, inflammatory state induced increased in KYNA could play part of the pathophysiology of noradrenergic neurotransmission in psychiatric disorders.

5. Future perspectives

The findings discussed above are the clear evidences that the interaction between immune activation and tryptophan metabolism and kynurenine pathway is involved in

pathophysiology of major psychiatric disorders. The manipulation of this metabolism is of interest for future therapeutic development and several studies are focusing on this aspect. There are some enzyme inhibitors that are already developed. However, it is important to consider the possible occurrence of imbalance between different metabolites when a particular enzyme is blocked or manipulated to enhance or reduce the particular metabolite. Therefore, such manipulation should be carried out with clear indication such as evidence of change in metabolites or ratios between metabolites as biomarkers. Moreover, close monitoring on those changes during therapy would also be necessary. Since TRP metabolism is the metabolism in which there is crosstalk between peripheral and central, use of peripheral markers as indirect evidence of central changes for diagnostic and prognostic purpose is not unrealistic.

Future studies should be carried out not only on manipulation of the metabolism for therapeutic purpose but also on the use of KYN pathway metabolites as biomarkers in evidence based management for early detection, choice of correct medication and monitoring. The normal values of those metabolites in different population are not yet known. Clear association between central and peripheral markers should be investigated. The validation of the usefulness of those biomarkers should be carried out in multicentre approach. Since currently available technologies to detect those metabolites are expensive and sophisticated, the studies on development of user-friendly and cost-effective technologies for detection of those metabolites are also necessary to be carried out.

The indirect manipulation of this pathway through anti-inflammatory medication could be considered as another therapeutic strategy. The indirect manipulation of this pathway through anti-inflammatory medication could also be another strategy. The use of COX-2 inhibitor celecoxib as add-on therapy to standard anti-depressant or anti-psychotics is a promising approach. The prevention of inflammation and oxidative stress using some medications such as n3-fatty acid which is more or less harmless or lifestyle intervention through diet, exercise and mindfulness practices could also be an option. However, this type of treatment should start timely and kynurenines could be the possible biomarkers as early indicators of immune-metabolic-neurochemical imbalances.

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9

The Impact of Cardiometabolic Risk in Patients with Severe Mental Illness: From Evidence to Clinical Management

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1. Introduction

People with severe mental illness have an excess burden of physical comorbidity and mortality, especially due to cardiovascular illness, compared to persons without psychiatric disorders. Individuals with schizophrenia and bipolar disorder have an increased risk for obesity, type 2 diabetes, and other cardiometabolic risk factors but they usually receive inconsistent and insufficient physical monitoring and management. There is a wide array of variables that may potentially contribute to the increased comorbidity and mortality rates associated with major mental disorders and this is partly related to lifestyle factors such as poor diet, lack of exercise and smoking.

A final important source of cardiometabolic risk in major mental disorders is treatment itself although before the introduction of the antipsychotic drugs it was acknowledged that patients with schizophrenia and bipolar disorder may be at a higher risk of abnormal glucose metabolism and metabolic disorders compared to general population. The reasons for this difference may include an inherent increased risk of diabetes associated with the illness itself and an increased metabolic risk related to behaviors having a negative impact on health.

Although the main aim of the treatment of severe mental illness is to control psychotic symptoms and enable patients to function as normally as possible it is really important to considerer in choosing a treatment the impact on physical as well as mental health. The safety and tolerability of psychotropic drugs are especially important because of the chronicity of the illnesses being treated, the need for long-term therapy and the poor insight and motivation of many of the patients. The occurrence of side effects determines not only a reduction of the physical health of patients as a whole but also a reduction of compliance and we know that sub-optimal adherence to psychotropic medication, in particular antipsychotics, greatly increases the risk of relapse and rehospitalisation.

About antipsychotics, between-drug differences in efficacy are relatively modest for the atypicals, or between atypicals and conventionals, while differences in safety and tolerability are larger and more clinically relevant. The lower risk of extrapyramidal symptoms and tardive dyskinesia with atypical antipsychotics has allowed a greater focus on other physical health risks associated with these treatment. Antipsychotic drugs have side effects such as weight gain, lipid abnormalities and disturbance of glucose regulation

that increase the risk of the metabolic syndrome, a recognized cluster of features (hypertension, central obesity, glucose intolerance / insulin resistance and dyslipidaemia) that is predictive of both type-2 diabetes and atherosclerotic vascular disease.
About the side effect of antipsychotics, in the past few years, particular attention has been paid to the ability of these drugs to prolong the corrected QT (QTc) interval, which may result in torsades de pointes and sudden cardiac death. Other factors that could lead to QTc lengthening in psychotic patients are the presence of abnormalities in glucose metabolism and comorbid cardiovascular diseases witch are increased in patients treated with antipsychotics.
These matters emphasize that cardiovascular safety of antipsychotic drugs is of paramount importance because patients diagnosed with schizophrenia, schizoaffective disorder, or bipolar disorder are at high risk to begin with.
All reviews of the association between psychotic illness, metabolic syndrome and antipsychotic medication point to the need for routine physical health screening of patients prescribed antipsychotic drugs, whatever the indication for such treatment. The maintenance of physical health is an important factor in the successful global management of these patients. For these reasons there is clearly a need for clinicians to employ multiple strategies to minimize metabolic risk in schizophrenia patients, including using metabolically more neutral medications, promoting healthier lifestyle habits, developing expertise in switching antipsychotics for metabolic reasons and, most importantly, practicing good preventive care through regular monitoring of metabolic parameters.
In recent years the importance of physical health in people with psychotic illness treated with antipsychotics has led to monitoring recommendations cosponsored by different associations (endocrinology, cardiology and psychiatry) in United States and in Europe although general health care needs in psychiatric population are commonly neglected and psychiatrists mainly focus on efficacy of treatment of psychotic symptoms.
The aim of this chapter is to evaluate the clinical importance of cardiometabolic risk factors among persons with mental disorders, addressing the contribution of antipsychotic medications to increased cardiometabolic risk, and suggesting monitoring strategies for modifiable risk factors relevant to the treatment of serious mental illness.
A Medline search was performed to examine published data from 1990 through June 2011.
The search included the following keywords: 'diabetes', 'weight gain', 'weight management', 'dyslipidaemia', 'metabolic syndrome', 'QTc interval', 'metabolic and cardiovascular risk', and were used interchangeably and were also combined in the search together with 'schizophrenia', 'bipolar disorder', 'severe mental illness' and 'antipsychotic drugs'.
Papers were included if they were published in English, with a diagnosis of schizophrenia or bipolar disorder and treatment with antipsychotic medication.
Studies were also included if the focus was on monitoring and improvement in metabolic profile through the application of different strategies, such as psychoeducational (exercise and dietary) interventions or switching patients to less metabolically offending medications.

2. The burden of cardiometabolic illness

Individuals with major mental disorder, including schizophrenia, bipolar disorder and schizoaffective disorder, are prone to many different physical health problems (De Hert et

al., 2011). While these diseases are also prevalent in the general population, their impact on individuals with major mental disorder is significantly greater (Maj, 2009).
Subjects with major mental disorder tend to have more illnesses and a shorter lifespan than the general population, having a life expectancy that is approximately 20% shorter (Newman & Bland, 1991). Recently, a multistate study in U.S, supported by the Center for Mental Health Services in collaboration with the National Association of State Mental Health Program Directors, found that patients with serious mental illness lost an average of 25 years of potential life expectancy compared to current life expectancy in the general population. (Table 1) (Colton & Manderscheid, 2006).

Year	Arizona	Missouri	Oklahoma	Rhode Island	Texas	Utah	Virginia
1997		**26.3**	**25.1**		**28.5**		
1998		**27.3**	**25.1**		**28.8**	**29.3**	**15.5**
1999	**32.2**	**26.8**	**26.3**		**29.3**	**26.9**	**14.0**
2000	**31.8**	**27.9**		**24.9**			**13.5**

Table 1. Mean Number of Years of Potential Life Lost (YPLL) per Public Mental Health Client Who Died During a Year in Which a Service Was Received (modified from Colton & Manderscheid, 2006)

Modifiable Risk Factors	Estimated Prevalence & Relative Risk (RR)	
	Schizophrenia	Bipolar Disorder
Obesity	**45–55%, RR: 1.5-2**	**21–49%, RR: 1-2**
Smoking	**50–80%, RR: 2-3**	**54–68%, RR: 2-3**
Diabetes	**10%–15%, RR: 2**	**8–17%, RR: 1.5-2**
Hypertension	**19–58%, RR: 2-3**	**35-61%, RR: 2-3**
Dyslipidemia	**25-69%, RR: ≤5**	**23-38%, RR: ≤3**
Metabolic Syndrome	**37-63%, RR: 2-3**	**30-49% RR: 1.5-2**

Table 2. Estimated prevalence and relative risk of modifiable cardiovascular disease risk factors in patients with schizophrenia and bipolar disorder compared to the general population (modified from Correl, 2007)

This mortality gap has been noted in different study (Saha et al., 2007; Robson & Gray, 2007) even in countries where the quality of the health care system is generally acknowledged to be good (Osby et al., 2000). The excess mortality was attributable to physical illness (Saha et al., 2007; Robson & Gray, 2007), with cardiovascular disease (CVD) being the major contributor (Colton & Manderscheid, 2006). A recent cohort study of primary care patients in the UK has confirmed the increased prevalence of CVD associated with severe mental illness (Osborn, 2007) and different authors agree that cardiovascular illness may partly

explain why patients with schizophrenia die at least 10 years earlier than the general population (Heald et al., 2010; De Hert et al., 2011).

Risk factors for cardiovascular morbidity and mortality in the general population include those that are inherently non-modifiable (gender, age, family history) and those that are modifiable through behavioural changes and improved care (Heald et al., 2010). The differential risk for morbidity and mortality from CVD in patients with schizophrenia and bipolar disorder compared to the general population can be explained by a 1–5-fold (Tab. 2) relative risk for modifiable risk factors for CVD (Correll, 2007). These risk factors include smoking (Hennekens et al., 2005; S. Davidson et al., 2001; Goff et al., 2005; Herran et al., 2004; Ucok et al., 2004), obesity (Hennekens et al., 2005; Fagiolini et al., 2005), diabetes (Fagiolini et al., 2005; Goff et al., 2005; Kilbourne et al., 2004), arterial hypertension (Hennekens et al., 2005; Fagiolini et al., 2005; Goff et al., 2005;), dyslipidemia (Hennekens et al., 2005; Fagiolini et al., 2005; Nasrallah et al., 2006) and metabolic syndrome (Meyer et al., 2005; McEvoy et al., 2005; Cohn et al., 2004; Kato et al., 2004; Heiskanen et al., 2003; Birkenaes et al., 2007; Yumru et al., 2007).

2.1 Metabolic syndrome

With regard to cardiovascular risk in persons with severe mental illness, of most concern is the development of metabolic syndrome (Casey, 2005; Angst et al., 2002). It has also been found in 37% of patients with long-term schizophrenia (Heiskanen et al., 2003) compared with 24% in the general population and after adjusting for age, these data suggest that persons with schizophrenia have double the incidence of the metabolic syndrome compared with the general population (Ford et al., 2002). Metabolic syndrome rates in patients with bipolar disorder and schizoaffective disorder have been reported to be 30-49% (Fagiolini et al., 2005; Pacholczyk et al., 2008; De Hert et al., 2011) and 42% (Basu et al., 2004), respectively.

With the metabolic syndrome, individuals have approximately a 5-6 fold increased risk of developing diabetes and a 3-6 fold increased risk of mortality due to coronary heart disease (Grundy, 2006; Hanson et al., 2002; Laaksonen et al., 2002, Fagiolini et al., 2005; Li & Ford, 2006; Bhargava, 2003; Grundy, 2006; Pacholczyk et al., 2008). In a study of 3606 general population subjects (Isomaa et al., 2001) over a median follow-up of 6.9 years, the presence of the syndrome was associated with significantly higher all-cause mortality (18.0% versus 4.6%; $p < 0.001$) and cardiovascular mortality (12.0% versus 2.2%; $p < 0.001$).

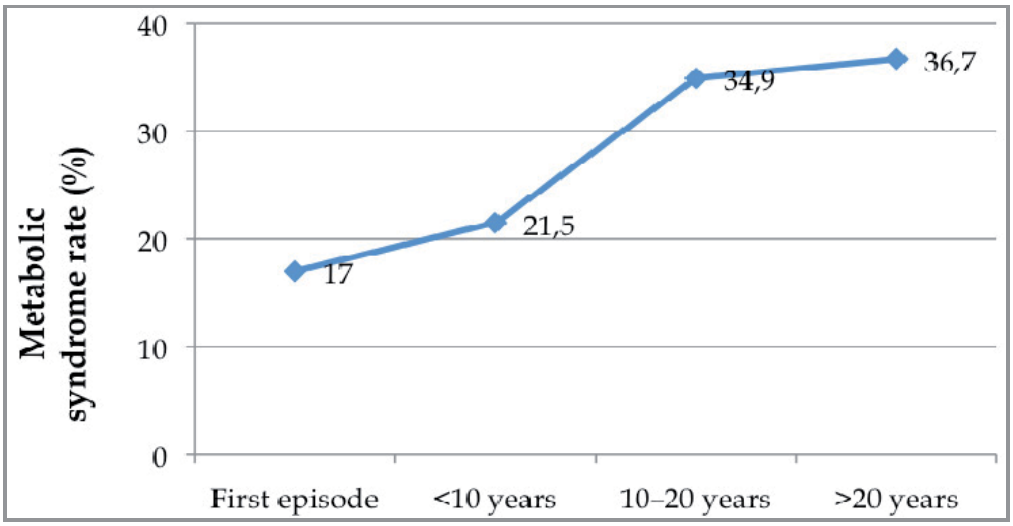
Despite several definitions of the metabolic syndrome have been proposed over the years (Tab. 3), there is agreement that the major characteristics of the syndrome include central obesity, hypertension, dyslipidemia, glucose intolerance or insulin resistance (Li and Ford, 2006; Grundy et al., 2005; De Hert et al., 2011).

Alarmingly, the metabolic syndrome risk appears to be relatively highest in younger patients, which is likely to be responsible for the dramatically reduced life expectancy (Colton and Manderscheid, 2006), with an increased risk over the course of the illness (Fig.1). In a cross-sectional study (Graph.1) metabolic syndrome rate, using NCEP ATP III definition, for first-episode patients (<1.5 years) was 17%; for recent onset patients (1.5– 10 years) it was 21.5%; for subchronic patients (10–20 years) it was 34.9%; and for chronic patients (>20 years) it was 36.7% (De Hert M et al., 2006).

Criteria	NCEP ATP III (2001)	NCEP ATP III A (2004)	IDF (2005)	IDF & AHA/NHLBI (2009)
Required factor	None but any 3 or more of the following	None but any 3 or more of the following	Central obesity plus any 2 of the following	None but any 3 or more of the following
Additional factors				
Obesity	waist circumference ≥102 cm (men) ≥88 cm (women)	waist circumference ≥102 cm (men) ≥88 cm (women)		Elevated waist circumference and country-specific definitions as defined by the IDF and AHA/ NHLBI until more data are available
Triglycerides	≥150 mg/dL (≥1.7 mmol/L) or on elevated triglycerides Rx	≥150 mg/dL (≥1.7 mmol/L) or on elevated triglycerides Rx	≥150 mg/dL (≥1.7 mmol/L) or on lipid abnormality Rx	≥150 mg/dL (≥1.7 mmol/L) (Rx for ele- vated triglycerides is an alternate indicator)
HDL - cholesterol	<40 mg/dL (<1.03 mmol/L)(men) <50 mg/dL (<1.29 mmol/L) (women) or on reduced HDL-cholesterol Rx	<40 mg/dL (<1.03 mmol/L)(men) <50 mg/dL (<1.29 mmol/L) (women) or on reduced HDL-cholesterol Rx	<40 mg/dL (<1.03 mmol/L)(men) <50 mg/dL (<1.29 mmol/L) (women) or on lipid abnormality Rx	<40 mg/dL (<1.0 mmol/L)(men) <50 mg/dL (<1.3 mmol/L) (women) (Rx for reduced HDL-cholesterol is an alternate indicator)
Blood pressure	≥130/85 mm Hg or on hypertension Rx	≥130/85 mm Hg or on hypertension Rx	≥130/85 mmHg or on antihypertensive Rx	≥130/85 mm Hg (antihypertensive Rx in a patient with a history of hypertension is an alternate indicator)
Glucose	≥110 mg/dL (≥6.1 mmol/L) (includes diabetes mellitus) or on elevated glucose Rx	≥100 mg/dL) (≥5.6 mmol/L) (includes diabetes mellitus) or on elevated glucose Rx	≥100 mg/dL (≥5.6 mmol/L) or previously diagnosed type 2 diabetes mellitus	≥100 mg/dL (≥5.6 mmol/L) (Rx of elevated glucose is an alternate indicator)

NCEP ATP III: Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)
IDF: International Diabetes Federation
AHA/NHLBI: American Heart Association/National Heart, Lung, and Blood Institute

Table 3. Definitions of the metabolic syndrome (modified from De Hert et al., 2011)



Graphic 1. Metabolic syndrome prevalence over the disease course of schizophrenia (modified from De Hert M et al., 2006)

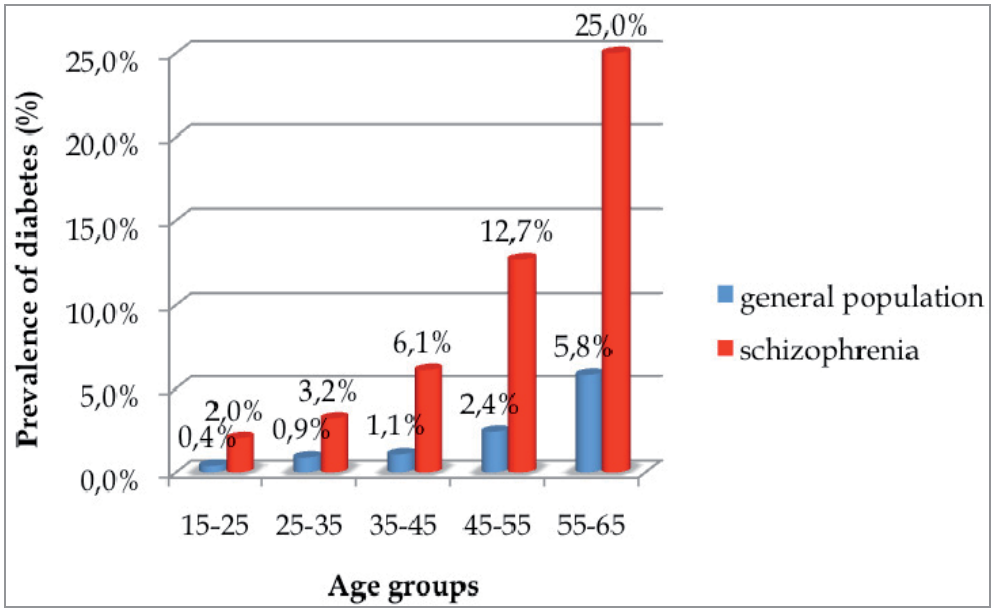
2.2 Diabetes

Currently, 70% of people with diabetes live in developing countries, and while diabetes is increasing across the world, its greatest increase will be in these countries (De Hert et al., 2011). By 2030 more than 80% of people with diabetes mellitus will live in developing countries (Whiting et al., 2010). Persons with diabetes have an increased risk of CVD, and CVD is the cause of death in 70% to 80% of these individuals (Sicree et al., 2003). Evidence suggests that the prevalence of diabetes in people with schizophrenia as well as in people with bipolar disorder and schizoaffective disorder is 2-3 fold higher compared with the general population (Bushe and Holt, 2004;).

The reason for the increased risk of diabetes mellitus in patients with major mental disorder is multifactorial and includes genetic and lifestyle factors as well as disease and treatment specific effects (Fig. 1). An increase in well-established diabetes risk factors in these patients partially accounts for much of the increased risk (De Hert et al., 2011). However, additional factors (disease, treatment) are important as well, and research suggests that, compared to the general population (De Hert M et al., 2006), the prevalence of diabetes in schizophrenia patients is 4 to 5 times higher in different age groups (Graph. 2).

In the general population two important factors that contribute to the development of diabetes are insulin resistance and obesity (Fig. 1). The link between obesity and diabetes is well established (Heald, 2010). A 10 year follow-up study has shown that people with a body mass index (BMI) of ≥35 are approximately 20 times more likely to develop diabetes than age and gender-matched subjects with a BMI of <25 (Field et al., 2001).

The reasons of an higher prevalence of diabetes in schizophrenia patients over the course of the illness is probably an effect of an increased prevalence of obesity, often attributed to antipsychotic treatment (Montejo, 2010; Mulnier et al., 2006).



Graphic 2. Prevalence of diabetes in schizophrenia patients over the disease course compared to the general population (modified from De Hert M et al., 2006)

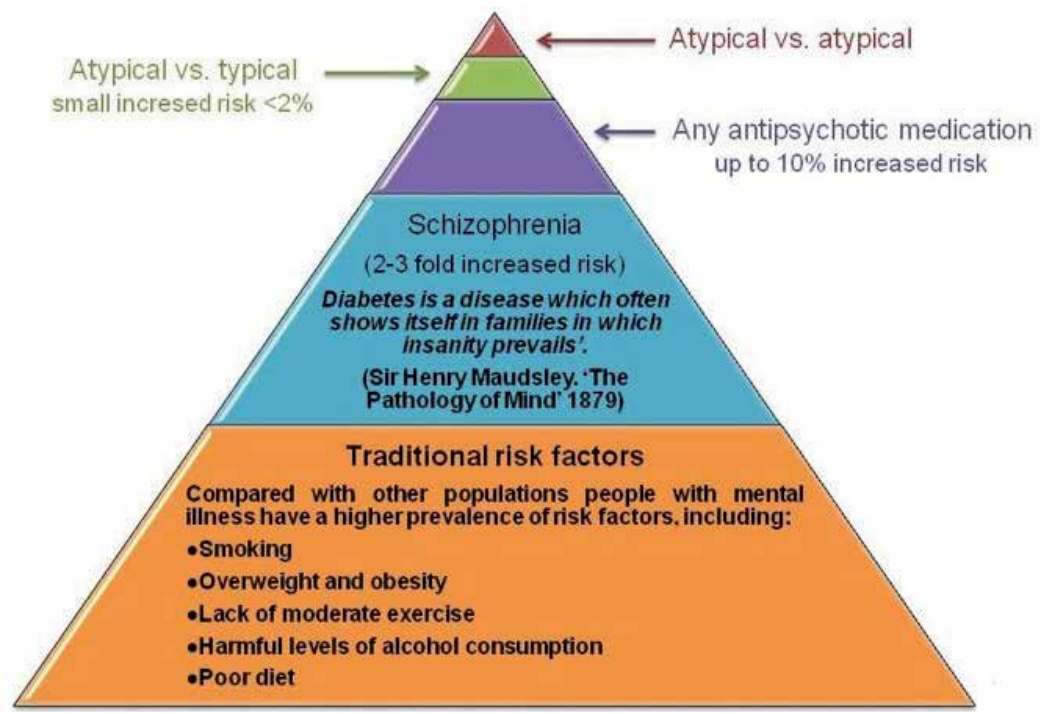
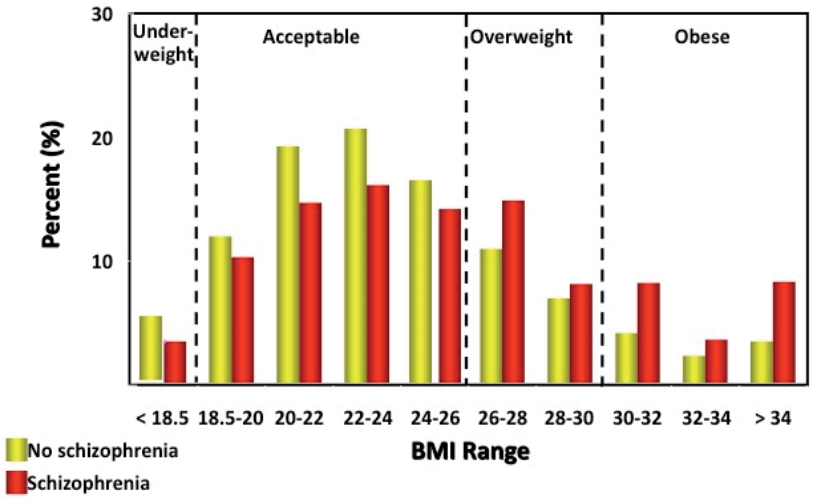


Fig. 1. Factors influencing the risk of diabetes among patients with schizophrenia (M. Smith et al., 2008)

2.3 Obesity

Obesity is becoming a significant and growing health crisis, affecting both developed and developing countries (Haslam & James, 2005; De Hert et al., 2011). People with obesity have shorter life spans and are at increased risk for a number of general medical conditions, including type 2 diabetes mellitus, diabetes mellitus (relative risk, RR >3), cardiovascular disease, CVD (RR >2-3), dyslipidemia (RR >3), hypertension (RR >2-3), respiratory difficulties (RR >3), reproductive hormone abnormalities (RR >1-2) and certain cancers (e.g., colon) (RR >1-2) (McElroy, 2009; Bray & Wilson, 2008). Levels of obesity are higher in those with schizophrenia and depression, as well as the mortality from obesity-related conditions such as coronary heart disease (Allison et al., 2009). Increasing evidence suggests that persons with major mental disorder are, compared to the general population, at increased risk for overweight and obesity (Graph. 3) (Allison et al., 1999; Dickerson et al, 2006).



Graphic 3. BMI distributions in schizophrenia patients and the general population (Allison et al., 1999)

This excess prevalence, however, has not been reported consistently in the past. Despite some early reports of obesity in the pre-antipsychotic era (Kraepelin, 1919), classical descriptions of schizophrenia refer to a thin 'neurasthenic' body habitus and many people with first-episode psychosis are not overweight (Green et al., 2006; Lieberman et al., 2003). Some recent studies show that drug-naive schizophrenia does not present with higher rates of obesity and metabolic problems than a normal population with comparable lifestyle (Padmavati et al., 2010; Verma et al., 2009). Taken together these findings suggest that other factors such as treatment or lifestyle factors may be play an important role in the development of weight gain in these patients over the course of the illness.

2.4 Dyslipidemia

Any increase in cholesterol levels has significant health implications, as a 10% increase in cholesterol levels is associated with a 20% to 30% increase in the risk of coronary heart disease (LaRosa et al., 1990).

Elevated fasting triglycerides (TG) are a direct result of insulin resistance, because insulin-dependent lipases in fat cells are normally inhibited by insulin (Stahl et al., 2009). As insulin resistance worsens, inappropriately high levels of lipolysis lead to the release of excess amounts of free fatty acids that are hepatically transformed into TG (D.A. Smith, 2007). Elevated fasting TG levels thus become a sensitive marker of insulin resistance, with fasting TG to high density lipoprotein (HDL) ratios (TG : HDL) ≥ 3.0 performing better than fasting glucose in predicting insulin resistance (McLaughlin et al., 2003).

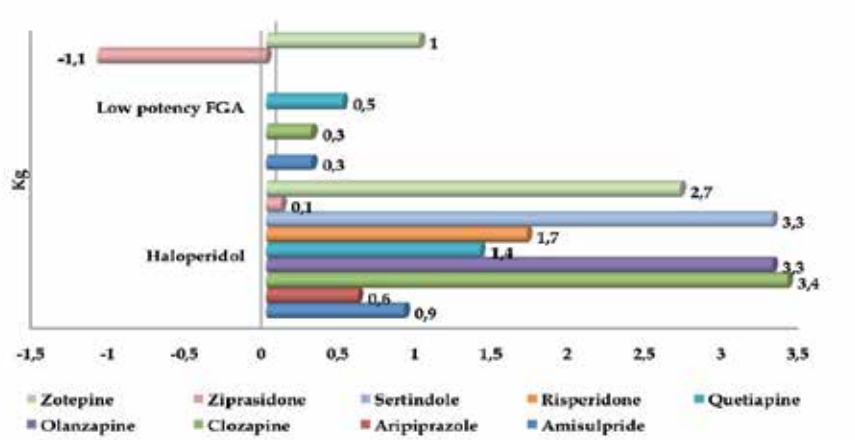
While fasting TG values provide important information on insulin resistance, fasting TG and especially non-fasting TG, also correlate with cardiovascular risk. recent studies indicate that nonfasting TG may be more important for the development of atherosclerotic arterial injury and subsequent CV risk.

The basis of this assertion lies in the concept that arterial injury may occur primarily during the postprandial period, when TG-rich particles are at their highest level and penetrate arterial intimal cells (Eberly et al., 2003). Results of a large (n = 13 981) European trial with extensive follow-up (mean 26 years), indicate a significant correlation between non-fasting TG levels and risk of major cardiovascular events (Nordestgaard et al., 2007).

3. Treatments exacerbate cardiometabolic risk factors

In addition to increased vulnerability to developing physical health problems, it has also been reported that side-effects of antipsychotic drugs have been linked to other physical health conditions such as weight gain, diabetes, and dyslipidaemia (Bobes et al., 2010). Equally, antidepressants (AD) such as paroxetine (Fava et al., 2006), and mood stabilizers, such as lithium and valproate (Bowden et al., 2000), have been associated with weight gain.

While first-generation antipsychotics (FGAs) might also lead to weight gain, especially the less frequently used low-potency FGAs, certain second-generation antipsychotics (SGAs) are now known to induce much greater weight gain (Graph. 4) and cardiometabolic changes in certain patients (Leucht et al., 2009).



Graphic 4. Effect of second generation versus first-generation antipsychotic on weight gain (modified from Leucht et al., 2009)

Of these agents, clozapine and olanzapine are generally associated with the greatest impact on body weight during both shorter- and longer-term (Leucht et al., 2009) therapy. Data suggest that risperidone has an intermediate effect on weight in the short term, and quetiapine appears to have a short-term weight gain potential similar to that of risperidone (Leucht et al., 2009). By comparison, the newer antipsychotic agents, aripiprazole and ziprasidone, are associated with minimal weight gain (Leucht et al., 2009).
The paliperidone extended release, the active metabolite of risperidone, has the same weight gain profile as its parent drug (M. Davidson et al., 2007).
No agent, however, should be considered as truly weight-neutral, as the proportion of individuals experiencing ≥7% weight gain is greater with any SGAs than with placebo (Citrome, 2007), and all antipsychotics have been found to cause significant weight gain in antipsychotics naïve or first-episode patients (Alvarez-Jiménez et al., 2008; Correll et al., 2009; Saddichha et al., 2007) (Tab. 4).
Another important issue is that the weight gain during treatment with antipsychotics occurs in the first weeks (4-6), therefore careful monitoring is necessary to start from the beginning of treatment (Jones et al., 2001; Kinon et al., 2005).

Drug	Weight gain	Glucose effects	Lipid effects	QTc prolungation
Clozapine	**+++**	**+++**	**+++**	**0**
Olanzapine	**+++**	**+++**	**+++**	**0**
Risperidone	**++**	**++**	**++**	**+**
Quetiapine	**++**	**++**	**++**	**0**
Amisulpride	**+**	**+**	**+**	**0**
Aripiprazole	**0**	**0**	**0**	**0**
Ziprasidone	**0**	**0**	**0**	**++**
Paliperidone	**++**	**0**	**0**	**0**
Sertindole	**++**	**++**	**++**	**++**
Zotepine	**+++**	**+++**	**+++**	**+**
Haloperidol	**+**	**0**	**0**	**+ (IV)**
0 = no risk or rarely causes side effects at therapeutic dose, + = mild or occasionally causes side effects at therapeutic dose, ++ = sometimes causes side effects at therapeutic dose, and +++ = frequently causes side effects at therapeutic dose.				

Table 4. Cardiometabolic side effects of antipsychotics (modified from Marder et al., 2004)

Although the mechanisms underlying weight gain are still unknown after initiation of antipsychotic treatment, a strong increase of appetite is combined with immediate substantial weight gain (Theisen et al., 2003; Gebhardt et al., 2007). The level of H1 antagonism associated with different antipsychotic medications is hypothesized to modulate feeding behavior (increased appetite and decreased sensation of satiety), based on the significant association of weight gain and the binding affinity for this receptor. Antipsychotics with minimal affinity for H1 receptors, such as aripiprazole, ziprasidone, and haloperidol, are associated with limited weight gain, while antipsychotics with a high affinity for H1 receptors, such as clozapine, olanzapine, thioridazine, and chlorpromazine, are associated with clinically significant increases in weight (Newcomer, 2005).
Serotonin 2C receptors have been another area of focus, based on data derived from mice with the 5HT2C gene "knocked out" (Stahl et al., 2009). The combined blockade of H1 and

5HT2C receptors has been especially associated with weight gain – sometimes profound – and could explain why atypical antipsychotics such as olanzapine and clozapine, which have high 5HT2C as well as H1 affinities, might have greater weight gain liabilities than an agent such as chlorpromazine, which lacks appreciable 5HT2C effects, even though it has H1 antagonist properties (Cutler et al., 2008; Kroeze et al., 2003).

The high interindividual variability in medication-induced weight gain suggests that genetic factors influence the risk to gain weight (Holt and Peveler, 2009).

Studies of genetic predictors of weight gain under antipsychotic therapy have mainly but not exclusively (Vehof et al., 2010) focused on HTR2C (Mulder et al., 2007; Opgen-Rhein et al., 2010) and LEPR (Opgen-Rhein et al., 2010; Gregoor et al., 2009) gene polymorphisms.

Second generation antipsychotics seem also to have a stronger diabetogenic risk than first generation antipsychicotics (Scheen and De Hert, 2007; Okumura et al., 2010; Citrome et al., 2007), the risk being 1.3 fold higher in people with schizophrenia taking SGAs compared with those receiving FGAs (M. Smith et al., 2008). However, the risk of diabetes-related adverse events differs between SGAs. specifically olanzapine (Ramaswamy et al., 2006; Yood et al., 2008; Koller & Doraiswamy, 2002; Starrenburg & Bogers, 2009) and clozapine (Yood et al., 2008; Starrenburg &Bogers, 2009; Koller et al., 2001) and, to a lesser extent, quetiapina (Koller et al., 2004) and risperidone (Koller et al., 2003), are associated with an increased risk of diabetes (Strassnig et al., 2003) in people who have schizophrenia or bipolar disorder (Guo et al., 2007; Guo et al., 2006). A recent large-scale pharmacoepidemiologic study (including 345.937 patients) found low to moderate, but significantly increased rates of incident DM compared with the general population for clozapine (RR=1.45), olanzapine (RR=1.29) and risperidone (RR=1.23). Rates increased two or more times with ziprasidone and sertindole. Aripiprazole, amisulpride and quetiapina did not have a significantly increased rate (Kessing et al., 2010).

Other psychotropic drugs such as antidepressants may also increase the risk of diabetes mellitus, probably partly due to side effects such as sedation, increased appetite, and weight gain (Sussman et al., 2001; L.C. Brown et al., 2008). Given the heterogeneity and small sample sizes of the few currently available studies, it is unclear whether or not specific antidepressants themselves may increase the risk of diabetes mellitus. Nevertheless, it seems that an increased risk of diabetes is associated with the concurrent use of tricyclic antidepressants and serotonin reuptake inhibitors (SSRIs) (OR=1.89) (L.C. Brown et al., 2008), the long-term use of both tricyclic antidepressants (incidence rate ratio, IRR=1.77) and SSRIs (IRR=2.06) in at least moderate daily doses (Andersohn et al., 2009), as well as the use of antidepressant medication in high-risk patients (Rubi net al., 2008). Furthermore, although understudied, certain mood stabilizers, especially valproate, have been associated with an elevated risk for the development of insulin resistance (Verrotti et al., 2009; Pylvänen et al., 2006), conferring a risk for diabetes mellitus, which is possibly related to weight gain (Masuccio et al., 2010), and/or fatty liver infiltration (Luef et al., 2004), but also to valproate itself (Pylvänen et al., 2002).

Additionally to weight gain and diabetes, some SGAs cause hypertriglyceridaemia, which is an independent risk factor of coronary arteriosclerosis (Tschoner et al., 2007). A prospective study comparing the effects of the SGAs clozapine, olanzapine, risperidone and the FGA sulpiride on glucose and lipid metabolism in first-episode schizophrenia at baseline and 8 weeks after inclusion showed that besides higher C-peptide, fasting insulin and insulin resistance index (IRI), cholesterol and triglyceride levels were significantly increased in the clozapine and olanzapine groups (Wu et al., 2006). Because of these results the authors

recommend that baseline and 6-month monitoring of fasting blood glucose, fasting cholesterol and triglyceride levels should be obtained in routine clinical practice with all antipsychotics to monitor the risk for development of hyperglycaemia and hypercholesterolaemia. Another study described a negative effect of olanzapine administration on total cholesterol and triglycerides, whereas favourable metabolic effects were observed in ziprasidone-treated patients with regard to total cholesterol, LDL and HDL (R.R. Brown & Estoup, 2005). These results were confirmed in different studies (Lieberman et al., 2005; Rettenbacher et al., 2006) and the authors suggest ziprasidone as a favourable alternative treatment for already overweight patients.

In the assessment of cardiometabolic risk, in recent years, particular attention has been paid to the ability of psychotropic drugs to prolong the corrected QT (QTc) interval, which may result in torsades de pointes and sudden cardiac death (Glassman, 2005; Zareba, 2007). An increasing number of psychotropic drugs, are known to delay cardiac repolarization and to induce torsade de pointes. Antipsychotic drugs have a dose-dependent effect on the myocardial repolarization by inhibiting the delayed potassium rectifier current (IKr) (Yap & Camm, 2003). There is a consensus that QTc values >500 msec, or an absolute increase of 60 msec compared with drug-free baseline, puts a patient at significant risk of torsade de pointes, ventricular fibrillation and sudden cardiac death (Haddad and Sharma, 2007; Pies, 2001; Elbe & Savage, 2010). Most antipsychotics and some antidepressants may be associated with QTc prolongation (Glassman, 2005). Patients using AP have higher rates of cardiac arrest or ventricular arrhythmias than controls, with ratios ranging from 1.7 to 5.3 (Ray et al., 2001; Hennessy et al., 2002; Reilly et al., 2002). Antipsychotics associated with a greater risk of QTc prolongation include pimozide, thioridazine and mesoridazine among the FGAs (Vieweg, 2002; Reilly et al., 2002) and sertindole and ziprasidone among the SGAs (Thomas et al., 2010). However, the largest randomized study to date (n=18,154) did not find a statistically significant difference in the risk of sudden cardiac death between ziprasidone and olanzapine treated patients with schizophrenia (Strom et al., 2011).

3.1 The time of monitoring

The maintenance of physical health is an important factor in the successful global management of schizophrenia patients. Research studies have continued to draw attention to monitoring the physical health of patients with schizophrenia in order to successfully enhance these individuals' quality of life (Nasrallah, 2005). In the past decades physical health monitoring of patients with severe mental disorder looked for the extrapyramidal symptoms and tardive dyskinesia often associated with conventional antipsychotics. Atypical antipsychotics were developed to overcome extrapyramidal side effects associated with the use of typical antipsychotics at clinically effective doses, and this has led to widespread use since their introduction over a decade ago (Balf et al., 2008). Despite these benefits, the use of second generation antipsychotics has also been associated with reports of dramatic weight gain, diabetes and atherogenic lipid profiles (Newcomer et al., 2002).

Over recent years, both national and international groups have developed screening and monitoring guidelines (ADA, 2004; De Hert et al., 2009). These guidelines are based on the principle that it is particularly important to establish baseline CVD risk at initial presentation so that any subsequent change during treatment can be monitored. The medical history and examination should therefore include: history of previous CVD, diabetes or other related disease; family history of premature CVD, diabetes or other related

disease; smoking habit; weight and height in order to calculate body mass index (BMI) and waist circumference; fasting blood glucose; fasting blood lipids: total cholesterol, triglycerides, LDLcholesterol (by calculation) and HDL-C; blood pressure (measured twice and average taken), heart rate, heart and lung auscultation, foot pulses; ECG (De Hert et al., 2009).

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 12
History of previous CVD or other related disease	X							
Smoking habit	X							
Weight	X	X	X	X	X	X	X	X
Heigh	X							
Waist circumference	X	X						
Fasting blood glucose	X						X	X
Total cholesterol	X						X	X
Triglycerides	X						X	X
LDL-C	X						X	X
HDL-C	X						X	X
Blood pressure	X							
ECG	X		X					

Table 5. Screening and monitoring of cardiovascular disease risk factors (modified from De Hert et al., 2009).

It is recommended that measurements should be taken at the initial presentation and before the first prescription of antipsychotic medication (Tab. 5). The frequency of testing will depend on the patient's medical history and the prevalence of baseline risk factors. For patients with normal baseline tests, it is recommended that biochemical measurements are repeated at 6 weeks and 12 weeks after initiation of treatment and at least annually thereafter. The frequency of testing will depend on the presence of risk factors and detected abnormalities. During the initial phase of treatment, it is important to measure weight weekly to identify those individuals who gain weight rapidly with psychotropic treatment. In patients with diabetes, an assessment of glycaemia control by HbA1c should be made regularly (approximately every 3 months).

The huge amount of data on cardiometabolic side effects of antipsychotics have shifted over the years the attention of the clinicians to a greater perception of cardiometabolic diseases in patient with severe mental illness (Fig. 2) although still several studies indicate that mentally ill patients receive substandard care regarding routine metabolic monitoring (Haupt et al., 2009).

Since the publication of monitoring guidelines in 2004 (ADA 2004) the following recommendations have been generally accepted as the standard of care: assessment of CVD risk factors and all five components of the metabolic syndrome (ie, weight and waist circumference, blood pressure, and fasting glucose and lipids) prior to antipsychotic initiation; weight assessments at each visit (or monthly for the first 3 months and then

quarterly); and assessment of all components of the metabolic syndrome at 3 months and annually. However a retrospective study which evaluated plasma lipid and glucose testing rates in patients receiving second-generation antipsychotics before and after guidelines were published revealed monitoring for plasma lipids and glucose in this population remains low (Haupt et al., 2009).
Reasons are complex and involve patient nonadherence with medical appointments and interventions, suboptimal monitoring and management behaviors of mental and medical health care providers, and systems issues of fragmented care and poor access to care.

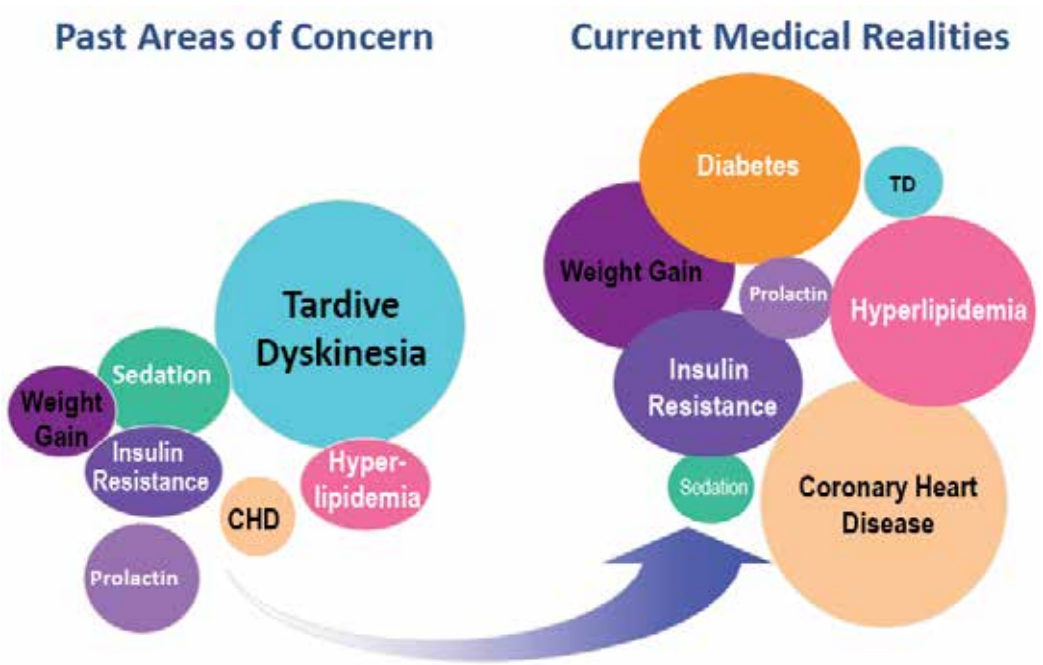


Fig. 2. Shift in risk perception of antipsychotics

3.2 Practical issue to reduce cardiometabolic risk

Given the increased incidence of CVD mortality in people with schizophrenia and bipolar disorder, efforts should be made to lower the modifiable risk factors in this population. A reduction in the prevalence of metabolic syndrome is an important target to improve the physical health of patients with severe mental illness (Heald, 2010). If the patient has central obesity, hypertensive blood pressure (≥130/85 mm Hg), pre-diabetes (fasting plasma glucose =100-125 mg/dL or hemoglobin A1C =5.7-6.4%) or DM (fasting plasma glucose ≥126 mg/dL or hemoglobin A1C >6.4%), or marked dyslipidemia (total cholesterol >350 mg/dL; LDLcholesterol >160 mg/dL; triglycerides >300 mg/dL), he/she should be referred

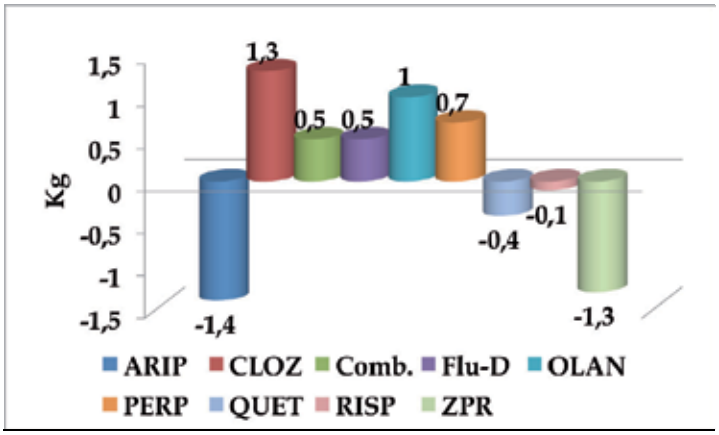
to primary care provider to treat these conditions, unless simple healthy lifestyle guidance or behavioural adjustment and/or switching to a lower cardiometabolic risk medication can address these medical conditions adequately (De Hert et al., 2009).

Non-pharmacological interventions, incorporating dietary and physical activity modifications, demonstrated promise in terms of preventing weight gain in schizophrenia (De Nayer et al., 2005; Sáiz Ruiz et al., 2008; Buckley et al., 2005; Haupt et al., 2009; Vreeland, 2007; Faulkner et al., 2007; Alvarez-Jiménez et al., 2008). The impact on one's overall health, even with simple life style changes, is considerable. A healthy diet, regular physical activity and quitting smoking are the key components of lowering the prevalence and impact of modifiable risk factors. However, if lifestyle interventions do not succeed, medication, including statins, anti-hypertensive therapy or antidiabetic agents, may be indicated. These drugs should be prescribed and managed as for the general population and are generally well tolerated (Cormac, 2009; Laurent & Simons, 2009). Moreover, pharmacologic treatments added to reduce antipsychotic-related weight can be tried. To date, most evidence exists for metformin (500 to 1000 mg bid with meals) or topiramate (50-200 mg in divided doses) (Maayan & Correll, 2010).

If these strategies fail, the clinician should consider switching from a medication with a higher weight-gain liability to one with a lower weight gain liability. Ziprasidone and perphenazine treatments in the CATIE trial (Lieberman et al., 2005) were associated with mean weight loss, most likely related to the switch from a previous antipsychotic treatment. Of those patients who had gained > 7% of their body weight in initial phase of the CATIE who were then randomly assigned to ziprasidone in the second phase of the trial (Stroup et al., 2006), 42% lost more than 7% of their body weight; 20% of those randomly assigned to risperidone lost more than 7% of their body weight; and 7% of patients randomly assigned to quetiapina lost 7% of their body weight. None of the patients who gained >7% of their body weight in the initial phase of the study and were then randomly assigned to olanzapine in the subsequent phase lost more than 7% of their body weight. In phase 3 (Stroup et al., 2009), participants selected openly from the following nine possible treatment regimens: antipsychotic monotherapy with oral aripiprazole (ARIP), clozapine (CLOZ), olanzapine (OLAN), perphenazine (PERP), quetiapine (QUET), risperidone (RISP), or ziprasidone (ZPR); long-acting injectable fluphenazine decanoate (Flu-D); or a combination of any two of these treatments (Comb). If the selected treatment was not discontinued because of inadequate efficacy, intolerability, or any other reason, patients could continue taking this regimen until the completion of 18 months of study treatment. Of the common choices, those who selected aripiprazole and ziprasidone had the highest body mass index and the most monthly weight loss was associated with aripiprazole and ziprasidone (Graph. 5).

Clinicians should consider switching antipsychotics when there is a clear relationship between antipsychotic exposure and change in healthrisk category (i.e., obesity, diabetes, sleep apnea), the patient is about to stop or has stopped antipsychotic use because of weight gain, the patient has bulimia or the patient is abusing weight loss drugs due to newly developed weight gain on antipsychotic treatment. Current evidence (Weiden, 2007) indicates that switching is an effective strategy primarily in patients whose weight gain is attributable to preswitch antipsychotic and in whom long-term monotherapy with a weight-neutral agent can be maintained. In this population, the effectiveness of switching appears to be related to a reversal of the weight-increasing effects of a prior antipsychotic medication.

Regarding the effect of antipsychotics on the QTc interval, the use of lower doses and monotherapy may represent an effective strategy in reducing the risk of QTc lengthening (Di Sciascio et al., 2011).



Graphic 5. Weight change among the commonly selected treatments in Phase 3 of CATIE (Stroup et al., 2009)

4. Conclusion

The mortality gap between patients with severe mental illness and the general population has substantially widened in recent decades, warranting close attention to the cardiovascular health of this patient population. Reasons for the increased prevalence rates of CHD risk factors are complex, but include effects of mental illness, poor lifestyle behaviors, weight gain, and metabolic abnormalities conferred by psychiatric treatments, particularly by SGAs. While the mechanisms for weight gain are still unclear and direct, weight-independent mechanisms for at least some SGAs regarding glucose and lipid abnormalities have been discussed, it is clear that antipsychotics differ in their risk for adverse changes in body weight and metabolic dysregulation (Correll, 2007).

As individuals with mental illness are more likely to be overweight or obese than the general population, weight should be routinely monitored in all patients, especially in those receiving treatment with atypical antipsychotic medications associated with weight gain (Balf et al., 2008).

Routine adverse-effect monitoring should be part of any pharmacologic treatment. For antipsychotics, this should include baseline assessments of EPS and abnormal involuntary movements, sleep duration and quality, daytime sedation, sexual and reproductive dysfunction, and risk factors for cardiovascular disease, including unhealthy lifestyle (Correll, 2007).

By using the charts and tables in this article, clinicians will be better informed to educate the patient in a variety of interventions that will diminish the potential for medication side effects, promote better pharmacologic efficacy from prescribed medications, and improve the overall quality of life.

In conclusion, the management of patients at risk of cardiometabolic disease can be complex, but if performed systematically and in conjunction with healthcare professionals

who can address the metabolic complications in a complementary fashion, it can provide a clinical outcome that will be potentially very beneficial to the individual patient. The reintegration of psychiatric care and general somatic services seems to represent one of the most important challenges for psychiatric care today.

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10

Psychiatric Comorbidity and Pharmacotherapy in Patients with Oral Lichen Planus

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1. Introduction

Lichen planus is a relatively common chronic mucocutaneous disease that exact etiology is not well understood so far. However immune system plays a primary role in development of this disease (Neville B 2009; Greenberg MS 2008). Prevalence of Lichen planus varies in different regions of the world (Greenberg MS 2008). It is reported about 1% for cutaneous lesions and 0.1-2.2% for oral lesions (Greenberg MS 2008). This disease was first described by Wilson in 1869(Neville B 2009).

Lichen planus is described as an adult disease. Most patients are in fifth decade of life with mean age of 55 years at the time of diagnosis (Silverman et al. 1991; Neville B 2009). Thirty five percent of patients are above 50 years old; however development of this disease also has been reported in children and adolescents (Silverman et al. 1991; Neville B 2009). Some familial cases have been reported in literature (Bermejo-Fenoll and Lopez-Jornet 2006). Although there is not any race predilection, the females are more affected than males (FreedbergIM 1999; Greenberg MS 2008).

In a study done on 420 Iranian patients, 64.9% were women with the mean age of 41.6 years (Pakfetrat 2009).

Prevalence of concurrent cutaneous and oral lesions is 20-50% in different studies and cutaneous lesions may be encountered in approximately 15% of patients with oral lichen planus (Greenberg MS 2008). Oral lesions are more frequent and 30-70% of the patients have oral lesions (Neville B 2009; FreedbergIM 1999; Greenberg MS 2008). In one study done in north -east of Iran, 83% of lichen planus patients had only oral lesions and the rest of the patients (17%) had lesions in other sites such as skin, hair and nail (Pakfetrat 2009).

2. Clinical findings

Lichen planus is a member of lichenoid reactions lesions. Lichenoid reactions are a family of lesions with various etiologies and similar clinical and histopathological appearance. Oral

lichenoid reactions include: lichen planus, lichenoid contact reactions, lichenoid drug eruption, lichenoid reactions of graft-versus-host disease (GVHD)(Greenberg MS 2008).
Cutaneous lesions of lichen planus appear as purple pruritic polygonal plaques or papules which are usually self limiting in contrast with oral lesions (Greenberg MS 2008).Initially, these lesions are erythematous macules which change into flat-topped purple papules in several weeks (Neville B 2009; FreedbergIM 1999; Burns T 2004). The skin lesions appear on the flexor surfaces of the forearm and wrist. Vagina, esophagus, anal canal and larynx may also be affected (FreedbergIM 1999; Burns T 2004).Nikolsky's sign could be positive in some patients.(Vincent et al. 1990)
Oral lesions are observed as either reticular, papular, plaque-like, atrophic (erythematous), erosive-ulcerative or bullous lesions (Greenberg MS 2008; Neville B 2009; FreedbergIM 1999). Some researchers divide the lesions into two group of erosive and non-erosive and other describe them as keratotic and non-keratotic. (Lacy, Reade, and Hay 1983; Bagan-Sebastian et al. 1992; Neville B 2009; Greenberg MS 2008). The most common oral site is buccal mucosa followed by lingual, gingival and labial mucosa. The majority of studies, revealed reticular type as the most common type of oral lesions which appears as bilateral lingual and buccal lesions. In reticular lichen planus, characteristic pattern of interlacing white lines (Wickham's striae) may be observed (Greenberg MS 2008; Neville B 2009). In one study done on 690 oral lichen planus patients, reticular form was the most common type of the disease and 95% of lesions appeared as bilateral (Ingafou et al. 2006). In another study done in Mashhad, Iran, the most common type was reticular form with 77% prevalence. Sixty six percent of lesions were associated with other types of disease. Atrophic was the second common lesions (38%). The most common sites of lesions were buccal, lingual, gingival and lower labial mucosa (Pakfetrat 2009).
Because of burning in erosive- atrophic type, most patients referring to clinics for treatment suffer from this form of disease. Atrophic (erythematous) lesions are defined as inflamed regions that are covered with a thin and red epithelium. Erosive lesions appear as red regions indicating loss of epithelium integrity. Erosive changes and pseudo-membrane formation associated with an ulcerative lesion (Greenberg MS 2008). The keratotic lesions appear as reticular, anular, papular and plaque-like which are mostly without any symptoms (Neville B 2009; Greenberg MS 2008). Because erosive-ulcerative and atrophic lesions are mostly associated with reticular pattern, finding of reticular lesions is important in clinical examination for confirming the diagnosis in suspicious lesions (Greenberg MS 2008).

3. Histopathological findings

In histophathological evaluation these changes are observed:

1. Hyperparakeratosis or hyperorthokeratosis on the surface of epithelium associated with increasing in thickness of spinous layer.
2. Ret ridges may be absent or hyperplastic and classically have a "saw- toothed" appearance.
3. Hydrophic degeneration or destruction in basal cell layer.
4. Eosinophilic band under the basal cell layer may be present.
5. Band-like dense infiltrate of T lymphocytes at subepithelial layer which is characteristic of the disease.
6. Deposition of antibodies and complement may be observed that is not pathognomonic (Neville B 2009) (Greenberg MS 2008).

4. Risk of malignancy transformation

Oral lichen planus (OLP) is a premalignant condition. Risk of malignancy transformation is higher in erosive-atrophic type and in lateral border of tongue. Some studies revealed that plaque- like lesions have much more risk for malignant transformation .(Neville B 2009; FreedbergIM 1999; Greenberg MS 2008).

5. Association with other diseases

Idiopathic lichen planus is associated with other auto- immune diseases and immune disorders. In different studies, diseases such as ulcerative colitis, alopecia, areata, vitiligo, dermatomyositis, morphia, thymoma, myasthenia gravis, hypogammaglobulinemia and primary biliary cirrhosis are reported to occurredin lichen planus patients (Burns T 2004; Greenberg MS 2008).

Some studies showed association of lichen planus with HIV and HCV (Gandolfo et al. 1994; Roy and Bagg 1999; Klanrit et al. 2003; Pilli et al. 2002; Emadi et al. 2010). Recent studies revealed that specific T lymphocytes related to chronic HCV infectionhave been defined in oral mucosa of chronic HCV and OLP patients (Pilli et al. 2002). Another study defined that patients with acute hepatitis or chronic liver disease or high level of liver enzymes or positive HBS antigen, may have OLP lesions twice than normal population (Gandolfo et al. 1994).

In some studies reported that patients affected by multiple endocrinopathy such as Turner's syndrome, psoriasis, lupus erythematosus, scleroderma, Crohn's disease, may have OLP lesions, because of more probably of association of multiple autoimmune diseases (Gardner 1967; Parodi et al. 1998; Kurgansky and Burnett 1994).

There are some challenges about relationship of OLP and diabetes. Some studies did not find any significant correlation between them; in contrast, other researchers reported glucose intolerance in OLP patients (Albrecht et al. 1992). It is not confirmed that OLP are more susceptible for diabetes. More OLP lesions in diabetic patients are as erosive-atrophic form and are much more located on lingual mucosa (van der Meij et al. 1999). Some researchers believed that higher prevalence of OLP lesions in diabetic patients is related to anti- diabetic drugs that cause lichenoid reactions (Albrecht et al. 1992).

6. Etiology and pathogenesis

OLP is an immunologic disorder by a T-cell mediated immune response. TCD8+ (cytoxic) cells trigger apoptosis process in oral epithelial cells (Eisen 2003; Sugerman et al. 2002). Cell mediated immunity begins by endogen or exogen cells and consequently TNF-α and TNF-β are produced (Scully, Eisen, and Carrozzo 2000; Lodi et al. 2005). Some researchers have divided mechanisms of OLP pathogenesis into mechanisms of non-specific and specific for antigens (Sugerman et al. 2002). Specific mechanisms include:

1. Expression of antigen limited by MHC molecule class I and II by kerationcytes.
2. Activation of specific TCD8+ and TCD4+ helper cells for antigen (In OLP, most lymphocytes of epitelium are CD8+ and lymphocytes of lamina propria are CD4+).
3. Clonal specific lymphocytes for antigen.
4. Apoptosis of kerationocytes begins specific TCD8+ for antigen (Sugerman et al. 2002). Firstly, in development of OLP lesions, CD8+ cells in lesion can identify antigen in relation to MHC class I on keratinocytes surface. After defining antigen and activation

of TCD8+, apoptosis of kerationcytes begins. Activated TCD8+ cells and kerationcytes release cytokines that attract more lymphocytes and other cells (Yamamoto et al. 1994).

Accumulation of cytokines plays an important role in development and progression of OLP (Santoro et al. 2003). Rhodus et al confirmed that the levels of TNF-α, IL-1, IL-6 and IL-8 decreased in whole saliva following the treatment of erosive OLP (Rhodus et al. 2006). Another study revealed that TNF-α plays an important role in pathogenesis of OLP. Treatment with fluocinolone acetonide decreases its expression (Thongprasom et al. 2006).

Other factors that play a role in development and progression include: Matrix metalloproteinase (MMP) (causes lymphocyte migration), MMP/TIMP (inhibitors of MMP), RANTES (mast cell trafficking and degranulation) and release of TNF-α, impairment in suppression of Transforming Growth Factor B1 (GF- β1), expression of epithelium adhesion molecules via TNF-α stimulated by mast cells, heat shock proteins, activation of TMMP and lymphocytes by mast cells chymase (Zhao et al. 2002; Sugerman et al. 2002).

In recent years, it has been confirmed that antioxidant imbalance, in addition to cytokines and cell mediated immune response play a role in OLP pathogenesis. Free O2 radicals produced by inducing lipo-peroxidase cause damage to cell membrane and consequently cell apoptosis and necrosis. In one study, a decrease in antioxidant defense and a significant increase in peroxidation products and increased oxidative damage to lipids and DNA and proteins mainly within the basal cell layer of the epidermis and at the dermoepidermal junction, have been demonstrated (Sander et al. 2005). One study in 2010 showed the serum level of nitritoxide and superoxide dismutase was greater than control group. In contrast, a decrease in erythrocyte catalase levels was observed (Aly and Shahin 2010). Mast cells and macrophage degranulation causes the release of cytokins; chymase and TNF-α (Tumor Necrotizing Factor-α), leading to expression of ELAM1(endothelial leukocyte adhesion molecule-1) , ICAM (intercellular adhesion molecule) and leukocytes adhesion molecules (Carrozzo and Thorpe 2009). Chymas released from mast cells acts as MMP. (Matrix metalloproteinase) and lead to basal layer degeneration. ICAM plays a role in the attraction and migration of lymphocytes to oral epithelium (Ismail, Kumar, and Zain 2007).

6.1 Psychiatric comorbidity and oral lichen planus

Although etiology OLP is unknown but, cell-mediated immune system plays an important role in OLP pathogenesis(Greenberg MS 2008) (Neville B 2009). Therefore, any factor that can influence the cell-mediated immune response can play a role in the development of the disease. Factors such as stress and psychological problems, especially depression and anxiety, have been mentioned as etiologic factors in lichen planus, but there is still controversy concerning the role of stress as a major or minor etiologic factor in the pathogenicity of lichen planus (Greenberg MS 2008).

Different studies have been done for the evaluation of the relationship OLP and psychiatric disorders. These studies used various psychiatric questionnaires, but any treatment intervention has not been used but in our study, after diagnosis of psychiatric disorders by psychiatric interview, we treated these disorders with psychiatric pharmacotherapy (Delavarian 2010). Among different studies, some found a positive correlation between OLP and psychiatric disorders; however other studies did not establish such a relationship.

One study with different psychiatric tests such as "General Health Questionnaire", "Hamilton Anxiety Scale", "Melancholia scale, depression", Hamilton Depression Scale" demonstrated that OLP patients had higher depression and anxiety scores (Colella et al.

1993). Another study showed 53% depression in OLP patients and 20% in control group by "Beck Depression Score". This study confirmed importance of depression assessment in skin diseases like lichen planus and psoriasis (Akay et al. 2002). Also, one study demonstrated that some skin diseases such as lichen planus develops in relation to stress, moreoveremotional events and stressful life events exacerbate the lesions (Onder et al. 2000). A case-control study revealed that patients with cutaneous lichen planus had more been exposed to stressful life events and suggested the need for concurrently dermatological and psychological treatment intervention (Mansur, Kilic, and Atalay 2004). Also, another study showed OLP lesions became worse during times of mental stress, but most patients did not feel any need for psychiatric treatment (Hampf et al. 1987).Psychological Minnesota Multiphasic Personality Inventory (MMPI) was used in comparison of OLP patients and healthy persons. It showed prolonged emotional stress in OLP patients may lead to psychosomatization and can affect its expression. This study confirmed clinical trials is needed for determine effects of adjunctive psychological treatment of OLP patients (Ivanovski et al. 2005). Furthermore, significantly higher stress, anxiety, and depression levels were found in OLP patients than the general population that suggest probably role of stressors in OLP (Chaudhary 2004). Although there is a significant association between the stage of OLP, hypothalamic-pituitary-adrenal dysregulation, and altered responses of CD4+ cells, there is the need for studying the detail of these relationships in OLP (Prolo et al. 2002).

The rate of salivary cortisol can be an indicator of higher level of stress. Salivary cortisol and its correlation to OLP have been evaluated. A study on salivary cortisol showed the salivary cortisol and state and trait anxiety levels in OLP group were significantly higher than healthy group that concluded that oral lichen planus is closely related with stress. The findings suggested that besides routine treatment of OLP patients, psychological support isneeded (Koray et al. 2003). Some studies on salivary cortisol showed that the salivary cortisol and also anxiety, depression, and stress levels in OLP patients were higher than healthy group. This result demonstrated a positive correlation between psychiatric disorders and salivary cortisol levels in OLP patients (Shah, Ashok, and Sujatha 2009) .

In contrast to these studies that show stress, anxiety, and depression had a positive effect on OLP, some studies didn't find any positive association between stress and OLP.

In one study, despite higher levels of anxiety in OLP patients, it was not confirmed that psychiatric changes aredirect etiologic factor in OLP development or psychiatric disorders are OLP consequences (Rojo-Moreno et al. 1998).

Another study measured anxiety level on the Hospital Anxiety and Depression (HAD) Scale and demonstrated that there were no statistically significant association between erosive oral lichen planus and either anxiety or depression (McCartan 1995).

Salivary cortisol and dehydroepiandrosterone (DHEA) levels were measured in OLP patients. Furthermore, Beck Depression Inventory, Beck Anxiety Inventory and Lipp's Inventory of Stress Symptoms for Adults were used for evaluation symptoms of depression, anxiety and stress. Although the results suggested an association of OLP with anxiety, DHEA and cortisol levels did not differ between different groups, which does not support any neuroendocrine etiology for OLP (Girardi et al. 2011). In anotherstudy, saliva samples of ten OLP patients were collected and the amount of salivary cortisol was measured for assessment of temporary stress, OLP patients did not have higher level of stress (Rodstrom et al. 2001).

Briefly, studies revealed that there is a close correlation between immune system and central nervous system (CNS) that plays an important role in establishment of homeostatic condition in body and health maintenance or disease development. (Sadock BJ 2005). Immune system cells express some receptors for many molecules that are modulated by nervous system. These are receptors for neurotransmitters, neuropeptides and steroid hormones. Immune system response includes induction stage, activation stage and finally effectors stage. The consequences of system effect are dependent on which stage is influenced by the nervous system (Sadock BJ 2005). For example, norepinephrine in induction stage causes the acceleration of the immune system function. Inhibition or exacerbation of immune system function in activation stage is dependent on the concentration of epinephrine, but epinephrine leads to inhibition effect in effectors stage (Sadock BJ 2005). Therefore, both stage of effect and amount and type of substance play a role in the process (Sadock BJ 2005).In vitro and in vivo effects of these molecules are various. For example, β adrenergic system causes inhibition of lymphocyte activity in vitro. In contrast, increase in susceptibility of suppressor T lymphocytes with increase in number of receptors can lead to a higher immune response in vivo (Sadock BJ 2005).

Neuropeptides such as endorphins cause an increase in T lymphocytes and natural killer cells proliferation; and cause production of cytokines and cytotoxic T cells in vitro (Sadock BJ 2005). Inhibition effect of stress on natural killer cells acts as a mediator in vivo and in vitro (Sadock BJ 2005).Different studies demonstrated that stress influences development and exacerbation of disorders related to immune system such as infectious, cancerous and autoimmune diseases (Fink 2000). Stress can change immune response to antigens and alter ability ofcells for expression of peptides to T lymphocytes (Fink 2000).Different agents influence final result of stress effects on immune system include: severity and type and duration of stress, coping with stress, type of affected immune system and host immune system (Sadock BJ 2005).For example; crowding stress causes increase in lymphocyte stimulation to antigens (Sadock BJ 2005). Institutionalizing of elderly (stress of care-giving) can cause depression and consequently a change in the immune system and increase in TCD8+ and reduction in natural killer cells activity. Professional stress is associated with altered immune cells function (increase in IL-2 expressing cells) and probably suppressing effect (reduction in natural killer cells). Post traumatic stress disorder (PSTD) is associated with an increase in IL-6. Influence of stress on humoral and cell-mediated immune system is different. Also, the amount of the effect of stress is dependent on the host psychological condition. In depression, immune system changes are various include: increase in white blood cells, increase in IL-6 and macrophages activity and neutrophilia, lymphopenia and impaired T cell function (Sadock BJ 2005). Coping with stress causes a change in immune response and reduction of its harmful effects. Prohibiting of the patient from doing what he likes (restraint), increases IL-6 (Sadock BJ 2005; Fink 2000). Considering the ability of stressful events to stimulate cytokines and the ability of cytokines in regulating CNS function, immune system may play a role in response to stress even without presence of pathogens (Sadock BJ 2005).Studies confirmed reduction in natural killer cells activity in stressful events e.g. test taking period. Also, stress can lead to reduction in interferon, antibody response, lymphocytes and lymphocytes response to mitogen.

Briefly, researchers showed a decrease in immune system activity in chronic stressful event (Sadock BJ 2005).Response to stress or psychological pressure can include changes in hormonal balance such as release of catecholamines, glucocorticoids and increase in

expression of heat shock proteins (Fink 2000). The studies confirmed role of released neuropeptides from non-myelinated axon terminals such as Substance P (SP), Vasoactive Intestinal Peptide (VIP), Calcitonin Gene-Related Peptide (CGRP) in stimulation of various immune cells, resulting cytokines release, chemotaxis, phagocytosis in cutaneous diseases. For example; Substance P causes stimulation of release of IL-1, Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) from keratinocytes, proliferation of IL-2 in lymphocytes, release of IL-6, IL-1, TNF from macrophages and migration of lymphocytes into skin (Fink 2000; Sadock BJ 2005). Also, CGRP causes proliferation of keratinocytes and increase in chemotactic T cell proliferation (Robert A 2001).

The role of proliferation and activation of lymphocytes and keratinocytes and release of cytokines in lichen planus has been confirmed. The evidences show stressful life events and psychological agents play a role in development and exacerbation of skin diseases (psoriasis) and patients with higher level of distress, experience exacerbated skin lesions (Robert A 2001).

It is confirmed that stress and hypothalamo-hypophyseal-adrenal axis and autonomous nervous system-as mediator of CNS effect on immune system- lead to reduction in humoral and cellular immune responses. Stimulation of release of various cytokines such as IL-1β, IL-1α, Il-2, IL-6 and TNF by corticotropin-releasing hormone (CRH); followed by stimulation of local inflammation, could be important in OLP development. On the other hand, different factors are effective in immune responses and effect of stress on immune system.

Conclusively, stress can play a role as a contributing factor in immune system function disturbance leading to production and release of cytokines and consequently destruction function of cytotoxic T cells (Sadock BJ 2005). Our experiences and different studies with various scales about association of psychiatric disorders and lichen planus showed that OLP patients respond to stress by development of oral lesions while other people may not react in the same way. Because of impaired immune system function, the possibility of development of other diseases such as neoplasm, infectious diseases and autoimmune disease should be considered in OLP patients.

7. Differential diagnosis

Oral lesions of lichen planus may be difficult to distinguish from other white and red and also chronic ulcerative lesions of oral mucosa. Lichenoid contact reactions, lichenoid drug eruption, lichenoid reactions of graft-versus-host disease (GVHD), lupus erythematosus, idiopathic leukoplakia, squamous cell carcinoma, benign mucous membrane pemphigoid and candidiasis should be mentioned in differential diagnosis of oral lichen planus. Obtaining complete history and proper examination of oral mucosa are useful. Although bilateral reticular or annular pattern on the buccal mucosa is pathognomonic, in erosive-atrophic form, biopsy is recommended for ruling out lupus erythematosus.Sometimes immunofluorescence tests are required for accurate diagnosis (Greenberg MS 2008; Neville B 2009).

8. Management

Because oral lichen planus is chronic disease, some patients seek treatment for many years. The mainstay treatment for OLP is topical corticosteroids (Lodi et al. 2005; Eisen 2003; Dalirsani 2010; Greenberg MS 2008). The topical Corticosteroids are used in different types,

forms and doses which are prescribed according to location, number, and extension of lesions. The topical corticosteroids which are used in the forms of paste, lotion, spray, mouthwash and intralesional injection, include dexamethasone, betamethasone valerate, clobetasol propionate, triamcinolone acetonide, fluocinolone acetonide, hydrocortisone, fluocinonide which have different potencies. Topical corticosteroids in orabase such as triamcinolone in orabase have better effect because of adhesion to oral mucosa (Dalirsani 2010; Lodi et al. 2005; Greenberg MS 2008).

The second alternate for OLP treatment are systemic corticosteroids which are prescribed in diffuse lesions or lesions that are resistant to topical treatment (Lodi et al. 2005). It is suggested that systemic corticosteroid prescribed as 1 mg/kg/day prednisolone for 7 days that is tapered with reduction in drug dose as 10 mg/day. In tapering duration, topical steroid may be needed (Greenberg MS 2008).

Topical corticosteroid may cause a wide spectrum side effects such as candidiasis, taste disorder, nausea, xerostomia, sore throat, oral inflammation and mucosal atrophy (in intra-lesional injection) (Thongprasom and Dhanuthai 2008). For the prevention of candidiasis after using topical corticosteroid, topical anti-fungal drugs are prescribed (Greenberg MS 2008). Systemic corticosteroid can cause fatigue, insomnia, fluid retention, moodalteration, hypertension, plasma glucose increase, osteoporosis, and adrenal suppression (Lin AN 2002).

Other alternates in OLP treatment include: topical immune suppressor or immune modulator agents e.g. cyclosporine (calcinorin inhibitor) or systemic immune suppression; azathioprine, dapson, levamisole, hydroxychloroquine, anti-inflammatory drugs: doxycyclin. Furthermore, other strategies suggested such as griseofulvin, glycurrhizin, interfron, tacrolimus, retinoids, phototherapy with ultra violet (UV) and laser. (Jajarm, Falaki, and Mahdavi 2011; Greenberg MS 2008).

Concurrent use of several drugs causes different problems for patients. Some studies used combination of several drugs which is necessary especially in diffuse lesions with various forms (reticular, atrophic or ulcerative lesions).

In one study done in Tabriz, Iran demonstrated that mouthwash of combination of triamcinolone acetonide and vitamin A is significantly more effective than triamciolone acetonide mouthwash alone in treatment of OLP lesions(Dalirsani 2010). In another study, combination of amitriptyline, ketokonazole, and clobetasole in mouthwash form was useful in OLP patients (Javadzadeh 2008).

For the first time, in one study, we evaluated the effects of concurrent routine treatment of OLP lesions with topical corticosteroid and psychiatric therapy of patients with psychiatric disorders (Delavarian 2010) .

8.1 Suggestion of psychiatry therapy as a novel supplementary treatment for oral lichen planus

A randomized clinical trial study was designed to evaluate the effect of the drug therapy of psychiatric disorders on lichen planus. We filled out special examination forms for 55 OLP patients referring to the Oral Medicine Department in Mashad Faculty of Dentistry. Then, the patients were evaluated by a psychologist. Out of 55 patients, 53 patients were diagnosed with one of the psychological disorders according to the criteria set by DSM-IV-IR. The patients filled out informed written consent forms. The subjects having the inclusion criteria were chosen for the study (Delavarian 2010).

Inclusion criteria include:
1. patients with oral lichen planus (all forms) with or without skin involvement;
2. affliction with psychiatric disorders.

Exclusion criteria include:
1. patients exhibiting dysplasia in histopathological evaluation (1 patient);
2. patients with lichenoid reaction potential as evidenced by histopathological examination, drug intake or other predisposing conditions (5 patients);
3. patients diagnosed with acute psychosis with the potential of harming themselves or others (no patients);
4. patients who had received any medications for lichen planus during the past month (1 patient).

Forty-six patients; 31 subjects from the case group and 15 subjects from the control group were followed for 6 months. Patients' demographic information and location, form and size of the lesions and pain sensation of each patient were recorded in the questionnaires.

The severity of the signs in lichen planus depends on the form and size of the lesions. Oral lesions were described and classified in 3 forms:
1. keratotic (reticular form, plaque form or both).
2. atrophic (atrophic lesion with or without keratotic lesion).
3. erosive-bullous (erosive or bullous lesion with or without keratotic lesion).

The oral cavity was divided into ten areas to determine the percentage of lichen planus extension in the oral cavity. These areas were: oral vestibule, alveolar mucosa, lips, buccal mucosa, oral floor, fauces, gingiva, palate and the dorsal and ventral aspects of the tongue. Therefore, the percentages of the involvement for all areas of the oral mucosa were calculated and subsequently the percentage of the involvement of the oral cavity was calculated.

The severity of pain and pain sensation was evaluated according to following scales:

Scale 0: no pain: VAS=0

Scale 1: mild pain: $0< VAS\leq 3.5$

Scale 2: moderate pain: $3.5 <VAS\leq 7$

Scale 3: severe pain: $7< VAS\leq 10$(Greenberg MS 2008).

Both groups received routine treatment for oral lichen planus consisted of topical corticosteroids, mostly triamcinolone paste along with nystatin (antifungal) mouthwash. Some patients suffered from diffuse lesions treated with dexamethasone mouthwash. Furthermore, the case group received drug therapy for psychiatric disorders. Then the patients were subjected to regular oral examinations every two weeks, carried out by an oral medicine specialist who was blinded to the treatment received by each patient, until the signs and symptoms were brought under control. The patients in the case group were evaluated for possible side effects of the medication(s) 2 weeks after the initiation of the study and afterwards were monthly examined by the psychologist, too. Treatment of patients continued until remission of signs and symptoms (Delavarian 2010).

The recovery rate (response to treatment) in each patient was evaluated according to Tables 1 and 2, based on the percentage of the area involved, form of the lesion and the severity of the pain. The psychiatric recovery of the patients has been classified in Table 3.

The comparison of the case and control groups regarding complete or partial response to treatment was carried out in the second and sixth months according to the codes depicted in

Tables 1 and 2. The results of the two groups as to the remission of the signs and symptoms of oral lichen planus were compared using the non-parametric Mann-Whitney test.

Response to treatment	Scale	Criteria
Excellent	0	recovery ≥ 75%
Good	1	50% ≤ recovery < 75%
Fair	2	25% ≤ recovery < 50%
Poor	3	0% ≤ recovery < 25%
Exacerbation	4	increase in lesion size and extension

Table 1. Scaling of response to OLP treatment according to lesion size and extension

Response to treatment	Scale	Criteria for lesion form	Criteria for severity of pain
Excellent	0	conversion of scales1,2 & 3 to 0 (without lesion)	conversion of scales 1,2 & 3 to 0 (without pain)
Good	1	conversion of scale3 to 1	conversion of scale 3 to 1
Fair	2	conversion of scale2 to 1 or conversion of scale 3 to 2	conversion of scale 2 to 1 or 3 to 2
Poor	3	no conversion in scale	no change in pain
Exacerbation	4	conversion of scale1 to 2 or 3 or conversion of scale 2 to 3	conversion of scale 0 to1 or 2 or 3 or conversion of scale 1 to 2 or 3

Table 2. Scaling of response to OLP treatment according to the form of the lesion and severity of pain.

Scale	Response to treatment
0	complete response
1	good response
2	little response
3	no response

Table 3. The classification of the psychological recovery of the patients

Also, the patients in the case group were subjected to Spearman's test to be evaluated in relation to the correlation between psychological recovery and oral lesion recovery, given the size and form of the lesions and the pain sensation.

The protocol of this study was approved by the Medical Ethics Panel of Mashhad University of Medical Sciences and all the patients were informed of all the procedures involved in the study and all had information about the anecdotal nature of the study (Delavarian 2010).

In this study; out of 55 patients, 53 patients were diagnosed with at least one of the psychological disorders according to the criteria set by DSM-IV-IR.Among them, 76.8% were above 40 years old with mean age of 47.2 ±13 years and 39 patients (73.5%) were women.

Their psychiatric disorders consisted of anxiety, mood, somatoform, adaptation, drug withdrawal and personality disorders. Table 4 indicates prevalence of psychiatric disorders among studied patients. Nearly 93.5% of our patients, who had OLP, suffered from anxiety disorders, about 52.5% suffered from mood disorders, 10.2% had somatoform disorders. Some patients had several concomitant psychiatric disorders.

Type of Psychiatric Disorders	Psychiatric Disorders	Number	Percent
Anxiety Disorders	Generalized anxiety disorder	29	54.2
	Phobia	3	5.6
	Post traumatic stress disorder	2	3.7
	Obsessivecompulsive	6	11.3
	Nonotherwise specified anxiety	10	18.8
Depression disorders	Major depression disorder	21	35.5
	Dysthymia	9	16.9
Somatoform disorders	Somatization	1	1.8
	Hypochondriasis	1	1.8
	Conversion	3	5.6
	Pain disorder	0	0
Personality disorders	Obsessive-compulsive personality	1	1.8
Adjustment disorders	Adjustment disorders	1	1.8
Substance-related disorders	Substance- related disorders	1	1.8

Table 4. Prevalence of psychiatric disorders among studied OLP patients

The cases treated with psychiatric agents include anti-depressant, anti-anxious, anti-convulsive, non-selective beta blockers, anti-psychotic and muscle relaxer drugs (Table 5).
Comparison of response to treatment between the patients in two groups was evaluated according to:
Size of the lesions: Table 6 demonstrates that the patients in the case group had given a better response to lichen planus treatment. The size of the lesions had decreased to different degrees and this difference in response was significant in the sixth month (P=0.026).
Formof the lesions: According to Table 7, although there were differences in the response to treatment between the study group and the control group as to the conversion of severe symptomatic cases (erosive and atrophic) to milder cases (keratotic), these differences were not statistically significant in the sixth months (P=0.31) (Figures 1,2 and 3).

Drug Group	Name of Drugs	Percentage of patients taken drugs (the first visit)	Percentage of patients taken drugs (the visit)	Mean of the lastdose prescribed(mg)
Anti-depressant Agents	Tricyclic and tetracyclic antidepressant			
	Clomipiramin	0.8	1.1	25
	Nortriptyline	6.8	8.2	64.3
	Doxepin	5.1	4.7	27.5
	Amitryptilin	0.8	1.1	75
	Trimipramin	0.8	0	0
	Maprotilin	7.9	9.4	60.9
	Selective Serotonin Reuptake Inhibitor			
	Citalopram	6.77	5.81	35
	Fluvoxamine	25.6	29.4	28.8
	Fluoxetine	0.8	1.1	100
Anti-anxious Agents	Benzodiazepine			
	Alprazolam	22.88	16.27	0.52
	Diazepam	0.8	1.1	10
	Clonazepam	0.8	1.1	1
	Chlordiazepoxide	3.4	3.5	8.3
	Aza spiro decadion			
	Buspiron	2.5	3.5	16.7
Non-selective Beta Blockers	Metoral	1.7	0	0
	Propranolol	8.5	8.2	45.7
Anti-convulsive Agents	Carbamazepine	0.8	1.1	600
	Lamotrigin	1.7	2.3	37.5
Anti-psychotic Agents	Risperidone	1.7	2.3	1
Muscle relaxer Agents	Baclofen	0.8	1.1	75

Table 5. Prevalence of patients taken psychiatric drugs in the first and last visits

Month		Six			
Response to treatment	Scale of response	Case		Control	
		Number	Percent	Number	Percent
Excellent	0	6	19.4	0	0.0
Good	1	8	25.8	4	26.7
Fair	2	7	22.6	2	13.3
Poor	3	8	25.8	4	26.7
Exacerbation	4	2	6.5	5	33.3
Total		31	100	15	100
Mann-Withney test		Z=-2.22P=0.026			

Table 6. The comparison of the response to treatment between the case and control groups as to lesion size in the sixth months

Pain severity: According to Table 8, a higher proportion of patients in the case group had no pain or had mild pain in the sixth month compared to the patients in the control group. The difference was not statistically significant in the sixth months (P= 0.476).

Month		Six			
Response to treatment	Scale of response	Case		Control	
		Number	Percent	Number	Percent
Excellent	0	11	55.0	4	40.0
Good	1	1	5.0	0	0.0
Fair	2	3	15.0	2	20.0
Poor	3	3	15.0	4	40.0
Exacerbation	4	2	10.0	0	0.0
Total		20	100	10	100
Mann-Withney test		Z=-0.712 P=0.476			

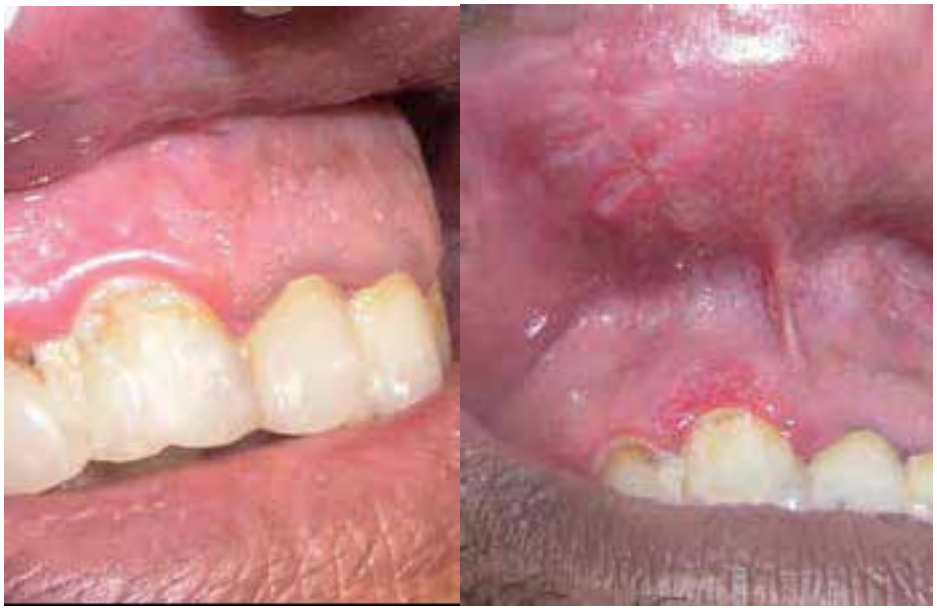
Table 7. The comparison of response to treatment between the case and control groups as to the form of the lesions in the sixth months

Month		Six			
Response to treatment	Scale of response	Case		Control	
		Number	Percent	Number	Percent
Excellent	0	0	0.0	0	0.0
Good	1	4	12.9	2	13.3
Fair	2	14	45.2	3	20.0
Poor	3	11	35.5	10	66.7
Exacerbation	4	2	6.5	0	0.0
Total		31	100	15	100
Mann-Withney test		Z=-1.002 P=0.31			

Table 8. The comparison of response to treatment between the control and case groups as to the severity of pain in the sixth months

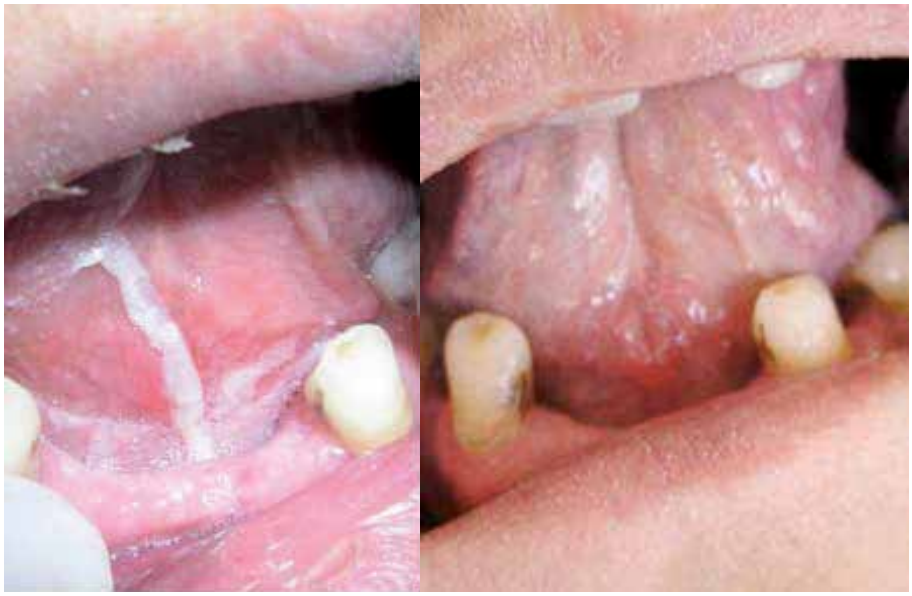
Correlation of response to treatment Spearman's correlation coefficient analysis demonstrated that, only, in the sixth month there was a significant and direct relationship between recovery from the psychiatric disorders and response to treatment of OLP lesions concerning the form of the lesions (P=0.058, r=0.377)(Delavarian 2010).

Briefly, our study determined the type of the psychiatric disorders through an interview with a psychologist. Contrary to present study; the vast majority of other studies have already been carried out on the role of psychiatric disorders in oral lichen planus, have used different questionnaires to compare anxiety and depression level of OLP patients with a control group. Some of these studies detected a higher level of stress and depression in patients suffering from OLP than healthy subjects but these studies were not interventional studies. Also, contrary to the vast majority of earlier studies which have only evaluated atrophic and erosive-bullous lesions, we incorporated keratotic lesions, too, into our study (Delavarian 2010). Keratotic lesions do not respond well to routine treatment and the evaluation of the effect of psychotherapy on these lesions is of utmost significance.



AB

Fig. 1. The patient in the case group had atrophy, erosion and moderate keratosis on the upper lip mucosa and atrophy and mild keratosis on the mucosa of the anterior upper gingival (A). Complete recovery was observed after psychiatric and routine OLP treatment (B).



AB

Fig. 2. The patient in the case group had large ulcer and keratosis on the ventral of the tongue and floor of the mouth (A). Complete recovery was observed after psychiatric and routine OLP treatment (B).

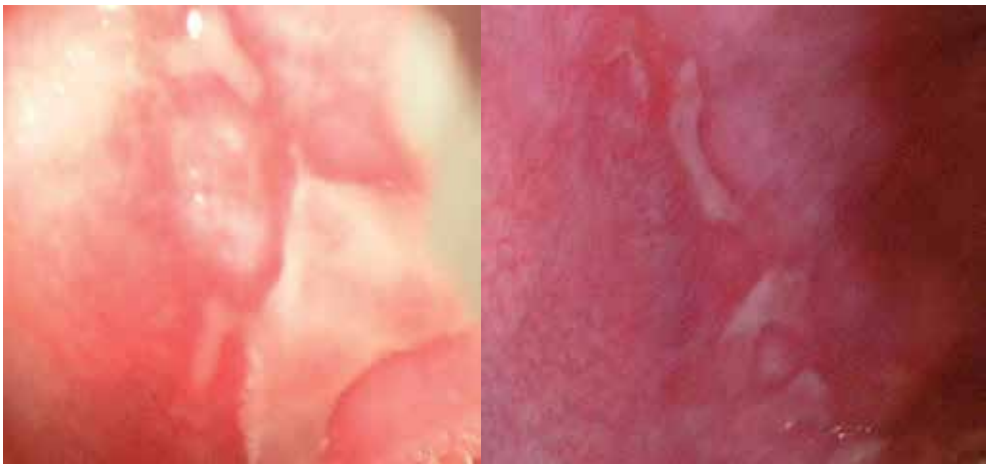


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Fig. 3. The patient belonged to the case group and had erosion and moderate keratosis on the right buccal mucosa (A). Relative recovery was observed after treatment (B).

The most important consideration in this study is determining all psychotic disorders. Most of our OLP patients suffered from anxiety disorders. Some patients had several concomitant psychiatric disorders. The most common disorder among our patients was generalized anxiety disorder (GAD) with a prevalence of about 54%; major depression disorder ranked second with a prevalence of 35.5% and only 5.08% of the patients did not have any psychiatric disorder (Delavarian 2010), which is consistent with the results of a study carried out by Collela, who had observed a higher level of anxiety and depression in OLP patients compared to a control group (Colella et al. 1993) . Chaudhary concluded from a study in 2004 that OLP patients have a higher level of stress, anxiety and depression compared to healthy individuals (Chaudhary 2004) . The level of depression observed in our patients was comparable to the level observed by Akay, who reported depression in 53% of the patients suffering from OLP (Akay et al. 2002).

However, here is controversy over the role of stress as a possible etiologic factor in OLP: some studies have demonstrated that stress may not result in OLP development but OLP may alter the individual's self-image and influence his/ her public relations and lead to secondary depression.

Some other studies have failed to establish a direct cause-and-affect relationship between psychiatric disorders and lichen planus (Rojo-Moreno et al. 1998). In addition, although there seemed to be a parallel relationship between the general response to psychotherapy and the general response to OLP treatment, we were not able to confirming this using Spearman's analysis of correlation coefficient (Delavarian 2010).

In study period, we observed some OLP patients were suffering from other diseases that have relationship with stress. Among them, one patient had Recurrent Aphthous Syndrome (RAS), another affected by Myofascial Pain Dysfunction Syndrome (MPDS) and four patients suffered from Burning Mouth Syndrome (BMS).

Before, another study revealed that the stress level is higher in patients with RAS and OLP, depression is particularly high in patients with BMS, and levels of anxiety are raised in the three diseases, in comparison with the group control(Soto Araya, Rojas Alcayaga, and Esguep 2004).

Our observation concerning the exacerbation of the signs and symptoms of the lesions concomitant with stressful experiences of the patients during study period, established the role of stressful life events in OLP process. Such stressors consisted of family members' disease, financial or legal problems, cancerophobia, and family disagreements (a second marriage of the husband, marriage of children despite parents' opposition, lack of understanding between spouses), loneliness, worries concerning childbirth, accidents, assault and battery and death of family members and relatives (Delavarian 2010). Exacerbation of OLP lesions associated with stressful experiences of the patients and the effect of psychotherapy in reduction of lesion size demonstrated that psychotherapy can be used, at least as an adjunct to routine OLP treatment, to minimize the use of corticosteroids and reduce their side effects.

9. Conclusion

Briefly, drug therapy of psychiatric disorders on OLP indicates that psychiatric treatment along with traditional OLP treatment can be effective in reducing the size of the lesions. With regards to the discussion above, it seems logical to claim that psychiatric evaluation and appropriate treatment of the patients along routine treatment of oral lichen planus lesions should be recommended.

10. Acknowledge

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Part 4

Risk Factors

11

Borna Disease Virus and Psychiatric Disorders: Can Viruses Influence Psychiatric Disorders?

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1. Introduction

1.1 Psychiatric disorders and infectious diseases

Psychiatric disorders are a wide group of diseases with a heterogeneous aetiology (genetic predisposition, environmental factors, exposure to stress, for example). Several infectious agents preferentially affect the central nervous system and these infections are associated with psychic and neurologic symptomatology. It has been suggested that some infectious diseases can influence the development and the course of several psychiatric disorders. Infectious agents of zoonotic diseases with the ability to cause persistent infections of the central nervous system and influence the development and functions of this system include *Toxoplasma gondii*, *Borrelia burgdorferi* and Borna disease virus (BDV). Other neurotropic viruses that affect humans and which are associated with neurologic and psychiatric symptoms include herpes viruses, HIV and rabies virus, among others. *Toxoplasma gondii* is associated with cognitive dysfunctions in infected subjects (human and animals). Studies have shown that there is a direct statistical link between incidences of schizophrenia and toxoplasmosis infection. Several studies reported significantly higher seropositivity of this infection in schizophenic patients (Torrey & Yolken 2003). Lyme borreliosis is caused by the Gram-negative spirochete *Borrelia burgdorferi*, which has a high affinity with the central nervous system. There may be a long latent period between infection and the development of clinical neuropsychiatric symptoms. Several studies associated borreliosis with affective, anxiety (panic) and organic disorders and psychosis. A higher seropositivity was demonstrated in psychiatric patients compared to healthy individuals (Hájek et al., 2002).

1.2 Borna disease virus characteristics and animal infection

Borna disease virus (BDV) is an enveloped non-segmented negative-stranded RNA virus that belongs to the family *Bornaviridae*, order *Mononegavirales*. Examples of other virus families that belong to the order *Mononegavirales* are *Filoviridae*, *Paramyxoviridae* and *Rhabdoviridae*. Borna disease virus is a neurotropic virus that affects the central nervous system, especially limbic structures. Borna disease virus infects warm-blooded animals (birds and mammals, including humans). The clinical symptoms of BDV infection range from asymptomatic or a mild symptomatology to severe neurologic and behaviour disturbances and lethal non-purulent encephalitis.

The BDV genome consists of a linear non-segmented single-stranded RNA with negative polarity. The genome is divided into three main gene blocks: the first codes for nucleoprotein (N) and polymerase cofactors represented by p40 and p24 proteins, the second codes for matrix (M) and virus envelope proteins, represented by p16 and p56 proteins, the third codes for the viral polymerase. The entry of BDV is via receptor-mediated endocytosis; protein p56 is sufficient for receptor recognition and virus entry (Briese et al., 1994; Cubitt et al., 1994). The BDV ribonucleic protein is transported into the cell nucleus where BDV transcription and replication occur. The replication of this virus in host cells is typical of the family *Bornaviridae* (de la Torre et al., 1994).

1.3 History of BDV infection

The first description of Borna disease infection was found in seventeenth century literature that describes this disease as affecting horses; later, behavioural changes in other farm animals were described. By the twentieth century, many cases of this infection in farm animals had been described, especially in horses and later in sheep; this disease causes a high mortality rate in infected animals. Borna disease virus owes its name to the town Borna in Saxony (Germany), where a large number of military horses died during an epidemic of this infection in 1885. It was originally thought that BDV only infected horses and sheep; BDV infection has since been described in other species across the world, including birds, cats, cattle, primates, rats, mice and others.

In the 1920s and 1930s the aetiology of Borna disease was discovered by Zwick and colleagues in Giessen (Germany). They successfully transmitted brain homogenates from naturally infected horses to experimental animals. Borna disease virus was isolated in the following years by Zwick, Siefried, Nicolau and Galoway (Durrwald & Ludwig, 1997).

Borna disease virus antigens were isolated in the 1950s and 1960s (Durrwald & Ludwig, 1997; Ludwid & Bode, 2000) and in 1976 viral antibodies were detected in humans (Ludwig, unpublished data from 1985 in psychiatric patients (Rott et al., 1985). In the 1990s, the structures of BDV and viral RNA were described and isolated, BDV was integrated into the order *Mononegavirales* and the new family *Bornaviridae* (Durrwald & Ludwig 1997, Ludwig & Bode 2000) was created.

1.4 The course of BDV infection in animals

The symptomatology of BDV infection in animals ranges from asymptomatic, to a mild subclinical infection to lethal meningoencephalitis. The majority of infected individuals have subclinical, mild symptoms and BDV infected hosts are generally asymptomatic carriers. Some infected subjects develop relapsing mood disorders and behaviour disturbances (changes in appetite and sleeping, apathy or aggressive behaviour and cognitive impairments such as in memory or learning functions, for example) or neurological symptoms (movement or posture impairments, cramps and motor disturbances). A minority of infected animals have a lethal course of BDV infection and die from non-purulent meningoencephalitis.The course of BDV infection is influenced by several factors, including the age of animal at the time of infection, its immune status, genetic background and the type of animal, among others. This viral infection is associated with neurological, behavioural, mood and cognitive changes. This symptomatology leads to the possible connection with human psychiatric disorders such as affective and psychotic disorders and the possibility that BDV infection could contribute to the aetiology of several psychiatric disorders.

1.5 Epidemiology of Borna disease virus infection

Borna disease virus infection was originally believed to be limited in horses and sheep in endemic areas in Central Europe, especially in Germany. But over the years, the use of new diagnostics methods discovered the presence of natural BDV infections in other regions, such as Australia, the United States of America (Kao et al., 1993; Richt et al., 2000), China (Hagiwara et al., 2001), the United Kingdom (Reeves et al., 1998), Japan (Watanabe et al., 2006), Israel (Teplitski et al., 2003), other European countries (Italy, Poland, Czech Republic, France, Switzerland) (Galabru et al., 2000; Pisoni et al., 2007) and others. Natural BDV infection was detected not only in horses and sheep but also in other animal species: cats (Berg et al., 2001; Reeves et al., 1998), dogs (Weissenbock et al., 1998), cattle (Watanabe et al., 2006), birds (Berg et al., 2001), foxes (Dauphin et al., 2001), and ostriches (Weismann et al., 1994). Borna disease virus infection differs in its course according to the species; the most serious form of Borna disease is described in horses and sheep with severe neurologic symptoms and high mortality rates, in contrast to other species (Ludwig & Bode 2000).

1.6 The transmission of BDV infection

There are several supposed routes of transmission of BDV infection between humans and animals: by direct contact with infectious secretions through the nasal mucosa (Durrwald & Ludwig 1997; Hatalski et al., 1997; Ludwig and Bode 2000; Richt et al., 1993, 2000, 2001), vertically during pregnancy (Hagiwara et al., 2000; Okamoto et al., 2003), and indirectly by infected (contaminated) food or water (Durrwald & Ludwig 1997; Hatalski et al., 1997; Ludwig & Bode 2000; Richt et al., 1993, 2000, 2001). Findings of BDV RNA and proteins in peripheral blood mononuclear cells indicate the possibility of hematogenous transmission (Solbrig et al., 2003; Vahlenkamp et al., 2000). Pisoni and colleagues reported the possible sexual transmission of BDV infection. They detected higher BDV seropositivity in sexually active female horses compared to lower BDV seropositivity in animals that had never had sexual contact (Pisoni et al., 2007). Human-to-human transmission of BDV infection is supported by several studies that described higher BDV positivity in mental health workers and family members who were in contact with BDV-positive psychiatric patients (Chen et al., 1999a). Some studies described higher BDV positivity in humans who were in contact with infected animals; this BDV positivity was positively correlated with the degree of contact with infected animals. These findings proved the animal-to human transmission of BDV infection, which is typical of zoonotic infections (Takahashi et al., 1997; Thomas et al., 2005; Weismann et al., 1994).

Infected rodents and wild birds are considered to be reservoirs of BDV infection (Berg et al., 2001), but pets and farm animals represent a greater risk of human BDV infection because of the closer contact with them. Experimentally infected rodents developed persistent BDV infection, which is associated with the presence of the virus in saliva, urine and faeces. Borna disease virus was also found in the excrement of migrating birds. These reports suggest that wild birds could be a reservoir because of the possibility of water or food contamination by infected secretions.

The most frequent route of BDV infection transmission is probably via contact with infected saliva or other secretions through the nasal mucosa. The olfactory route of BDV transmission is efficient; the olfactory bulbs in naturally infected horses show oedema and inflammation early in the course of infection. After infection, BDV initially replicates in the neuroreceptor cells of the olfactory epithelium; then, BDV spreads intra-axonally and trans-synaptically towards olfactory structures and then preferentially to the limbic system. In the

nuclei of infected neurons, aggregates of virus material form Joest-Degen inclusion bodies that are typical of BDV infection. The spread of this virus is not just restricted to the limbic system; during later stages of infection BDV diffuses though the central nervous system and can be detected in oligodendrocytes, astrocytes, Schwann cells and ependymal cells in the peripheral nervous system. In the late stages of BDV infection the virus spreads centrifugally and virus markers can be detected in the peripheral nerves of all tissues. The spread of BDV infection within the CNS is mediated by ribonucleoprotein particles rather than by the enveloped virus. A minimum incubation period of 3 to 4 weeks is estimated for horses and sheep with nonspecific signs such as hyperthermia, anorexia, colic and constipation in the initial phase (Carbone et al., 1987; Gonzales-Dunia et al., 1997, 2000; Gosztonyi & Ludwig, 1984, 2001).

1.7 Mechanism of action, persistent infection, and the course of infection

Borna disease virus can cause persistent infection in the central nervous system. Persistent viral infection is characterized as circumstances in which the virus is not cleared but remains in the cells of infected individuals. There are three types of persistent viral infection: latent, chronic and slow infection. The latent type of persistent infection is typical of BDV. Latent infection is associated with a lack of demonstrable viral particles. The reactivation of persistent latent BDV infection can be triggered by several stimuli: super-infection by other infectious agents, trauma, stress factors, medication or other diseases that lead to changes in immune system. After reactivation, it is possible to detect viral structural proteins that interfere with neurotransmitter receptors and their functions. During infection, BDV influences the central nervous system in several ways: firstly, there is a direct influence through the binding of viral proteins with neurotransmitter receptors (monoamine, serotonin and dopamine systems), and secondly there is an indirect influence though the immune response and inflammatory reactions. Both types of mechanisms contribute to neurotransmitter changes and lead to mood, emotional or behaviour changes in infected subjects, and they may also be associated with psychiatric disorders. The severity of clinical symptoms and the course of BDV infection depend on several factors: immune status and response of the host, the age at infection, and genetic vulnerability (predisposition) to the development of psychiatric disorders, among others (Dietrich et al., 1998). The third mechanism by which BDV can possibly influence CNS functions is due to the fact that viral infections are able to influence the human genome. Some human genetic material originates from viruses and viral sequences being assimilated into the host genome. After infection, BDV sequences are integrated into the genome of brain cells. These sequences are not heritable but they can cause mutations that interfere with brain functioning and can contribute to the development of psychiatric disorders (Feschotte, 2010).

1.7.1 Borna disease virus and its influence on the central nervous system

Animal models have been used to study and help explain the influence of BDV infection on the central nervous system. Changes in several neurotransmitter receptors have been described. Research on adult experimental rats has shown how BDV infection causes long-term changes in cognition, emotions and behaviour. Research on neonatal animals has explained how BDV infection influences brain development with subsequent changes in behaviour and cognition.

Changes in the dopamine system of infected adult rats were described, where disturbances were found in the levels of dopamine in the caudate-putamen (D2 receptors) and the nucleus accumbens (D2 and D3 receptors): pre- and postsynaptic sites of dopamine receptors were damaged in the striatum, dopamine reuptake sites were reduced in the caudate-putamen and nucleus accumbens, postsynaptic D2 receptors were reduced in the caudate-putamen and D2 and D3 receptor binding was decreased in the nucleus accumbens. Postsynaptic dopamine receptors (D1 and D2) remain intact in the prefrontal cortex; this imbalance leads to D1 hypersensitivity and neurobehavioural disturbances in BDV-infected animals. Partial dopamine deafferentation and compensatory hyperactivity of the remaining striatal nerve terminals in the nigrostriatal projections are associated with locomotor activity and stimulant sensitivity. Decreased numbers of dopamine D2 and D3 receptors and the remaining numbers of D1 receptors in the striatum are associated with dyskinesias and dystonia (Solbrig et al., 1994, 1996, 2000, 2010). These changes in dopamine neurotransmission support a connection between BDV and neuropsychiatric disorders such as schizophrenia and addiction and extrapyramidal disorders.

In addition to the altered dopamine system the dysfunction of serotonin and noradrenergic systems is present and is associated with other symptoms. There is evidence of a serotonin system dysfunction in the striatum and norepinephrine dysregulation in the prefrontal and anterior cingulate cortex. Changes caused by BDV infection include reduced serotonin transmission, which is associated with autistic disorders and depression.

The course of BDV infection in adult rats is more severe in comparison to infected neonate rats, which have a milder symptomatology in BDV infection. These animals developed behaviour and cognitive changes, learning difficulties, increased motor activity, abnormal anxiety responses, deficits in motor coordination and postural stability and impairments in social behaviour, and they also showed abnormally early locomotor development. They also showed altered circadian rhythms and appetite changes. Damage to or dysfunction in the CNS of these animals is associated with direct viral effects on the morphogenesis of the hippocampus and cerebellum (Dietz et al., 2004; Pletnikov et al., 2000, 2001, 2002; Solbrig et al., 2010). Borna disease virus infection impairs synaptic plasticity, which is important for learning and memory (Volmer et al., 2007).

Behaviour disturbances were reported in other experimentally infected animals: altered social and sexual behaviours such as abnormal dominance relationships and a failure to mate were described in primates (tree shrews and rhesus monkeys). Rhesus monkeys were initially hyperactive and later became apathetic (Sprankel et al., 1978; Stitz et al., 1980).

Neonatal Borna disease virus infection in rats is associated with the activation of microglia and astrocytes and the loss of neurons in the dentate gyrus in the hippocampus, cortex and cerebellum (Gonzales-Dunia et al., 2000; Pletnikov et al., 2002; de la Torre, 2002). Ovanesov and colleagues were the first to find a significant increase in microglial activation and secondary neuronal loss (Ovanesov et al., 2008). Borna disease virus infection also affects astrocytes, which play an essential role in the maintenance of homeostasis in the CNS. Borna disease virus infection is also associated with impairment in the ability of astrocytes to take up glutamate; this impairment leads to increased levels of extracellular glutamate, the activation of NMDA receptors and an increased calcium influx, and results in neurotoxicity and cell death (Billaud et al., 2000).

In the pathogenesis of Borna disease, Borna disease virus infection also plays an important role in the inflammatory reaction (the BDV-specific T-cell response and the activity of CD8+

T-cells cause the destruction of virus-infected neurons). The inflammatory reaction is associated with the symptomatology of infection (Stitz et al., 1995).

1.7.2 Viro-psycho-immunological disease model and schematic (in connection with psychiatric disorders)

The connections between viral infections, stress and immune functions are described and explained by the viro-psycho-immunological disease model. Acute or chronic stress or other factors (other infections, diseases, immunosupressive medications, for example) cause changes in immune functions. These alterations in the immune system are responsible for the reactivation of latent forms of BDV infection in the central nervous system. The reactivation of BDV directly influences CNS function due to the affinity of viral proteins to neurotransmitter receptors and indirectly influences it via the inflammatory reaction, which also leads to changes in neurotransmission. Individuals with a greater vulnerability (predisposition) for developing psychiatric disorders (genetic disposition) can develop psychiatric symptoms (Dietrich et al., 1998) (see Figure 1).

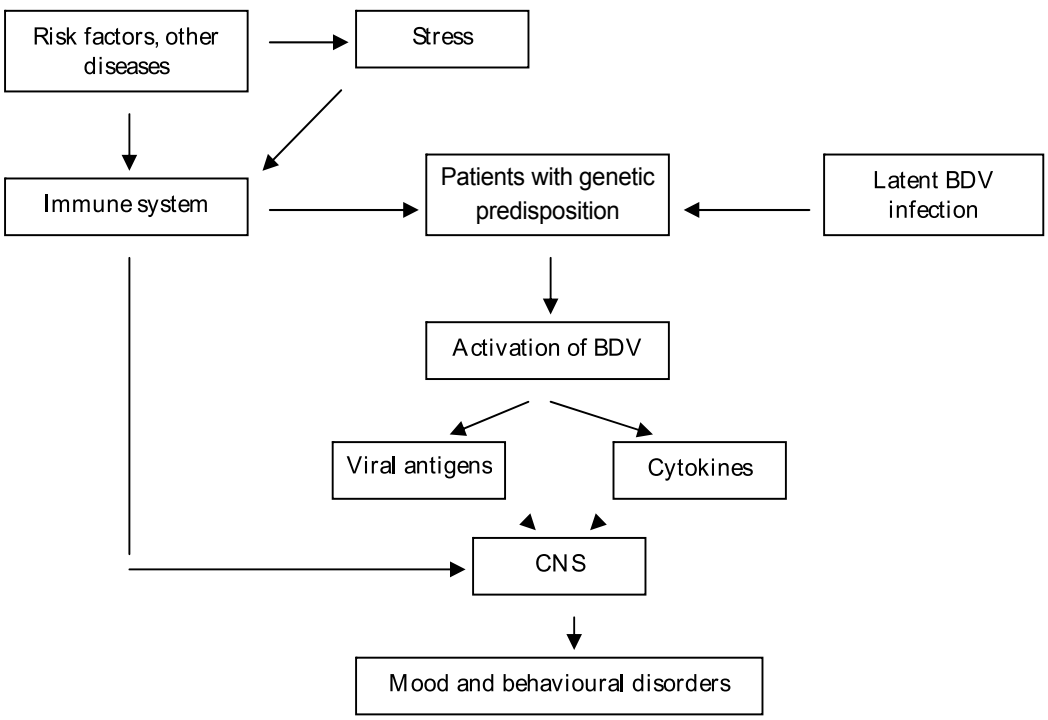

Fig. 1. Viro-psycho-immunological disease model of BDV infection and psychiatric disorders adapted from Dietrich et al., 1998

1.8 Laboratory diagnosis of BDV infection

The aims of laboratory diagnostics in BDV are the detection of BDV infection and the determination of infectious activity and its severity. Several questions can be asked: is the patient infected by BDV? Is this infection active? How intense or severe is this infection? Is treatment of BDV infection suitable?

Borna disease virus antigens (Ag), antibodies (Ab), circulating immunocomplexes (CIC) and viral ribonucleic acid (RNA) can be isolated and detected in brain tissue, cerebrospinal fluid (CSF), serum, plasma or in peripheral blood mononuclear cells (PBMCs).

The original diagnostics for BDV infection consisted of the detection of viral Ab via serological methods, especially immunofluorescence assays (IFA). These methods, which only detected BDV Ab, were not very sensitive and were not able to detect acute phases of BDV infection. Enzyme-linked immunosorbent assays (ELISA) were based on recombinant viral proteins and were used in several studies to detect BDV Ab, but they showed a surprisingly low sensitivity, which could explain the differences found in the study results. The use of electrochemiluminescence immunoassays (ECLIA) did not show any great advantages in the diagnosis of BDV infection.

Another laboratory method that has been used for the detection of BDV Ab is Western blotting (WB), but this was found to be less sensitive than new-generation ELISAs with native viral antigens. Positivity of BDV Ab can indicate a persistent form of infection (in the absence of active BDV infection) or previous contact with this infection, but not an acute state. The absence of BDV Ab in the serum does not mean the BDV infection result is negative; antibodies bind antigens and form circulating immunocomplexes.

Antigenaemia indicates an acute and productive phase of infection. During this phase of BDV infection antibodies bind to the viral antigens and form CIC, which are measurable for weeks or months. The frequency and stability of BDV CIC make them easily available screening markers of BDV infection. By using the ELISA method, it is possible to detect viral Ag in plasma. The disadvantage of this method of detection is the very short period of antigenaemia in the acute phase of BDV infection and the high risk of false negative results after the formation of BDV CIC.

Bode and colleagues developed an ELISA (triple ELISA) method that mainly detects BDV CIC but also free BDV antigens and antibodies (Bode et al., 2001).

Several authors used the detection of viral RNA in PBMCs (peripheral blood mononuclear cells) in brain tissue via polymerase chain reaction (PCR) for the diagnosis of BDV infection. However, other researchers did not use this method for the diagnosis of BDV infection and do not recommend RNA detection as the best diagnostic tool. The first reason is due to the possibility of sample contamination during the laboratory procedure (although contamination should not occur when the detection of BDV RNA is performed according to international security instructions). The second reason is because the absence of BDV RNA in samples does not exclude the possibility of BDV infection, since RNA detection is less reliable than the detection of other virus particles (Ag or CIC) because of the low replication rate of this virus and the small amount of RNA in PBMCs. Also, the presence of BDV RNA in the brain does not necessarily reflect an active state of BDV infection (Bode et al., 2001, Sauder & de la Torre, 1998; Thakur et al., 2009; Wolff et al., 2006).

Currently, the detection of BDV CIC by ELISA and viral isolation from PBMCs are recommended as the best screening methods of active BDV infection because of their relative stability and frequency. The best indicators (markers) of viral disease are antigen ELISA and CIC ELISA, which also both correlate well with the severity of the BDV infection. The ELISA method for the detection of BDV CIC was developed by Bode and Ludwig (Bode et al., 2001). Table 1 shows a summary of the diagnostic methods.

Test	Sample	Diagnostic parameter	Antigen	Sensitivity	Specificity	Indicative of infection	Indicative of disease
Complement fixation	serum	Ab	Native	Low	Good	Low	Poor
Double diffusion	serum	Ab	Native	Low	Good	Low	Poor
IFA	serum	Ab	Altered by fixation	Good	Very good	Good	Poor
	CSF			Poor	Very good	Very good	Poor
Cell ELISA	serum	Ab	Altered by fixation	Low	Good	Low	Poor
ECLISA	serum	Ab	Recombinant	Good	Very good	Good	Poor
Recombinant ELISA	serum	Ab	Recombinant	Good	Good	Good	Poor
Ab ELISA	serum	Ab	Native	Excellent	Excellent	Very good	Poor
Cell Ag ELISA	PBMCs	Ag	Native	Low	Excellent	Good	Good
Plasma Ag	serum	Ag	Native	Good	Excellent	Very good	Excellent
ELISA	CSF	Ag	Native	Low	Excellent	Very good	Excellent
CIC ELISA	serum	CIC	Native	Excellent	Excellent	Excellent	Excellent
WB	serum	Ab, Ag	Denatured	Low	Very good	Good	Poor
	CSF			Poor	Very good	Very good	Very good
Flow cytometry	PBMCs	Ag	Mild fixation	Good	Very good	Good	Good
RT-PCR	PBMCs	RNA		Very good	Excellent	Very good	Poor
	brain	RNA		Good	Excellent	Very good	Poor
	serum	RNA		Low	Excellent	Very good	Good
Isolation	PBMCS	virus		Poor	Excellent	Excellent	Very good
	brain	virus		Poor	Excellent	Excellent	Very good

Table 1. Diagnostic tools for the detection of Borna disease virus infection in humans (Thakur et al., 2009), abbreviations explained in text

1.9 Factors influencing BDV positivity

Borna disease virus positivity in psychiatric patients ranges from negative to highly positive. These differences in positivity can be caused by several factors; features of the psychiatric population (age, diagnosis, severity of the psychopathology, immune status), geographical region, differences in specificity and sensitivity of the laboratory methods used and which diagnostic parameters (Ab, Ag, CIC or RNA) are detected and which biological material (brain tissue, cerebrospinal fluid, serum) is used. Other factors include the seasonal occurrence of BDV infection and contact with animals.

1.9.1 BDV positivity and age

Several studies showed a higher rate of BDV positivity in younger individuals. Patti and colleagues investigated BDV CIC positivity in children in Italy; BDV positivity was detected in 57%. The prevalence of BDV infection was found to be significantly greater in children, particularly in the third year of life; then it decreased until 15 years of age, where another increase was observed (Patti et al., 2008). Another study performed by Scholbach and colleagues demonstrated higher rates of BDV Ag and CIC positivity in children. There were two age intervals of peak BDV positivity: the first was a peak at 6 months old and the

second was a peak around 2-3 years old. These findings support the possible vertical transmission of BDV infection. Two other possible explanations for the greater prevalence of BDV infection in children than in adults are the less well-developed immune status of children and the fact that children of 2-3 years old are more likely to have greater contact with animals and their secretions, which are associated with a greater risk of BDV transmission (Scholbach et al. 2008).

1.9.2 BDV positivity and the types of psychiatric disorder

Borna disease virus infection was detected in psychiatric patients with various disorders; the majority of these studies detected BDV in patients with affective (bipolar and depressive) disorders and psychotic disorders (schizophrenia and schizoaffective disorders). The highest rate of BDV positivity was found in patients with bipolar and depressive disorders (Ferszt et al., 1999). Rybakowski and colleagues reported significantly higher rates of BDV Ab seropositivity in Polish psychiatric patients with affective-anxiety spectrum disorders and mental retardation than in healthy controls, and the rate of BDV seropositivity was significantly higher in patients with recent disease onset compared to past disease onset (10.2% vs. 1.6%) (Rybakowski et al., 2001).

1.9.3 BDV positivity and psychopathology

Several research groups reported an association between BDV positivity and the type or severity of the psychopathology. In a study performed by Iwahashi and colleagues, a significantly higher rate of BDV seropositivity was detected in schizophrenic patients with a negative symptomatology than in patients with positive symptoms (Iwahashi et al., 1998). Waltrip and colleagues detected a higher rate of BDV seropositivity in schizophrenic patients with deficit syndrome than in patients with non-deficit syndrome (Waltrip et al., 1997).

Bode and colleagues detected a higher rate of BDV seropositivity (more than 30%) in patients with major depressive disorder and a lower rate of positivity (8%) in patients with dysthymia (Bode et al., 1993). Ferszt and colleagues confirmed the higher rate of BDV antigenaemia in patients with affective disorders. The number of previous depressive episodes with symptoms including fatigue and concentration difficulties was positively related to BDV Ag positivity (Ferszt et al., 1999). Bode and colleagues found significantly higher rates of BDV Ag and CIC positivity (including higher values) in severely depressed patients during an acute crisis and lower rates of BDV Ag and CIC positivity (lower rates and lower amounts of Ag and CIC) in patients with moderate depression. The severity of depressive symptoms correlated with the concentration and duration of antigenaemia (Bode et al., 2001). In study reported by Rackova and colleagues, a significantly higher rate of BDV CIC positivity was found in psychiatric patients with a more severe psychopathology than in patients with a milder symptomatology, as measured by psychiatric scales (Rackova et al., 2009).

1.9.4 Regional occurrence of BDV infection

Naturally occuring Borna disease virus infection is still confined to several areas of Central Europe, these regions are endemic for this infection. The presence of BDV infection in animals and humans has been detected not only in European areas but across the world (China, Japan, Israel and several other countries) (Durrwald & Ludwig 1997, Ludwig & Bode 2000).

1.9.5 BDV positivity and laboratory methods used

The high variability found for BDV positivity in humans can be influenced by the laboratory method used since they differ in terms of sensitivity and specificity. Another factor that can influence the detection of BDV infection is the infectious marker used: antibody, antigen, circulating immunocomplex or RNA.

The detection of BDV CIC by ELISA has shown a 10-fold higher incidence of BDV infection than was estimated for BDV Ab positivity by the immunofluorescence method in psychiatric patients with affective disorders. The rates of positivity of BDV Ab by IFA were 11% and 20% in patients with depression and 2% in blood donors vs. CIC positivity of 62%, 52% and 24% in the same groups (Bode et al., 2001). Similar results were reported by Bode and colleagues in 1994, where BDV Ab positivity was detected in 20% of psychiatric patients compared to the higher positivity of BDV Ag in 40-50% of the same psychiatric patients (Bode et al., 1994). Wolff and colleagues did not confirm these results. They analysed plasma samples with a high reactivity in the ELISA assay (high positivity of BDV antigens) by immunoaffinity purification and highly sensitive real-time RT-PCR (polymerase chain reaction): neither method provided any evidence for the presence of viral proteins or nucleic acids (Wolff et al., 2006).

1.9.6 Seasonal occurrence of BDV infection

Borna disease virus infection shows a seasonal prevalence, being more frequent in spring and early summer. Significantly higher numbers of seropositive animals (especially sheep and horses) have been detected during these periods and a higher occurrence of clinical cases was also observed (Durrwald & Ludwig 1997; Ludwig & Bode 2000; Staeheli et al., 2000; Vahlenkamp et al., 2002). The number of animals that become infected and succumb to the disease differs each year, but no correlation has been described between the seasonal occurrence of BDV in animals and humans.

1.9.7 Contact with animals

Several studies have described an association between the prevalence of BDV infection in humans and contact with animals, which are potential reservoirs of BDV infection. Weismann and colleagues reported a significantly higher rate of BDV antibody positivity (46%) in workers exposed to infected ostriches compared to controls (10%). There was a strong positive correlation between the intensity of exposure and the rate of seropositivity (Weismann et al., 1994). Takahashi and colleagues found a significantly higher rate of BDV seropositivity (from 2.6% to 14.8%) in blood donors from regions containing concentrations of horse farms compared to the BDV seropositivity of 1% in blood donors from other regions (Takahashi et al., 1997). These findings support the possible animal-to-human transmission of BDV infection. In contrast, another study from Bangladesh did not confirm this hypothesis. The authors surveyed horses and their caretakers for BDV antibody positivity and found a BDV positivity of between 25-30% in the horses but none of caretakers were positive for BDV (Khan et al., 2000). Thomas and colleagues measured BDV seroprevalence in agricultural workers in the United Kingdom. The seroprevalence was 2.3% in 1994, 3.1% in 1996 and 2.6% in 1999. People living or working on livestock farms had a higher rate of seroprevalence (2.6%) than those on mixed (2.3%) or arable (1.6%) farms, but this was not statistically significant. Exposure to horses, sheep and cats did not increase the risk of seropositivity. Furthermore, the seropositive people were not more likely to report symptoms of psychiatric morbidity (Thomas et al., 2005).

1.9.8 Other factors and BDV positivity

The activation of persistent BDV infection can be triggered by several stimuli (super-infection by other infectious agents and immunosuppressive medication, among others) that affect the immune system. This hypothesis (claim) is supported by studies reporting a higher rate of BDV positivity in HIV patients (Auwanit et al., 1996; Bode et al., 1992; Cotto et al., 2003). A lower rate of BDV seropositivity (4-8%) was detected in the early stages of HIV infection, which then increased (13.9%) during later stages of this disease (Bode et al., 1992).

1.10 BDV and psychiatric disorders

Borna disease virus infection in animals is characterized by various behavioural changes, such as changes in social behaviour, apathy, aggressive behaviour, changes in appetite and weight, and cognitive impairment, amongst others. Because these behavioural disturbances of naturally and experimentally BDV-infected animals resemble psychiatric symptoms and disorders in humans, especially affective disorders, early studies investigated a possible link between patients with these diagnoses and BDV infection. The possible connection between BDV infection and psychiatric disorders is explained in the viro-psycho-immunological model, shown in Figure 1 (Dietrich et al., 1998).

The earliest work that suggested a link between BDV infection and human psychiatric disorders was in 1985. Rott and colleagues examined serum samples from 979 psychiatric patients and 200 healthy volunteers for the presence of BDV Ab by indirect immunofluorescence. Borna disease virus antibodies were found in 16 of the psychiatric patients but none of the healthy volunteers. The patients who had positive serum samples also had a history of affective disorders (Rott et al., 1985).

Since 1985, several studies have demonstrated significantly higher rates of BDV infection positivity in psychiatric patients compared to healthy individuals, but several studies did not confirm these results. The rate of BVD positivity in psychiatric patients ranged from negative to highly positive (almost 100% in patients with affective disorders).

Several researchers found a significant association between BDV positivity (levels of BDV Ag and CIC) and severity of the psychopathology (Bode et al., 2001; Ferszt et al., 1999; Rackova et al., 2009) and between BDV seropositivity and negative symptoms in schizophrenia (Iwahashi et al., 1998; Waltrip et al., 1997). Borna disease infection is associated with a chronic course of the disease without full remission and with recurring psychiatric disorders. The reactivation of persistent BDV infection is caused by immune changes and influences neurotransmitter systems and, in vulnerable individuals, it can contribute to the onset of a new phase of a psychiatric disorder and influence its course.

1.11 Therapy of BDV infection

Non-pharmacological procedures that could lead to the elimination of BDV infection were used in the past. The separation of infected animals and improvements in hygiene were recommended, but these procedures only decreased the risk of BDV infection spreading but did not eliminate the infection. Vaccination with killed vaccines and then live vaccines became available in the twentieth century, but both types of vaccine were shown to be ineffective against the Borna disease virus. Vaccination against persistent viral infection in the central nervous system cannot be recommended (Ludwig & Bode, 2000).

Antiviral medications were also tested for the treatment of BDV infection. Hexamethylenetetramine was used for the treatment of horses, and then later hexamine

(Ludwig & Bode, 2000), ribavirine (Jordan et al., 1999), interferon alpha or beta (Hallensleben et al., 1999; Staeheli et al., 2001) and cyclosporine A (Stitz et al., 1989), but no effect was found on BDV infection. Some of these preparations showed a decrease in BDV replication in vitro, but they did not show efficacy in vivo.

Bechter and colleagues described several cases where an improvement in the psychic status of psychiatric patients with schizophrenia and depression was shown after cerebrospinal fluid filtration (Bechter et al., 2000).

Currently, amantadine is used for the treatment of BDV infection. Amantadine is a non-competitive N-methyl D-aspartate-type glutamate receptor antagonist that also binds to nicotinic acetylcholine receptors. Amantadine inhibits BDV replication. Initially, amantadine-sulphate was used in the prophylaxis of influenza A (Kandel et al., 2001), in the treatment of Parkinson's disease (Brenner et al., 1989), hepatitis C (Adinolfi et al., 2003) and cocaine dependence (Kampman et al., 2000). A mild antidepressant effect of amantadine was found in a double-blind study when compared to amitriptyline and a placebo in patients with depression without BDV infection (Vale et al., 1971). Amantadine is a virostatic agent effective in the treatment of BDV infection, since it influences BDV replication in vivo.

The use of amantadine was first described in two case reports in 1991 and 1997 in the treatment of two psychiatric patients with bipolar affective disorder, where improvements in the psychiatric status of both patients were associated with the decrease and elimination of BDV positivity (Bode et al., 1997). Later, several open trials were performed to test the efficacy of this drug in psychiatric patients and amantadine-sulphate was proven to be effective in the treatment of depression in BDV positive patients (Dietrich et al., 2000; Ferszt et al., 1999); the improvement in the depressive symptomatology was correlated with a decrease in BDV infection positivity. The patients were treated with 200 mg of amantadine per day for 12 weeks, and the majority showed significant improvements (clinical response) within the first three weeks (Dietrich et al., 2000). Ohlmeier and colleagues published the results of a double-blind trial that evaluated the effect of amantadine in the treatment of patients with the manic phase of bipolar disorder and amantadine reduced manic symptoms in BDV-infected bipolar patients (Ohlmeier et al., 2008).

2. Aims and methods

2.1 Aims

Because of the marked differences in BDV positivity in patients with different psychiatric disorders, we decided to review available studies on the detection of BDV infection in psychiatric disorders and attempt to explain these differences.

2.2 Method

We undertook a systematic review to determine the rate of positivity of Borna disease virus infection in psychiatric patients.

2.3 Data sources

PubMed, Medline, Journals@Ovid Full Text, Evidence-Based Medicine and the Cochrane database (1985-2011) were searched using the keywords 'Borna disease virus', 'psychiatric disorders' and 'prevalence' in conjunction with each of the following organic disorders,

addictions, psychotic disorders, affective disorders and anxiety disorders. Due to variations in the laboratory methods, materials and study groups used, a meta-analysis was not possible.

2.4 Study selection

The inclusion criteria were studies published from 1985 to January 2011, the study participants: psychiatric patients, investigation: antibody, antigen, circulating immunocomplexes or viral RNA, material: serum, peripheral blood cells, cerebrospinal fluid, brain tissue, and outcomes: prevalence data.

3. Results

We identified 53 studies published from 1985 to July 2011 describing Borna disease virus positivity in psychiatric patients (psychiatric disorders, affective and psychotic disorders, addictions, neurotic disorders), 29 studies investigated viral antibodies in the serum, 23 BDV RNA in peripheral blood cells, 4 detected circulating immunocomplexes, viral antigens and antibodies in serum, 2 detected BDV RNA in cerebrospinal fluid (CFS), 5 detected BDV RNA in brain tissue and 8 studies detected BDV RNA and Ab. The prevalence of BDV infection in these studies ranged from 0 to 100% for patients with bipolar affective disorder.
Between 1985 and 1993 the presence of BDV infection in groups of patients with various neuropsychiatric disorders was detected using IFA for BDV Ab. The majority of the studies identified found BDV in patients with schizophrenia and affective disorders.

3.1 Borna disease virus infection and organic disorders

Borna disease virus infection causes cognitive impairment (memory and learning impairment) in infected experimental animals. This impairment is linked to cholinergic loss in the forebrain and is associated with the pathology of Alzheimer's disease (Solbrig et al., 2010). Only a few studies reported BDV positivity in organic disorders, especially dementia. We identified five studies that detected the presence of BDV infection in patients with vascular and Alzheimer's dementia; the rate of BDV positivity ranged from 0% to 1% (see Table2).

Authors	Country	Method/marker	Sample	Diagnosis	Total no.	No. and % of positives
De la Torre et al., 1996	USA	PCR/Ag, RNA	Brain	Alzheimer's disease	7	0/0%
Sauder et al., 1996	Germany	WB/Ab	Serum	Alzheimer's, vascular and other organic disorders Control	34 203	7/20.5% 3/1.4%
Igata et al., 1998	Japan	IFA/Ab	Serum	Vascular dementia Control	10 36	0/0% 4/11%
Yamaguchi et al., 1999	Japan	ECLIA/Ab	Serum	Alzheimer's disease Vascular dementia Control	46 89 917	0/0% 1/1.12% 10/1.09%
Czygan et al., 1999	Germany	RT-PCR/RNA	Brain	Alzheimer's disease Control	14 52	0/0% 0/0%

Table 2. Studies that detected BDV infection in patients with organic disorders

3.2 Borna disease virus infection and addiction

Borna disease virus influences dopaminergic neurotransmission, including the reward system, which plays a crucial role in the pathology of addictive disorders. We found four studies that detected BDV infection in addicted patients. Only one study detected BDV positivity in addicted patients at the start of detoxification and at the end of treatment. Rackova and colleagues demonstrated BDV CIC positivity in 36.6% and 42.9% of patients with alcohol and drug abuse; the positivity of BDV infection was not significantly higher than in healthy individuals (Rackova et al., 2010). The rate of BDV positivity ranged from negative results to positivity in 42.9% (see Table 3).

Authors	Country	Method/marker	Sample	Diagnosis	Total no.	No. and % of positives
Sauder et al., 1996	Germany	WB/Ab	Serum	Alcohol and drug addictions Control	22 203	1/ 4.5% 3/1.4%
Yamaguchi et al., 1999	Japan	ECLIA/Ab	Serum	Alcohol addictions Control	42 917	1/ 2.38% 10/1.09%
Czygan et al., 1999	Germany	RT-PCR/RNA	Brain tissue	Addictions Control	27 52	0/0% 0/0%
Rackova et al., 2010	Czech Republic	ELISA/CIC	Plasma	Alcohol and drug addictions Control	41 28 127	15/36.6% 12/42.9% 47/37.3%

Table 3. Studies that detected BDV infection in patients with alcohol and drug addictions

3.3 Borna disease virus infection and psychotic disorders (schizophrenia, schizoaffective disorders)

Borna disease virus infection causes changes in dopaminergic neurotransmission in adult experimental animals and influences brain development in infected neonatal animals; these changes are important in the aetiology of psychotic disorders in humans. We identified 29 studies that detected BDV infection in patients with schizophrenia or schizoaffective disorders, 13 studies that detected BDV RNA, 9 that detected BDV Ab and 7 that detected both infectious markers: Ab and RNA. The rate of BDV infection positivity ranged from 0% to 63.6% in schizophrenic patients and from 0% to 13.86% in control groups of healthy individuals (see Table 4 and 5).

3.4 Borna disease virus infection and affective disorders (depressive disorder, bipolar affective disorders)

The first studies to detect BDV positivity in psychiatric patients reported higher rates of BDV positivity in patients with recurring affective disorders. We found 19 studies that described BDV positivity in patients with affective disorders (depressive and bipolar disorders, dysthymia), 8 studies that examined BDV RNA, 7 studies that detected BDV Ab, 2 studies that detected BDV RNA and Ag and 1 study that detected BDV CIC, Ag and Ab. The rate of BDV infection positivity ranged between 0% and 90% in patients with affective disorders. The highest positivity rate was reported in patients with bipolar depression and severe psychopathology. The rate of BDV infection was from 0% to 32% in the control group of healthy individuals (see Table 6).

Authors	Country	Method/marker	Sample	Diagnosis	Total no.	No. and % of positives
Waltrip et al., 1995	USA	WB/Ab	Serum	Schizophrenia Control	90 20	13/14.4% 0/0%
Sauder et al., 1996	Germany	WB/Ab	Serum	Schizophrenia Control	114 203	16/11.42% 3/1.4%
Kubo et al., 1997	Japan	IFA/Ab WB/Ab	Plasma	Schizophrenia Control	179 70	2/1.1% 0/0%
Waltrip et al., 1997	USA	WB/Ab	Serum	Negative schizophrenia Positive schizophrenia	15 49	5/33.3% 4/8.2%
Deuschle et al., 1998	Germany	EIA/Ag, Ab	CSF	Schizophrenia	?	0/0%
Iwahashi et al., 1998	Japan	WB/Ab	Serum	Schizophrenia Control	67 31	30/44.8% 0/0%
Chen et al., 1999a	Taiwan	WB/Ab	Plasma	Schizophrenia Family members Mental health workers Control	314 132 82 274	38/12.1% 16/12.1% 8/9.8% 8/2.9%
Yamaguchi et al., 1999	Japan	ECLIA/Ab	Serum	Schizophrenia Control	845 917	26/3.08% 10/1.09%
Tsuji et al. 2000	Japan	WB/Ab	Plasma	Schizophrenia Control	229 229	0/0% 0/0%
Selten et al., 2000	Netherlands	IFA/Ab	Serum	Schizophrenia Control	26 29	3/11% 6/21%
Fukuda et al., 2001	Japan	WB/Ab	Plasma	Schizophrenia Control	45 45	2/4% 1/2%
Yang et al., 2003	China	WB/Ab	Serum	Schizophrenia Control	116 ?	10/8.6% 0/0%
Terayama et al., 2003	Japan	WB/Ab	Serum	Schizophrenia Control	32 25	7/21.9% 1/4%
Matsunaga et al., 2005	Japan	RIA/Ab WB/Ab	Serum	Schizophrenia Control	57 41	8/14% 2/1%
Na et al., 2009	Korea	IFA/Ab	Serum	Schizophrenia Control	60 60	0/0% 0/0%
Karakose et al., 2011	Turkey	ELISA/Ab	Serum	Schizophrenia Control	207 137	66/31.88% 19/13.86%

Table 4. Studies that detected BDV Ab in patients with schizophrenic disorders

Authors	Country	Sample	Diagnosis	Total no.	No. and % of positives
Sierra-Honigmann et al., 1995	USA	CSF	Schizophrenia	48	0/0%
Igata-yi et al., 1996	Japan	Plasma PBMCs	Schizophrenia Control	49 36	5/10.2% 0/0%
Sauder et al., 1996	Germany	Plasma PBMCs	Schizophrenia Control	11 23	7/63.6% 0/0%
Kubo et al., 1997	Japan	Plasma PBMCs	Schizophrenia Control	? 12	0/0% 0/0%
Lieb et al., 1997	Germany	Plasma PBMCs	Schizophrenia Schizoaffective disorders	59 10	0/0% 0/0%
Richt et al., 1997	Germany	Plasma PBMCs	Schizophrenia	26	0/0%
Iwahashi et al., 1997	Japan	Plasma PBMCs	Schizophrenia Control	67 31	6/8.9% 1/3.2%
Salvatore et al., 1997	USA, Europe	Brain	Schizophrenia	17	9/53%
Haga et al., 1997	Japan	Brain	Schizophrenia Control	9 31	3/33.3% 2/6.5%
Iwata et al., 1998	Japan	Plasma PBMCs	Schizophrenia Control	77 84	3/4% 2/2%
Czygan et al., 1999	Germany	Plasma PBMCs	Schizophrenia Control	13 52	0/0% 0/0%
Kim et al., 1999	Korea	Plasma PBMCs	Schizophrenia	39	0/0%
Chen et al., 1999b	Taiwan	Plasma PBMCs	Schizophrenia Mental health workers Control	74 45 69	10/14% 7/15% 1/1,4%
Nakamura et al., 2000	Japan	Brain	Schizophrenia Control	4 2	2/50% 0/0%
Tsuji et al., 2000	Japan	Plasma PBMCs	Schizophrenia Control	229 229	4/1.8% 1/0.6%
Fukuda et al., 2001	Japan	Plasma PBMCs	Schizophrenia Control	45 45	0/0% 0/0%
Kim et al., 2003	Korea	Serum	Schizophrenia	62	0/0%
Nunes et al., 2008	Brazil	Plasma PBMCs	Schizophrenia, schizoaffective disorders Relatives with psychiatric disorders Relatives without psychiatric disorders Control	27 24 20 27	12/44.4% 9/37.5% 10/50% 4/14.8%
Na et al., 2009	Korea	Plasma PBMCs	Schizophrenia Control	60 60	0/0% 0/0%
Karakose et al., 2011	Turkey	Plasma PBMCs	Schizophrenia Control	207 137	0/0% 0/0%

Table 5. Studies that detected BDV RNA in patients with schizophrenic disorders

Authors	Country	Method/marker	Sample	Diagnosis	Total no.	No. and % of positives
Amsterdam et al., 1985	USA	IFA/Ab	Serum	Unipolar and bipolar depression Control	265 105	12/4.5% 0/0%
Bode et al., 1993	Germany	IFA/Ab	Serum	Major depression Neurotic depression, dysthymia	? ?	?/30% ?/8%
Fu et al., 1993	Japan	WB/Ab	Serum	Affective disorders Control	138 117	9/6.5% 1/0.9%
Sauder et al., 1996	Germany	WB/Ab	Serum	Affective disorders Control	52 203	6/11.5% 3/1.4%
Bode et al., 1994	Germany	RT-PCR/RNA	Plasma PBMCs	Depression Control	3 10	2/66% 0/0%
Igata-yi et al., 1996	Japan	RT-PCR/RNA	Plasma PBMCs	Depressive disorders Control	6 36	1/16.4% 0/0%
De la Torre et al., 1996	USA	RT-PCR/RNA, Ag	Brain	Depressive disorders	36	4/11.1%
Kubo et al., 1997	Japan	IFA/Ab	Plasma	Mood disorders Control	123 70	0/0% 0/0%
Lieb et al., 1997	Germany	RT-PCR/RNA	Plasma PBMCs	Depressive disorders Bipolar disorders	41 10	0/0% 0/0%
Iwata et al., 1998	Japan	RT-PCR/RNA	Plasma PBMCs	Affective disorders Control	49 84	2/4% 2/2%
Deuschle et al., 1998	Germany	RT-PCR/RNA	CSF	Recurrent depressive disorders	32	3/9.4%
Yamaguchi et al., 1999	Japan	ECLIA/Ab	Serum	Affective disorders Control	251 917	9/3.59% 10/1.09%
Czygan et al., 1999	Germany	RT-PCR/RNA	Brain	Affective disorders Control	11 52	0/0% 0/0%
Kim et al., 1999	Korea	RT-PCR/RNA	Plasma PBMCs	Bipolar disorders Depressive disorders	33 9	0/0% 0/0%
Fukuda et al., 2001	Japan	RT-PCR/RNA	Plasma PBMCs	Affective disorders Control	45 45	1/2% 0/0%
Fukuda et al., 2001	Japan	WB/Ab	Plasma	Affective disorders Control	45 45	1/2% 0/0%
Terayama et al., 2003	Japan	WB/Ab	Serum	Mood disorders Control	33 25	9/27.3% 1/4%
Bode et al., 2001	Germany	ELISA/CIC, Ag IFA/Ab	Plasma	Affective disorders	187	62% CIC, 11% Ab, 15% Ag
					103	52% CIC, 20% Ab, 23% Ag
				Control	100	24% CIC, 2% Ab, 0 Ag

Authors	Country	Method/marker	Sample	Diagnosis	Total no.	No. and % of positives
Bode et al., 2001	Germany	ELISA/CIC, Ag IFA/Ab	Plasma	Severe depression	28	90% CIC
				Mild depression	28	90% CIC
				Control	65	32% CIC
Matsunaga et al., 2005	Japan	WB, RIA/Ab	Serum	Mood disorders Control	80 41	11/13.75% 2/1%
Na et al., 2009	Korea	RT-PCR/RNA IFA/Ab	Plasma PBMCs	Affective disorders Control	138 60	0/0% 0/0%

Table 6. Studies that detected BDV infection in patients with affective disorders

3.5 Borna disease virus infection and neurotic disorders

Only a few studies reported BDV positivity in neurotic disorders: we identified 10 studies and 7 of them examined patients with chronic fatigue syndrome. Six studies detected BDV Ab, two detected BDV RNA and one detected both RNA and Ab markers. The rate of BDV positivity ranged from 0% to 34% in psychiatric patients and between 0% and 5.9% in healthy controls (see Table 7).

Authors	Country	Method/marker	Sample	Diagnosis	Total No	No and % of positive
Sauder et al., 1996	Germany	WB/Ab	Serum	Neurotic, personality disorders Control	54 203	8/14.8% 3/1.4%
Bode et al., 1994	Germany	RT-PCR/RNA	Serum	Panic disorder OCD Control	1 1 10	0/0% 1/100% 0/0%
Nowotny & Windhaber, 1997	Germany	?	Serum	Panic disorders Control	55 34	4/7.3% 2/5.9%
Bode et al., 1992	Germany, USA	IFA/Ab	Serum	Chronic fatigue syndrome	50	0/0%
Nakaya et al., 1996	Japan	RT-PCR/RNA	Plasma PBMCs	Chronic fatigue syndrome	25	8/32%
Kitani et al., 1996	Japan	ELISA/Ab	Serum	Chronic fatigue syndrome	89	30/34%
Gow et al., 1997	UK	WB/Ab	Serum	Chronic fatigue syndrome Control	21 13	2/10% 0/0%
Evengard et al., 1999	Sweden	WB, ELISA/Ab RT-PCR/RNA	Serum Plasma PBMCs	Chronic fatigue syndrome	18	0/0%
Yamaguchi et al., 1999	Japan	ECLIA/Ab	Serum	Chronic fatigue syndrome Control	75 917	0/0% 10/1.09%
Li et al., 2003	China	WB/Ab	Plasma	Chronic fatigue syndrome Control	61 73	7/11.8% 0/0%

Table 7. Studies that detected BDV infection in patients with anxiety disorders and OCD

3.6 Borna disease virus and unspecified psychiatric disorders

Several studies examined psychiatric patients with various diagnoses and it was not possible to divide these groups according the diagnosis. We found 17 studies that detected BDV infection in unspecified psychiatric (or neuropsychiatric) patients, 5 studies that detected BDV Ab, 1 study that detected Ab and Ag, 1 that only detected Ag, 7 studies that detected BDV RNA, 2 that detected BDV CIC and 1 study detected BDV Ab and RNA. The rate of BDV positivity ranged between 0% and 66.7% in psychiatric patients and between 0% and 37.3% in healthy individuals (see Table 8).

Authors	Country	Method/marker	Sample	Diagnosis	Total No	No and % of positive
Rott et al., 1985	Germany, USA	IFA/Ab	Serum	Psychiatric patients Control	979 200	16/1.6% 0/0%
Bode et al., 1992	Europe, USA, Africa	IFA, immunoprecipitation/ Ab, Ag	Serum	Chronic diseases of the brain, immune system, infection (HIV, parasitosis) Control	Total number 3000 	?/13-14% ?/2%
Bode et al., 1993	Germany	IFA/Ab	Serum	Psychiatric patients (screening)	70	1-3/2-4%
Bode et al., 1993	Germany	IFA/Ab	Serum	Psychiatric patients (follow-up test)	70	14/20%
Kishi et al., 1995	Japan	WB, ELISA/Ab	Serum	Control	100	1/1%
Kishi et al., 1995	Japan	RT-PCT/RNA	Plasma PBMCs	Psychiatric patients Control	60 100 72	22/37% 5/5% 3/ 4.2%
Bode et al., 1996	Germany	Ag	Plasma PBMCs	Recurrent depressive and bipolar disorders Other depressive and anxiety disorders Psychotic disorders	10 11 11	53 samples (collected in a week), 20 positive
Sauder et al., 1996	Germany	RT-PCR/RNA	Plasma PBMCs	Psychiatric disorders Control	26 23	13/50% 0/0%
Kubo et al., 1997	Japan	RT-PCR/RNA	Plasma PBMCs	Psychiatric patients Control	106 12	0.2% 0/0%
Salvatore et al., 1997	USA, Europe	RT-PCR/RNA	Brain	Neuropsychiatric disorders	75	11/14.7%
Lieb et al., 1997	Germany	RT-PCR/RNA	Plasma PBMCs	Psychiatric disorders	159	0/0%
Czygan et al., 1999	Germany	RT-PCR/RNS	Brain	Neuropsychiatric disorders Control	86 52	0/0% 0/0%
Vahlenkamp et al., 2000	Germany	RT-PCR/RNA	Plasma PBMCs	Psychiatric patients Control	27 13	10/37% 2/15.4%
Rybakowski et al., 2001	Poland	ECLIA/Ab	Serum	Psychiatric patients	946	23/2.4%

Authors	Country	Method/marker	Sample	Diagnosis	Total No	No and % of positive
Rackova et al., 2003	Czech Republic	ELISA/CIC	Plasma	Affective and schizophrenic disorders Control	46 126	12/26.1% 22.2%
Miranda et al., 2006	Brazil	RT-PCR/RNA	Plasma PBMCs	Schizophrenia and affective disorders Control	30 30	10/33.3% 4/13.3%
Matsunaga et al., 2008	Japan	RIA/Ab	Serum	Psychiatric patients Control	304 378	No significant difference
Rackova et al., 2009	Czech Republic	ELISA/CIC	Plasma	Affective and schizophrenic disorders Control	39 126	26/66.7% 28/22.2%
Karakose et al., 2011	Turkey	ELISA/Ab	Serum	Psychiatric disorders Control	131 137	17/12.98% 19/13.86%
Karakose et al., 2011	Turkey	RT-PCR/RNA	Plasma PBMCs	Psychiatric disorders Control	131 137	0/0% 0/0%

Table 8. Studies that detected BDV infection in psychiatric patients

3.7 Borna diasease virus and other disorders

The influence of BDV infection on other disorders was also studied, particularly on neurological and infectious diseases. Prudlo and colleagues did not find any increase in BDV Ab positivity in neurologic patients (with amyotrophic lateral sclerosis) compared to surgical patients (Prudlo et al., 2002). Li and colleagues detected BDV RNA in patients with viral encephalitis, but no BDV positivity was found in other neurological disorders (Li et al., 2009; Salvatore et al., 1997). Flower and colleagues reported higher rates of BDV CIC positivity in multitransfused patients (Flower et al., 2008), and BDV RNA and Ag were detected in the cerebrospinal fluid of patients with multiple sclerosis (Deuschle et al., 1998). A higher rate of BDV positivity was not detected in patients with epilepsy (Czygan et al., 1999; Hofer et al., 2006) or Parkinson's disease (Haga et al., 1997). Several studies detected higher rates of BDV infection positivity in HIV-positive patients (Auwanit et al., 1996; Bode et al., 1992; Cotto et al., 2003) but not in therapeutically immunosuppressed patients (Cotto et al., 2003).

4. Conclusions

The Borna disease virus is a neurotropic RNA virus belonging to the family Bornaviridae, order Mononegavirales, which has a high affinity for the central nervous system, especially for limbic structures. The Borna disease virus causes an infection in birds and mammals including humans. Some infected animals develop symptoms which are very similar to human psychiatric disorders (cognitive impairment, behavioural changes, changes in social behaviour, appetite, sleeping...). Because of this similarity BDV has begun to be associated with several psychiatric disorders, especially with mood and psychotic disorders. The association of BDV and psychiatric disorders is explained by the viro-psycho-

immunological disease model. A BDV persistent infection of the central nervous system is activated by changes in the immune system, an activated BDV infection influences neurotransmitter functions and contributes to the onset of psychiatric disorders in vulnerable individuals (with a genetic predisposition).
In the 1980s the presence of a BDV infection was found in patients with neuropsychiatric disorders. Since the 1980s many studies have detected a BDV infection in patients with psychiatric disorders (the majority of them tested BDV positive in affective disorders and schizophrenia) and in patients with neurological disorders, HIV infection and others. The positivity of a BDV infection ranges from negative results to very high positivity rates, more than 90% in patients with affective disorders in comparison with BDV positivity between 0%-40% in healthy individuals. The Borna disease virus positivity in psychiatric patients ranges from negative to highly positive. These differences in positivity can be caused by several factors; features of the psychiatric population (age, diagnosis, severity of the psychopathology, immune status), geographical region, differences in specificity and sensitivity of the laboratory methods used and others. The significantly higher rates of BDV positivity were detected in younger individuals, especially in children. Several research groups reported an association between higher BDV positivity and the severity of the psychopathology.The high variability of BDV positivity in humans can be influenced by the laboratory method used**.** The detection of BDV CIC by ELISA has shown a 10-fold higher incidence of BDV infection than was estimated for BDV Ab positivity by the immunofluorescence method.

4.1 Arguments supporting the association of BDV infection with psychiatric disorders include

Characteristics of the Borna disease virus - its ability to infect and spread through the central nervous system, causing persistent infection and its activation, have led to the connection with psychiatric disorders. An experimental BDV infection shows the influence of BDV on neurotransmitter receptors which lead to behavioural changes, cognitive impairment and neurological disturbances.
Many studies have detected the significantly higher BDV positivity in psychiatric patients in comparison with healthy individuals. The Borna disease virus was isolated from PBMCs in plasma, cerebrospinal fluid and brain tissue. Higher levels of BDV antigens and circulating immunocomplexes have been found in acutely depressed patients than in patients with mild depression. Levels of BDV antigens and circulating immunocoplexes correlate with the severity of psychiatric symptoms. Depressed patients who were treated with virostatic medication – amantadine, improved their psychopathology significantly and more quickly. The improvement of depression symptoms correlates with the decrease or disappearance of BDV positivity (levels of antigens).

4.2 Arguments against the BDV role in ethiopathology in psychiatric disorders include

Many studies have failed to detect BDV infection in psychiatric patients or did not find significant differences in BDV positivity between psychiatric patients and healthy individuals. Some researchers detected high BDV positivity in healthy individuals and considered BDV infection to be a normal part of human life without any influence on health.

There are reports about the effect of antiviral treatment with amantadine in BDV positive patients with depression disorders. The improvement of depression symptomatology during this treatment could be explained by the antidepressive effect of amantadine. Some studies did not prove the virostatic effect of amantadine in the treatment a BDV infection.
Several studies criticize the unreliability of some laboratory methods, in these studies BDV was not isolated from BDV CIC positive samples.
What can we conclude? The role of BDV in psychiatric disorders is still unclear. But very probably this infection can be involved in the onset and the course of psychiatric disorders in a determinate subpopulation of psychiatric patients. German and Italian researchers examined the presence of BDV infection in children. These studies are crucial to obtaining information about the possible influence of neurotropic viruses on brain development. A BDV infection in early life can contribute to the onset of psychiatric disorders in adults in predisposed individuals.
For future research, which is important for answering still unclear questions about the Borna disease virus we need more and larger studies testing comparable patient groups and using comparable laboratory methods. We are also missing more double-blind studies with amantadine in BDV positive psychiatric patients. Studies testing for a BDV infection from childhood to adulthood are necessary to answer the question: What is first?: BDV infection and secondly the development of psychiatric disorders or first psychiatric disorders which secondarily leads to several changes in the immune system and then the activation of the BDV infection.

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12

Explanations for Elevated Psychiatric Vulnerability in Nonheterosexuals: Environmental Stressors, Genetics, and the HPA and HPG Axes

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1. Introduction

In Western societies, around 2-5% of men and women identify as gay, lesbian, or bisexual (i.e. nonheterosexual), and at least 10% report at least some attraction to same-sex individuals (Sell et al. 1995; Kendler et al. 2000; Kirk et al. 2000). Nonheterosexuality is not limited to today's Western societies, but has been commonly observed in other cultures today and throughout history (e.g. Hinsch 1992; Murray and Roscoe 1998; Vasey and VanderLaan 2007). In this chapter I firstly outline extensive and robust evidence that sexual minorities are at greater risk of psychiatric disorder than are heterosexuals (Section 2). In Section 3, I explore possible explanations for why this might be the case. I discuss the dominant 'minority stress hypothesis' (Section 3.1); lifestyle factors associated with nonheterosexuality that may exacerbate psychiatric vulnerability (Section 3.2); and 'common cause' explanations involving genetic factors (Section 3.3.1) and adverse childhood experiences (Section 3.3.2), which appear to predispose to both nonheterosexuality and psychiatric disorder. I also propose a novel neurohormonal explanation to account for how the same genetic factors and childhood experiences might affect both sexual orientation and psychiatric risk (Sections 3.3.1.3 and 3.3.2). In Section 4 I conclude and draw attention to areas in which much more research is needed.

2. Nonheterosexuals are at elevated risk of psychiatric disorder

Prior to 1973, homosexuality was classified by the American Psychiatric Association as a disorder in and of itself. However, in that year homosexuality was removed from the DSM II and subsequent editions, and is not now considered a disorder in the psychiatric community (American Psychiatric Association 1973). This chapter describes and proposes explanations for robust findings that nonheterosexuals are at greater risk of psychiatric disorder than the general population. However, it cannot be emphasized strongly enough that this should in no way pathologise nonheterosexuality itself, any more than we should pathologise non-right-handedness, for example, which is also associated with higher rates of psychiatric disorder (Elias et al. 2001; DeLisi et al. 2002).

Several recent large-scale studies have indicated that nonheterosexuals are at elevated risk for many psychiatric symptoms and disorders, including mood disorders (e.g., major depression, bipolar disorder), anxiety disorders (e.g., generalized anxiety disorder, phobic disorders, obsessive compulsive disorder), eating disorders, conduct disorder, substance misuse, suicidal ideation, and suicide attempts (Fergusson et al. 1999; Sandfort et al. 2001; Meyer 2003; Mills et al. 2004; Sandfort et al. 2006; King et al. 2008; Frisell et al. 2010; Bolton and Sareen 2011). These studies have used population samples in several different countries, so the results are unlikely to be due to sampling bias, and the size of the samples and the numerous replications suggests that the findings are not due to sampling error. Furthermore, the size of the effects are by no means trivial – for example, a recent meta-analysis revealed that, compared to heterosexuals, nonheterosexuals are at approximately twice the risk of major depressive disorder (depression) and anxiety disorders, deliberate self harm and attempted suicide (King et al. 2008).

Some studies, particularly earlier ones, suffered from the problems associated with convenience sampling, potentially biasing the estimates of psychiatric risk. However, larger and more representative samples have confirmed the findings. **Table 1 shows results of major population-based studies comparing psychiatric risk in heterosexuals and nonheterosexuals** in which odds ratios (in comparison with heterosexuals) are provided.

Fergusson et al. 1999	Men and women pooled N= 1007 (2.8% identify nonheterosexual i.e. gay/lesbian/bisexual) Major depression - OR 4.0; 95%CI 1.8-9.3 Generalized anxiety disorder - OR 2.8; 95%CI 1.2-6.5 Conduct disorder - OR 3.8; 95%CI 1.7-8.7 Nicotine dependence - OR 5.0; 95%CI 2.3-10.9 Other substance abuse and/or dependence - OR 1.9; 95%CI 0.9-4.2 Multiple disorders - OR 5.9; 95%CI 2.4-14.8
Cochran and Mays 2000	N= 9,908 (2.0% had same-sex partner in previous year) Men Major depression - 2.94 (1.38-6.28) Generalized anxiety disorder - 2.32 (0.55-9.70) Agoraphobia - 4.85 (0.94-25.17) Panic attack - 4.30 (1.53-12.13) Drug dependency - 2.05 (CI 0.86-4.93) Alcohol dependency - 1.33 (0.55-3.22) Any psychiatric syndrome - 2.26 (1.34-3.89) Women Major depression - 1.79 (0.74-4.32) Generalized anxiety disorder - OR 1.54 (CI 0.49-4.86) Agoraphobia - 1.41 (0.52-3.84) Panic attack - 1.78 (0.40-8.33) Drug dependency - 3.27 (1.23-8.70) Alcohol dependency - 2.85 (1.16-6.98) Any psychiatric syndrome - 1.63 (CI 0.76-3.48)

(Sandfort et al.	Men N=2,878 (2.8% had same-sex partner in previous year)
2001)Sandfort et al.	Mood disorders – 3.11(1.91-5.05)
2001	Major depression – 2.35 (1.39-3.97)
	Dysthymia 2.33 (0.94-5.75)
	Bipolar disorder 7.27 (2.85-18.52)
	Anxiety disorders 2.67 (1.62-4.41)
	Panic disorder 4.21 (1.65-10.77)
	Agoraphobia (without panic) 4.54 (1.79-11.53)
	Simple phobia 3.61 (1.94-6.74)
	Social phobia 2.29 (1.17-4.50)
	Generalized anxiety disorder 2.88 (0.82-10.18)
	Obsessive compulsive disorder 6.20 (2.03-18.90)
	Substance use disorders total 0.79 (0.48-1.32)
	Alcohol abuse 0.48 (0.24-0.95)
	Alcohol dependence 1.23 (0.62-2.44)
	Drug abuse 1.34 (0.45-4.01)
	Drug dependence 2.47 (0.82-7.45)
	Women N=3,120 (1.4% had same-sex partner in previous year)
	Mood disorders 2.41 (1.26-4.63)
	Major depression 2.44 (1.26-4.72)
	Dysthymia 1.62 (0.65-4.02)
	Bipolar disorder 0.92 (0.12-6.97)
	Anxiety disorders 0.96 (0.46-1.97)
	Panic disorder 0.75 (0.18-3.20)
	Agoraphobia (without panic) 1.36 (0.41-4.56)
	Simple phobia 1.27 (0.51-2.97)
	Social phobia 1.81 (0.79-4.14)
	Generalized anxiety disorder 0.84 (0.11-6.28)
	Obsessive compulsive disorder --
Sandfort et al. 2001	Substance use disorders total 3.43 (1.60-7.33)
(continued)	Alcohol abuse 2.01 (0.60-6.79)
	Alcohol dependence 3.59 (1.16-11.18)
	Drug abuse 1.88 (0.23-15.33)
	Drug dependence 8.04 (2.49-25.91)

Gilman et al. 2001	Men N=2,384 (3.1% had same-sex partner in previous year) Anxiety disorders 1.3 (0.8-2.4) Agoraphobia 1.1 (0.3-3.9) Generalised anxiety disorder 2.8 (1.0-8.0) Panic 1.2 (0.2-6.5) Social phobia 1.6 (0.7-3.5) Simple phobia 1.0 (0.4-2.5) Post-traumatic stress disorder 1.1 (0.5-2.5) Mood disorders 1.3 (0.8-2.4) Major depression 1.5 (0.7-3.0) Dysthymia 1.1 (0.4-2.8) Substance use disorders 1.5 (0.8-2.8) Alcohol abuse 1.2 (0.7-2.3) Alcohol dependence 1.4 (0.6-3.0) Drug abuse 2.8 (1.6-5.1) Drug dependence 2.4 (1.2-4.8) Women N=2,526 (2.0% had same-sex partner in previous year) Anxiety disorders 1.8 (1.2-2.8) Agoraphobia 1.1 (0.2-5.9) Generalised anxiety disorder 3.2 (1.4-7.3) Panic 2.6 (0.9-7.7) Social phobia 1.5 (0.7-3.3) Simple phobia 1.8 (1.2-2.9) Post-traumatic stress disorder 2.7 (1.2-6.1) Mood disorders 2.0 (1.1- 3.5) Major depression 1.9 (1.0-3.3) Dysthymia 1.9 (0.8-4.4) Substance use disorders 2.4 (1.3-4.4) Alcohol abuse 1.8 (0.7-4.5) Alcohol dependence 2.2 (0.9-5.6) Drug abuse 4.4 (2.4-8.1) Drug dependence 1.7 (0.5-5.5)
Chakraborty et al.	Men and women pooled N=7,403 (8.8% identify nonheterosexual i.e. gay/lesbian/bisexual) Depressive episode - 1.80 (1.13–2.87) Generalised anxiety disorder - 1.49 (1.03–2.15) Obsessive–compulsive disorder - 2.24 (1.18–4.27) Phobic disorder - 1.91 (1.07–3.39) Probable psychosis - 3.75 (CI 1.76–8.00) Drug dependence - 1.70 (1.06–2.73) Alcohol dependence - 2.05 (1.45–2.90)

Bolton and Sareen 2011 * Using the same dataset, Bostwick et al (2010) show the elevation in psychiatric risk differs depending on the measure of sexual orientation used.	Men N=14,449 (1.3% identify gay, 0.6% bisexual, 0.5% not sure) Any mood disorder [Gay] 2.98 (2.11–4.20) [Bi] 2.36 (1.44–3.88) [Not sure] 1.93 (1.04–3.59) Any anxiety disorder 2.66(1.78–3.97); 2.09(1.20–3.64) ; 2.07 (1.06–4.03) Any substance use disorder 1.77 (1.25–2.51) ; 1.30 (0.71–2.36) ; 0.77 (0.41–1.45) Any personality disorder 1.82 (1.19–2.77) ; 1.66 (0.98–2.82) ; 2.46 (1.34–4.51) Schizophrenia, psychotic illness, or episode 2.85 (1.57–5.15) ; [—] ; 3.80 (1.44–10.04) Women N=19,896 (0.7% identify lesbian, 0.8% bisexual, 0.5% not sure) Any mood disorder [Lesbian] 1.60 (1.05–2.44) [Bi] 2.66 (1.83–3.89) [Not sure] 1.23 (0.70–2.16) Any anxiety disorder 1.53 (1.01–2.32); 3.09 (2.04–4.68); 1.17 (0.69–1.99) Any substance use disorder 1.37 3.41 (2.13–5.44); 3.90 (2.64–5.75); 1.88 (1.01–3.49) Any personality disorder 1.74 (1.13–2.69); 2.12 (1.43–3.13); 1.65 (0.87–3.15) Schizophrenia, psychotic illness, or episode [—]; 3.18 (1.78–5.69); [—]
Zietsch et al. in press	N= 9,884 Men (4.3% identify nonheterosexual i.e. gay/lesbian/bisexual) Lifetime depression 2.8 (2.0-3.9) Women (3.3% identify nonheterosexual i.e. gay/lesbian/bisexual) Lifetime depression 2.7 (1.9-3.7)

Table 1. Major population-based studies comparing psychiatric risk in heterosexuals and nonheterosexuals. Odds ratios are with reference to rates in heterosexuals (i.e. for whom OR=1), and are accompanied by 95% confidence intervals in brackets. Where applicable, odds ratios presented are those adjusted for possible confounds. NB: We focus here on psychiatric risk and do not include several studies on suicidality.

3. What might explain the elevated psychiatric vulnerability in nonheterosexuals?

3.1 The minority stress hypothesis

Perhaps the first explanation that comes to mind is that nonheterosexuality is stigmatised in many societies, and that it must be stressful and depressing to be frequently subject to prejudice and discrimination. Indeed, this is the basis of the "minority stress" hypothesis, the dominant explanation for explaining elevated psychiatric vulnerability in nonheterosexuals (Meyer 1995; Mays and Cochran 2001; Meyer 2003; Lehavot and Simoni 2011). Meyer (2003) describes a number of stress processes that may increase psychiatric risk in nonheterosexuals. These include the experience of prejudice events, expectations of rejection, hiding and concealing, internalized homophobia, and ameliorative coping processes. Some experiences of prejudice may be institutionalised discrimination, such as legal bans on gay marriage or religious intolerance of homosexuality, but many are likely to be everyday experiences of negativity, rejection, and labelling (Meyer 1995). Hatzenbuehler

(2009) describes a theoretical framework for understanding psychological mechanisms by which these stigma-related experiences may cause psychopathology.

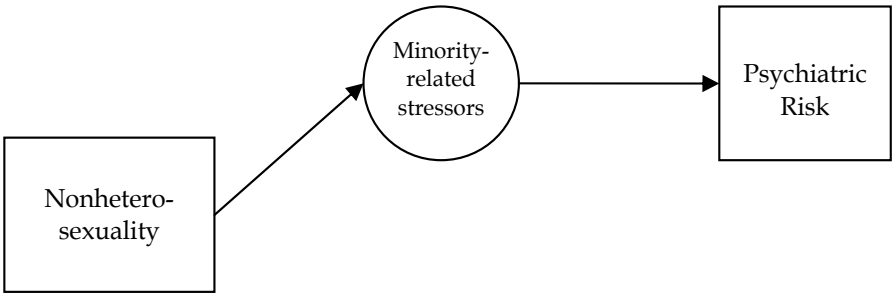

Fig. 1. Nonheterosexuality leads to exposure to minority-related stressors, which leads to elevated psychiatric risk.

Two studies provide strong evidence that homophobic prejudice and discrimination are indeed involved in elevated psychiatric risk in nonheterosexuals (Mays and Cochran 2001; Frisell et al. 2010). In community-based samples, both studies confirmed that nonheterosexuals reported more prejudice and discrimination than heterosexuals (e.g. being fired from a job, or threatened, harassed, or insulted), and found that controlling for reported levels of discrimination attenuated the relationship between sexual orientation and psychiatric disorder.

While it is tempting to dust off the hands and proclaim the mystery solved, **there are indications that minority stress may not be a complete explanation**. Firstly, in both studies mentioned above (Mays and Cochran 2001; Frisell et al. 2010), even after controlling for reported levels of prejudice and discrimination there remained considerable elevation in psychiatric risk in nonheterosexuals. Secondly, heterosexual relatives of nonheterosexuals are also at greater psychiatric risk than the general population (Frisell et al. 2010; Zietsch et al. in press), suggesting that familial (i.e. genetic or family environmental) factors other than minority stress are also important. Thirdly, studies show the relationship between sexual orientation and mental health is just as strong in The Netherlands, where there has long been greater cultural acceptance of homosexuality than in other countries (Sandfort et al. 2001; Lewis 2009). Fourth, racial-ethnic minorities in the US appear to have *lower* psychiatric risk than the majority white population, despite their experiences of minority-related prejudice and discrimination (Breslau et al. 2006). Nonheterosexuals' minority status probably impacts differently on their mental health because they normally have heterosexual family members who may also stigmatise nonheterosexuality. However, it appears that individuals with developmental physical disabilities (who may also be stigmatised and not have similarly affected family members) also have similar or lower risk of psychiatric disorder than the general population (Australian Bureau of Statistics 1998; Hagiliassis et al. 2005; Ostlie et al. 2010), reinforcing the suggestion that minority stress does not necessarily elevate psychiatric risk.

As such, **there may be additional mechanisms generating the link between sexual orientation and psychiatric risk**. This does not imply that I am skeptical of the role of minority stress, only that *additional* explanations warrant investigation. To date, additional

explanations have hardly even been discussed, let alone empirically investigated. Below I describe some of these possible additional explanations, and any relevant evidence.

3.2 Lifestyle factors associated with nonheterosexuality

It has been suggested that lifestyle factors associated with nonheterosexuality may explain some of its link with elevated psychiatric risk (Bailey 1999). This is a broad explanation that depends firstly on understanding how the lifestyles of nonheterosexuals tend to differ from those of heterosexuals, and secondly identifying those lifestyle differences that could be relevant to psychiatric risk. Below I outline a number of lifestyle factors for which are likely to differ with sexual orientation and may also be related to psychiatric risk, but the list is not intended to be exhaustive.

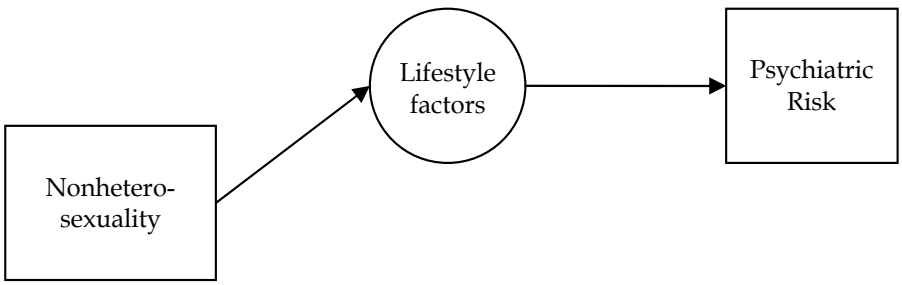

Fig. 2. Nonheterosexuality leads to associated lifestyle factors, which lead to elevated psychiatric risk.

3.2.1 Relationship stability

It appears that gay and lesbian relationships tend to be less stable than heterosexual relationships; in a 5-year study, both gay and lesbian cohabiting couples were more likely to breakup than were heterosexual married couples (Kurdek 1998). (Note that this could be related to legal barriers to a) homosexuals wishing to get married and b) heterosexual married couples wishing to break up.) If homosexual relationships are less stable, it could pose a risk to mental health to nonheterosexuals given that relationship dissolution is a major life stressor that can provoke psychiatric problems (Chung et al. 2002).

3.2.2 Difficulty of having children

An important lifestyle consideration distinctive to homosexual couples is that, without the aid of a third party, they cannot have children. In addition, homosexual couples wishing to have or adopt a child may face legal obstacles in many countries. The little evidence there is suggests that lesbian women's desire to have children is at least as strong as their heterosexual counterparts (Bos et al. 2003). The difficulty of fulfilling this desire could be a psychiatric risk factor, especially in light of findings infertile women have elevated risk of psychiatric disorder (Noorbala et al. 2009). In the absence of evidence to the contrary, it can only be assumed that the same issues apply to gay men.

3.2.3 Substance use

Substance use and dependence is more prevalent among nonheterosexuals (McKirnan and Peterson 1989a; Fergusson et al. 1999; Cochran and Mays 2000; Chakraborty et al. 2011), and

is also a risk factor for psychiatric disorder (Semple et al. 2005). It is unclear if drug use is more often part of nonheterosexuals' chosen lifestyles, and/or if increased drug use is a coping mechanism for the stressors and psychiatric difficulties nonheterosexuals are more likely to encounter. There is evidence that the latter is true (McKirnan and Peterson 1989b), but if the former is also true (e.g. Mansergh et al. 2001), one way to reduce mental health risk in nonheterosexuals may be to target recreational drug use in the gay and lesbian communities. Other mechanisms are also possible (e.g. common causes, see Section 3.3. below).

3.2.4 Sexually transmitted disease and general health

Sexually transmitted diseases, including AIDS, are more common in male nonheterosexuals than in male heterosexuals, due to higher incidence of risky sexual behaviours (Cates and Panel Am Social Hlth Assoc 1999; Stolte and Coutinho 2002). Acquiring sexually transmitted diseases is associated with distress (Cochran and Mays 2007), and AIDS is certainly a major life stressor. Both male and female nonheterosexuals report poorer physical health in general than heterosexuals (Sandfort et al. 2006; Cochran and Mays 2007), though it is unclear whether this is due to lifestyle choices, minority-related stressors, or some other mechanism (e.g. common causes, see Section 3.3. below).

3.2.5 Body image

Nonheterosexual men have greater concerns about body image and greater incidence of eating disorders than do heterosexual men; on the other hand, nonheterosexual women actually have fewer problems than heterosexuals with body image and eating disorders (Herzog et al. 1992; Gettelman and Thompson 1993; French et al. 1996). This may be because men are the sexual targets of homosexual men and heterosexual women, with men placing higher importance on physical appearance than women (Buss 1989).

3.3 Common causes of nonheterosexuality and psychiatric disorder

It is obvious to ask if the link between nonheterosexuality and psychiatric risk is due to factors that cause both, but it is difficult to answer in practice due to our limited understanding of the causes of either psychiatric disorder or, especially, nonheterosexuality. Here I will focus on genetic factors and adverse childhood experiences, which are associated with both sexual orientation and psychiatric risk.

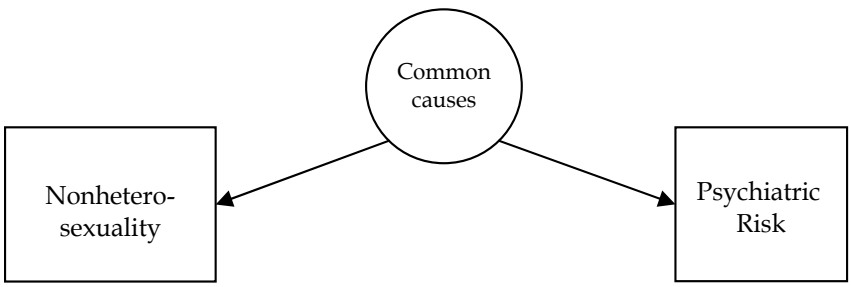

Fig. 3. Common causes lead to both nonheterosexuality and psychiatric risk.

3.3.1 Genetic factors

It is well established that **genetic factors influence sexual orientation**. Early family studies in men (Bailey and Pillard 1991) and women (Bailey et al. 1993) revealed that biological siblings (twins) were much more concordant in their sexual orientation than were adoptive siblings, suggesting that genes or intrauterine effects were more important than factors associated with the family environment. They also showed that identical (monozygotic; MZ) twins, who share 100% of their genes, were more concordant than nonidentical (dizygotic; DZ) twins, who share on average 50% of their genes – this indicated that the familial effects were at least partly genetic; statistical modeling procedures (Neale and Cardon 1992; Posthuma et al. 2003) yielded estimates that genetic factors accounted for at least half of the variance in sexual orientation (i.e. heritability > 50%).

These early studies were criticized for using convenience samples (Lidz 1993), which may have biased the heritability estimates. Indeed, the numerous subsequent studies using very large, representative, community-based twin samples, have often yielded somewhat lower heritability estimates (≈20-50%), but they have consistently replicated the finding that MZ twins are more concordant in their sexuality than DZ twins (Bailey et al. 2000; Kendler et al. 2000; Santtila et al. 2008; Zietsch et al. 2008; Langstrom et al. 2010). **Table 2 summarizes the findings of major twin studies on sexual orientation**.

Bailey and Pillard 1991	Recruitment nonheterosexual probands recruited through ads in gay-oriented publications Classification [homosexual/bisexual] vs heterosexual Men 52% MZ concordance (N=56 pairs) 22% DZ concordance (N=54 pairs) 11% adoptive brothers concordance (N=57 pairs)
Bailey et al. 1993	Recruitment nonheterosexual probands recruited through ads in gay-oriented publications Classification [homosexual/bisexual] vs heterosexual Women 48% MZ concordance (N=71 pairs) 16% DZ concordance (N=37 pairs) 6% adoptive sisters concordance (N=35 pairs)
Kendler et al. 2000	Recruitment national twin sample Classification [homosexual/bisexual] vs heterosexual Men and women combined .68 MZ twin pair correlation (N=324 pairs) .43 DZ twin/sibling pair correlation (1806 pairs)

Zietsch et al. 2008 *Bailey et al (2000) analyzed the same dataset but used a more complex, composite measure of sexual orientation, which yielded lower heritability estimates of female sexual orientation.	Recruitment community-based twin sample Classification [Kinsey attraction scale ≥ 1] vs [Kinsey attraction scale < 1] Men .57 (95%CI: .33-.74) MZ twin pair correlation (N=312 pairs) .20 (95%CI: -.11 -..49) DZ twin pair correlation (N=185 pairs) Women .47 (95%CI: .33-.74) MZ twin pair correlation (N=667 pairs) .37 (95%CI: .33-.74) DZ twin pair correlation (N=377 pairs) Opposite sex twin pairs -.01 (95%CI: .33-.74) DZ twin pair correlation (N=366 pairs)
Santtila et al. 2008	Recruitment community-based twin sample Classification potential for homosexual response: 6-point scale; quite impossible - very likely Men (N=3152 individuals) .53 (SE=.08) MZ twin pair correlation .23 (SE= .11) DZ twin pair correlation Women (N=6001 individuals) .53 (SE=.04) MZ twin pair correlation .26 (SE=.05) DZ twin pair correlation
Langstrom et al. 2010	Recruitment national twin sample Classification [any same-sex sexual partners] vs [no same-sex sexual partners] Men .39 MZ twin pair correlation (N=807 pairs) .19 DZ twin pair correlation (N=517 pairs) Women .36 MZ twin pair correlation (N=1513 pairs) .27 DZ twin pair correlation (N=989 pairs)
Zietsch et al. in press	Recruitment community-based sample Classification [homosexual/bisexual] vs heterosexual Men .50 (95%CI: .25-.60) MZ twin pair correlation (N=633 pairs) .27 (95%CI: -.12-.60) DZ twin pair correlation (N=503 pairs) Women .53 (95%CI: .33-.70) MZ twin pair correlation (N=1079 pairs) .33 (95%CI: .04-.57) DZ twin pair correlation (N=811 pairs) Opposite-sex pairs .43 (95%CI: .12-.66) DZ twin pair correlation (N=866 pairs)

Table 2. Tetrachoric correlations (i.e. twin similarity) for sexual orientation in identical (MZ) and nonidentical (DZ) twin pairs in major studies.

Many large twin studies have also consistently shown that **psychiatric disorders are substantially influenced by genetic factors** (see Sullivan et al. 2000; Bouchard and McGue 2003; Sullivan et al. 2003 for reviews), with a wide range of heritabilities from around 40% for depression to around 80% for schizophrenia. Many psychiatric disorders are highly comorbid (i.e. they are often found together in the same individuals), particularly those related to anxiety and depression, including phobias, generalised anxiety disorder, major depressive disorder, obsessive compulsive disorder, and substance use disorders (Rohde et al. 1991; Kendler et al. 1992). As well as estimating genetic influence on variation in a psychiatric disorder, twin studies can also be used to estimate the genetic influence on covariation between different disorders, by modelling cross-twin cross-trait correlations. If the cross-twin cross-trait correlation is greater in MZ pairs than in DZ pairs it suggests a genetic correlation between the traits, and modelling can estimate what proportion of the total correlation between the traits is due to this genetic correlation (as opposed to correlation of environmental factors); see Neale and Cardon (1992) or Posthuma et al (2003) for details. This type of multivariate genetic analysis has revealed that comorbidity between the various anxiety-related psychiatric disorders is largely due to overlapping genetic influences (Kendler et al. 1992; Hettema et al. 2005). This suggests that the genetic factors involved are pleiotropic (i.e. have multiple effects, e.g. predispose to multiple disorders), though it should be noted that these genetic factors could influence the different disorders via different genes that are in linkage disequilibrium (i.e. genes that tend to be inherited together).

Given that we know that **genetic factors influence both psychiatric disorder and sexual orientation**, the next question is, **do these genetic factors overlap?** A genetic correlation would be necessary for a genetic 'common causes' explanation to be plausible. My colleagues and I (Zietsch et al. 2011) first tested this possibility in a large twin sample (N=4904) by investigating the relationship between sexual orientation and Eysenck's personality traits Neuroticism and Psychoticism, putative measures of vulnerability to internalizing (e.g. depressive and anxiety) disorders and psychotic disorders (e.g. schizophrenic), respectively (Eysenck 1967; Eysenck and Eysenck 1976). Neuroticism has been shown to be a premorbid predictor of depression (Kendler et al. 1993; Ormel et al. 2004), accounts for comorbidity with anxiety (Andrews 1996; Khan et al. 2005), and is also associated with eating disorders (Cassin and von Ranson 2005). Similarly, Psychoticism is a premorbid predictor of schizophrenia and other psychotic disorders (Claridge et al. 1983; Laurent et al. 2002) and is related to antisocial behavior and conduct problems (Tranah et al. 1998; Miller and Lynam 2001; Cale 2006). Both Neuroticism and Psychoticism are related to suicidal behavior (Nordstrom et al. 1995). We found that nonheterosexual men and women scored significantly higher on both Neuroticism and Psychoticism than their heterosexual counterparts, consistent with their greater psychiatric risk found elsewhere. Using bivariate genetic models, we showed that the association of sexual orientation with both Neuroticism and Psychoticism was due primarily to significant genetic correlations, whereas the corresponding environmental correlations were not significant. This provides some support for the idea that overlapping genetic factors act as a common cause of both sexual orientation and psychiatric vulnerability.

In a second study testing this idea, my colleagues and I (Zietsch et al. in press) investigated the relationship between sexual orientation and depression in a large twin sample (N=9,884). We found that nonheterosexuals were at significantly greater risk of depression

and again we found that a significant genetic correlation was primarily responsible, accounting for 60% of the total correlation between sexual orientation and depression.
Since it appears that pleiotropic genetic factors may act as a common cause of nonheterosexuality and psychiatric risk, it is natural to ask: **what mechanisms might confer this shared genetic risk?** Below I describe why explanations involving specific genes or general mutation load are unlikely to be viable. I then propose a more plausible theory involving interaction between the hypothalamic-pituitary-gonadal (HPG) axis and the hypothalamic-pituitary-adrenal (HPA) axis.

3.3.1.1 Specific genes

The recent availability of high-density genotype information has enabled studies that test for association between hundreds of thousands of genetic variants (single nucleotide polymorphisms; SNPs) and any given trait. These genome-wide association (GWA) studies have yielded very few robustly replicated associations between specific genes and complex psychological traits, including psychiatric disorder (Manolio et al. 2009; Sullivan et al. 2009; Verweij et al. 2010). Genes previously 'identified' using earlier approaches (linkage, candidate gene association) as influencing traits such as personality (e.g. Ebstein et al. 1996), depression (e.g. Ogilvie et al. 1996), or substance use (see Agrawal and Lynskey 2009) have generally failed to replicate using these more powerful methods (Verweij et al. 2010; Bosker et al. 2011; Verweij et al. 2011). This suggests publication bias towards positive findings and replications may have resulted in a high proportion of the reports being false positives.
Early findings of linkage of a gene on the X-chromosome with sexual orientation (Hamer et al. 1993; Hu et al. 1995) failed to consistently replicate in subsequent studies (Rice et al. 1999; Mustanski et al. 2005). Sexual orientation has not yet been subject to GWA analysis (it is very expensive and requires very large samples), but **it seems highly unlikely that variation in sexual orientation could be explained with a small number of genes of large effect** given that this is not the case for any other psychological trait that has been studied with GWA methodology (Manolio et al. 2009).
Studies examining the combined effects of thousands of SNPs on complex traits suggest that 'missing heritability' (the discrepancy between high heritability estimates from twin-family studies and inability to identify the specific genetic variants responsible) is partly because of the extremely small effect sizes of any individual genetic variant, and partly because many of the genetic variants involved are rare in the population (conventional GWA studies cannot detect rare variants) (Manolio et al. 2009; The International Schizophrenia Consortium 2009; Yang et al. 2010). Variation in both sexual orientation and depression is likely to be due to thousands of genetic variants of tiny effect size. If this is the case, **the large genetic correlation between sexual orientation and depression could not be due to a few key genes**.

3.3.1.2 Mutation load

Bailey (1999) suggested that elevated rates of nonrighthandness that have been observed in both nonheterosexuals and the mentally ill may reflect a biological factor that manifests in unusual laterality, sexual orientation, and psychiatric problems.
Mutation load is an individual's aggregate of mildly deleterious mutations acquired in recent generations. It is thought to be related to psychiatric disorder via increased developmental instability (Yeo et al. 1999; Keller and Miller 2006). In theory, a high mutation load could predispose to both depression and nonheterosexuality via multiple downstream

effects of the destabilising mutations. Indeed, both nonheterosexuals and those with psychiatric disorders are more likely to be nonrighthanded (Hicks and Pellegrini 1978; Elias et al. 2001; DeLisi et al. 2002; Lippa 2003), which is thought to be an indicator of developmental instability (Yeo and Gangestad 1993; Yeo et al. 1993).
However, traits affected by mutation load are also expected to be associated with advanced paternal age, since the sperm of older men carry more de novo mutations (Crow 2000). Accordingly, advanced paternal age has been associated with higher risk of autism, bipolar, schizophrenia, and lower IQ (Auroux et al. 1989; Malaspina et al. 2001; Reichenberg et al. 2006; Frans et al. 2008; Saha et al. 2009). In contrast, paternal (or maternal) age appears to have no effect on either sexual orientation or depression (Zietsch et al. in press). Furthermore, previous studies found no correlation between sexual orientation and fluctuating asymmetry (Mustanski et al. 2000; Rahman and Wilson 2003b; Rahman 2005a), the best-documented marker of developmental instability (Gangestad and Simpson 2000). Therefore, **mutation load does not seem a viable explanation for the genetic correlation between sexual orientation and depression.**

3.3.1.3 Interaction between the HPA and HPG axes

I propose a novel and more plausible explanation involving a neurohormonal mechanism, but it is speculative and requires direct testing in future research. Its basis is that (unknown) genetic factors affect both sexual orientation and psychiatric risk via effects on the hypothalamic-pituitary-gonadal (HPG) axis, which stimulates sex hormone production (primarily, testosterone in men and estrogen in women). Though the details are far from clear, sex-atypical levels of gonadal hormones during development are thought to be involved in sexual orientation (Gooren 2006; Swaab and Garcia-Falgueras 2009), and the most robust correlates of nonheterosexual orientation relate to sex-atypicality in behavior, cognition, and brain structure (Bailey et al. 2000; Rahman and Wilson 2003a; Swaab 2008). Therefore, via low gonadal hormone levels during development, genetically low activity of the HPG axis might have organizing effects on the brain and predispose to a nonheterosexual orientation. Meanwhile, low gonadal hormone levels are also involved in the etiology of depressive and anxiety disorders. Depressed women have lower plasma levels of estrogen and depressed men have lower testosterone levels (Young et al. 2000; Swaab et al. 2005; Walf and Frye 2006; Zarrour et al. 2009), and administering testosterone and estrogen has been found to reduce depression in men and women, respectively (Soares et al. 2001; Walf and Frye 2006; Zarrour et al. 2009). Animal models suggest the effect in males is due to testosterone's suppression of the hypothalamic-pituitary-adrenal (HPA) axis (i.e. the stress system; Evuarherhe et al. 2009), whereas less established mechanisms in females appear to involve estrogen receptors in the hippocampus and amygdala, which in turn regulate HPA activity (Walf and Frye 2006). Also, gonadal hormone levels during development have programming effects affecting adult HPA reactivity (Evuarherhe et al. 2009; Romeo 2010). Thus, **genetic factors associated with low HPG axis activity (either throughout development or in critical phases) might predispose to development of both nonheterosexual orientation and vulnerability to disorders related to the stress response**.

3.3.2 Adverse childhood experiences – risky family environment and sexual abuse

Along with genetic factors, other possible common causes of both nonheterosexuality and psychiatric risk are adverse childhood experiences such as 'risky' family environment and sexual abuse.

Risky family environments are those characterized by conflict and relationships that are cold, unsupportive, and neglectful (Repetti et al. 2002). Such family environments are known to be associated with a range of psychiatric problems, including aggression, conduct disorder, delinquency and antisocial behaviour, anxiety, depression, and suicide (Felitti et al. 1998; Kendler et al. 2002; Repetti et al. 2002; Kendler et al. 2006). These associations are partly a function of genetic predispositions that underlie the damaging parental behaviours and are inherited by the children (Plomin 1994), but other research (including longitudinal studies) suggests that risky family environment also plays a direct role in predisposing to disorder (O'Connor et al. 1998; Johnson et al. 2001). Childhood sexual abuse has also been strongly linked to psychiatric risk (Felitti et al. 1998; Kendler et al. 2002; Nelson et al. 2002; Kendler et al. 2004; Kendler et al. 2006; Fergusson et al. 2008). Though the mechanisms involved are not yet entirely clear, there is mounting evidence that these associations between adverse childhood experiences and psychiatric risk are mediated by permanent effects of repeated stressors on HPA axis reactivity (Heim et al. 2008; Pariante and Lightman 2008; Lupien et al. 2009; Romeo 2010; Young and Korszun 2010).

Several studies have shown elevated rates of childhood sexual abuse and risky family environment in nonheterosexuals (Cameron and Cameron 1995; Lenderking et al. 1997; Fergusson et al. 1999; Paul et al. 2001; Tomeo et al. 2001; Balsam et al. 2005; Arreola et al. 2008; Alanko et al. 2009; Zietsch et al. in press). A meta-analysis of studies examining the prevalence of childhood sexual abuse in nonheterosexuals (Rothman et al. 2011) yielded higher rates than corresponding rates in a meta-analysis of studies of the general population (Stoltenborgh et al. 2011). A problem with most studies comparing rates of childhood sexual abuse by sexual orientation is that nonheterosexual samples are usually selected based on their sexual orientation (e.g. recruiting in gay-oriented magazines), leading to unpredictable biases on the results. To my knowledge only one study has directly compared rates of childhood sexual abuse in heterosexuals and nonheterosexuals in a large population-based sample selected without reference to sexual orientation or child abuse (Zietsch et al. in press) – it found that rates of childhood sexual abuse (and risky family environment) were significantly higher (odds ratios ≈2-3) in nonheterosexuals than heterosexuals and were also associated with higher rates of depression. These dual effects (i.e. childhood risky family environment and sexual abuse) contributed to the elevated rates of depression in nonheterosexuals, but only to a modest degree (their combined effect accounted for around 16% of the sexual orientation-depression link).

It is not at all clear how adverse childhood experiences might affect adult sexual orientation, and indeed the prevailing scientific view is that sexual orientation is fixed before birth (Rahman 2005b; Swaab and Garcia-Falgueras 2009). **I propose that the aforementioned interaction of the HPA and HPG axes also provides a possible mechanism for stressful childhood experiences to influence sexual orientation** in already predisposed individuals. Again, this is speculative and the hypothesis requires direct empirical testing.

Persistent or repeated stress exposure (activation of the HPA axis) inhibits activity in the HPG axis (Kirby et al. 2009), so repeated stressors during development may chronically disrupt gonadal hormone levels (low testosterone and estrogen levels in males and females, respectively). The deficiency in gonadal hormones (either throughout development, or in critical stages such as puberty, when gonadal hormone levels surge; Romeo 2010) may have organizing effects on the brain (van Goozen et al. 2002; Gooren 2006; Neufang et al. 2009; Peper et al. 2010), decreasing sexual differentiation and increasing the likelihood of same-

sex attraction. This could explain the effect of childhood risky family environment and sexual abuse on sexual orientation.

An alternative version of this explanation could involve prenatal transmission of maternal stress, and this would fit better with the conventional wisdom that sexual orientation is largely determined before birth. As well as directly posing problems for a developing child, a risky family environment may also impact the child before it is born via the impact of family dysfunction on the mothers' stress levels during pregnancy. Maternal stress during certain prenatal periods may predispose the offspring increased HPA axis reactivity (Tollenaar et al. 2011) and to various psychiatric disorders (Koenig et al. 2002; Beydoun and Saftlas 2008). Animal models suggest that maternal stress can decrease behavioural sexual differentiation (Goel and Bale 2009) and increase homosexual behaviour (Meek et al. 2006). There is also some human evidence that maternal stress may have (modest) effects on the offspring's adult sexual orientation (Ellis and Cole-Harding 2001), though other negative findings on child gender-role behaviour casts doubt on this (Hines et al. 2002). Both the human and animal literature is complicated by findings that maternal stress has different effects in males and females (Ellis and Cole-Harding 2001; Weinstock 2007). A further problem, particularly for the human studies, is the difficulty of distinguishing the prenatal effects of maternal stress from genetic predispositions or postnatal stressful experiences of the child (Beydoun and Saftlas 2008). Nevertheless, whether directly or via prenatal maternal effects it is possible that stressors during development may have an impact on both sexual orientation and psychiatric risk through the interactions of the HPA and HPG axes.

4. Conclusion

There is good evidence to suggest that minority stress increases the psychiatric risk of nonheterosexuals, but other evidence suggests that additional mechanisms also contribute. These may involve lifestyle factors associated with nonheterosexuality, and also common causes of both nonheterosexuality and psychiatric risk. These common causes appear to involve both genetic factors and adverse childhood experiences. Of course, it is likely that numerous factors are responsible, and the importance of each factor probably differs across specific psychiatric disorders. For example, while minority stress appears to play an important role in depression, it could not be responsible for the elevated risk of eating disorders in nonheterosexual men, given that lesbian women are at lower risk than heterosexual women.

Very importantly, most of the findings described above involve great uncertainty regarding causation and specific mechanisms involved. For example, for simplicity I have assumed that the association of adverse childhood experiences with adult sexual orientation is due to the former predisposing to the latter, but there are many other causal possibilities, some more plausible than others. Longitudinal studies, especially those with genetically informative samples, may help to resolve some of these alternative explanations. Indeed, there is enormous scope for future work in this area, given the importance of the problem and how much is unknown. In particular, the neurohormonal mechanism I proposed above is potentially important, but is speculative and requires rigorous empirical testing and theoretical development.

It is crucially important to understand these and other issues so we can know how best to improve the psychiatric wellbeing of nonheterosexual individuals. Of course, the most sure-

fire steps involve reducing the stigma, prejudice, and discrimination that sexual minorities face in everyday life.

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Long-Term Neuropsychiatric Disorders After Traumatic Brain Injury

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1. Introduction

The long-term neuropsychiatric consequences of traumatic brain injury are numerous and outstrip their physical counterparts in terms of impact on quality of life and outcomes such as return to work. This chapter will describe the epidemiology, pathology and investigation of brain injury, with a focus on findings that have particular relevance to neuropsychiatric disorders. A discussion of the difficulties in understanding aetiology in the neuropsychiatry of mild traumatic brain injury (mTBI), including postconcussional syndrome, will be undertaken alongside a broader overview of the key predisposing factors for long term psychiatric presentations. A review of the current understanding of post-TBI neuropsychiatric disorder including personality change; cognitive disorders and dementia; aggression; affective and anxiety disorders; and psychosis will highlight controversies in the literature. Finally, a summary of pharmacological interventions and practical treatment recommendations based on the best available evidence and clinical utility is described.

2. Epidemiology and definitions of Traumatic Brain Injury

Traumatic brain injuries (TBI) cause significant disability and have a considerable impact on those who suffer them, as well as their carers, medical services and the economy in general. It has been estimated that the annual cost of acute and chronic care for patients with TBI in the United States is in the region of $60 billion and that the overall cost is in the region of $200 billion each year, when medical, work loss and quality of life costs are taken into account (Finkelstein *et al*. 2006)

The Centers for Disease Control (Faul *et al*. 2010) estimated that there were 1.7 million TBI's in the United States (580 per 100,000) between 2002 and 2006. Of these, 1.3 million attended accident departments; 275,000 were hospitalized (93.8 per 100,000) and 51,000 died (17 per 100,000). There is some variation in incidence reported between different data sources and the true numbers are most likely an underestimate as they do not account for all of the settings where TBI may present, missed diagnoses and those who do not seek medical attention.

The vast majority of injuries, some 85% of those seeking treatment, are mild (Bazarian *et al*. 2005). Among those who are admitted to hospital, 20% have severe TBI's. The peak incidence by age is in the very young (0-4 years), adolescents (15-19 years) and older adults

(>75 years), with the most common causes of injury being falls (35%), road traffic accidents (17%) and assaults (10%). Across age groups, TBI rates are higher in men than women.

Risk factors for TBI include alcohol use and a past history of head injury. The latter has recently been investigated by Saunders and colleagues (2009) who reported that, of those admitted to hospital for a brain injury, 7% had at least one subsequent, recurrent brain injury during the follow-up period varying by subject between 2.5 to 7 years after their initial admission.

The definition of TBI varies between studies, including different descriptions of both concussion and mild traumatic brain injury (mTBI), making comparison between investigations difficult.

The most recent definitions include statements from the Veterans Affairs and Department of Defense (2009) and a Position Statement by the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health (Menon *et al*. 2010). The latter states:

"*TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external force*."

Alteration in brain function is further defined as including one of any of the following clinical signs:

- Any period of loss or a decreased level of consciousness;
- Any loss of memory for events immediately before (retrograde amnesia) or after the injury (post-traumatic amnesia);
- Neurologic deficits (weakness, loss of balance, change in vision, dyspraxia, paresis/plegia [paralysis], sensory loss, aphasia, etc.);
- Any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc.).

Other evidence of brain pathology is suggested to include visual, neuroradiologic or laboratory confirmation of damage to the brain and external forces are defined as including injury sustained from the head being struck by or striking an object; the brain being subject to acceleration/deceleration movements; a foreign body penetrating the brain and forces generated by a blast or explosion or other force yet to be defined.

The severity of TBI is most commonly indicated by the length of loss of consciousness and post-traumatic amnesia, i.e. the time between the trauma and the return of normal day-to-day memory. The Glasgow Coma Score (GCS) is most often used for assessing the level of consciousness in the acutely head injured but is a poor indicator of outcome, and does not differentiate well between those with mTBI. Table 1 summarises the different indices for TBI severity, adapted from Fleminger (2008) and the Veterans Affairs and Department of Defense Guidelines (2009).

In terms of outcomes, injury severity measures are fairly poor indicators of prognosis. Roughly speaking, duration of post-traumatic amnesia (PTA) is the best indicator of neuropsychiatric outcome, and when longer than a month, is likely to result in reduced work capacity and if longer than three months, suggests voluntary work as the best outcome in terms of employment. PTA is more effective than GCS for predicting neurobehavioural outcomes at 6 months after injury (Tellier *et al*. 2009). There is a reasonable correlation between injury severity and developing cognitive impairment, personality and behavioural changes. Speed of information processing, memory and executive function are particularly affected.

	Mild	Moderate	Severe	Very Severe
GCS	13-15	9-12	6-8	3-5
LOC	≤ 30 mins	> 30 mins-6 hrs	>6 hrs-7 days	>7 days
PTA	≤ 24 hrs	> 24 hrs-14 days	> 14 days-8 weeks	> 8 weeks
AOC	A moment – 24 hrs	> 24hrs	-	-
Neuroimaging	Normal	Normal or abnormal	Normal or abnormal	Normal or abnormal

GCS – Glasgow Coma Score; LOC – Loss of Consciousness; PTA – Post-traumatic Amnesia; AOC – Alteration of Consciousness/Mental State

Table 1. After Fleminger & Veterans Affairs and Department of Defense

3. Key pathology of Traumatic Brain Injury

In addition to clinical approaches to classification as already described, other classifications take account of the mechanism and pathology of the injury. Pathological changes are often also considered as primary and secondary, the latter including injury secondary to raised intracranial pressure, cerebral herniation, ischaemia, anoxia and cerebral oedema.

Closed brain injuries that involve impact with an object, result in acceleration and deceleration forces being transmitted to the brain and are associated with vascular injuries or haemorrhages, as well as diffuse axonal injury. Rotational injuries, with the head moving from side-to-side, are more likely to result in loss of consciousness than those that are associated with a nodding movement of the head (Smith & Meaney, 2000). Crush injuries by comparison, are less likely to be associated with loss of consciousness (Gonzalez Tortosa *et al*. 2004).

Inertial injuries do not require contact with another object, but result from the movement of the brain within the skull and are more commonly associated with diffuse axonal injury. Penetrating injuries, where the dura is breached, such as those seen from a knife or spike, result in local tissue necrosis and parenchymal damage resulting from the transit of the object through brain tissue. The injury associated with a gunshot wound is more widespread and often devastating as a result of the high-velocity forces involved.

Contusions or bruising of the surface of the brain arise from extreme localized forces such as those seen in an impact injury, for example a fall or assault. A contrecoup injury, i.e. a contusion on the opposite side of the injury, may be present. Certain areas of the brain are more vulnerable to contusions as a result of their close proximity to the bony skull. These include the medial-orbital surface of the frontal lobes and the temporal poles. In terms of the neuropsychiatric sequelae of brain injury, this is of little surprise, as these areas are most likely to affect social behaviour.

Diffuse Axonal Injury (DAI) results from the shearing rotational and linear forces exerted on axons as a result of acceleration and deceleration forces in impact or inertial injuries. The changes are predominantly seen in the parasagittal white matter, corpus callosum, brainstem long tracts and grey-white matter interface in the hemispheres. There are three degrees of DAI: Grade 1 reveals microscopic changes in the cortical white matter, corpus callosum, brain stem and cerebellum; Grade 2 is distinguished by isolated focal lesions in the corpus callosum and Grade 3 reveals additional focal lesions in the rostral brain stem.

Clinically, DAI may present with protracted periods of coma without evidence of intracerebral contusions.
Intracranial haemorrhage is classified by its location anatomically. There are four main subtypes: extradural, subdural, subarachnoid and intracerebral.
Extradural haemorrhages are most commonly seen overlying the convexity of the temporo-parietal region but can also be seen in around a third of cases overlying the frontal and occipital areas. Around 50% of extradurals are associated with a fracture of the squamous temporal bone resulting in damage to the underlying middle meningeal vessels.
Subdural haematomas are reported in around 5% of head injuries, increasing in incidence with injury severity. Acute subdurals, like extradural haemorrhages, have a mass effect and therefore, can produce secondary effects in brain injury. Chronic subdurals, often in association with alcohol use or a history of dementia, can follow a relatively mild or trivial head injury, although it is not always evident that there has been any trauma in up to 50% of cases. In those who fail to improve or present with a deteriorated mental state, a chronic subdural should be considered.
Cerebral oedema or brain swelling may arise acutely in the region of contusions and haematomas, is commonly cytotoxic and results in raised intracranial pressure, with the risk of cerebral herniation. The latter can involve extrusion of brain tissue under the falx, through the tentorium or more severely, the foramen magnum.
Oedema, haemorrhage, hypotension and poor respiratory ventilation can result in cerebral anoxia and this is a common finding after brain injury. Maintenance of arterial oxygen saturation and blood pressure are key to acute management in order to limit anoxia.

4. Neuroimaging after Traumatic Brain Injury

In the early stages of the acute presentation of head injury, investigation of brain injury neuropathology is aided considerably by the Computed Tomography (CT) scan (Coles, 2007). Images delineate extradural, subdural and intracerebral haematomas and any mass effect that they may exert, revealed through midline shift or compression of the midbrain cisterns. CT is used in preference to Magnetic Resonance Imaging (MRI) in acute management as it can be performed quickly and does not carry the risk of the magnetic field required in MRI that can move intracranial metallic objects or affect life support equipment (Gallagher *et al*. 2007). In one study, only 5% of those with severe brain injury have scans that are reported normal in all respects (Eisenberg & Levin, 1989). More recently, Bigler and colleagues (2006) have examined 240 consecutive brain injury rehabilitation admissions, identifying that the range of day-of-injury CT findings across injury severity is diverse and that severe injury can be associated with normal scans and mild injury with demonstrable CT lesions. This diversity of findings on CT, means that the utility of scans in predicting neurobehavioural outcomes is limited, at least when considered without other outcome measures.
In the subacute and chronic stages of their recovery, MRI is used in preference to CT to consider neuropsychiatric questions regarding patients with TBI. As contusions are predominantly at the bone-brain interface and subject to artefact and white matter changes that may be found after DAI are more easily detected, MRI is superior to CT in this setting. Generally speaking, T1 weighted images are best for gross brain anatomy; T2 images for cerebrospinal fluid (CSF) and CSF-related changes, as well as providing good contrasts between white and grey matter structures; gradient echo sequences detect blood by-products such as haemosiderin and fluid-attenuated inversion recovery (FLAIR) sequences provide

high quality visualization of white matter abnormalities. In those without other cerebrovascular or cardiac risk factors, the presence of haemosiderin is considered an indicator for DAI (Hahnel *et al*. 2008). Indeed, three times as many lesions were found on gradient echo in comparison to T2 images in those who sustained DAI in one study (Scheid *et al*. 2003).

Having said this, as MRI becomes more sensitive, it also reveals previously subtle or hidden abnormalities that may be incidental findings or unrelated to the brain injury. In particular, non-specific white matter hyperintensities can be found in healthy controls, with an increase in these findings with age. A normal gradient echo sequence some time after TBI equally does not imply the absence of previous bleeding. 20% of low-signal lesions consistent with haemosiderin deposits seen in the first year post-injury were no longer identified at two years in the study of Messori and colleagues (2003).

The relationship between clinical and neuroimaging findings on MRI has suggested some useful correlations. Jenkins and colleagues (1986) identified that the number of lesions and their location is related to degree and duration of consciousness. The deeper the lesions from the cortex, the more severe the injury. Levin and colleagues (1987) showed that there is a relationship between the size and location of frontal and temporal lobe lesions and deficits in neuropsychological assessment. Wilson and colleagues (1992) reported on the associations between MRI findings and outcome up to 18 months after injury. Neuropsychological outcomes correlated with MRI abnormalities, especially in deep brain regions, and ventricular enlargement correlated with persisting deficits at follow-up. Other changes that have been associated with clinical outcomes include atrophy of the corpus callosum and worse outcome in severe injury; slow information processing and generalized white matter atrophy; third ventricle enlargement and poor outcome. Hippocampal damage is a common finding in TBI where volume loss and temporal horn expansion indicate reduced structural integrity of the medial temporal lobe. The latter is useful for the psychiatrist in considering changes such as mood disorders or emotional lability, as well as abnormalities of memory. In those with a history of alcohol use, studies have suggested that atrophy may be greater after TBI, particularly in frontal grey matter (Jorge *et al.* 2005). Lesion location has been less readily associated with outcomes, although frontal lesions are associated with early agitation, aggression and behavioural problems.

Increasingly Diffusion Tensor Imaging (DTI) is being used to image white matter tracts and their connections after TBI and has been particularly useful in delineating the subtle changes in white matter pathways after mTBI (Singh *et al*. 2010; Lipton *et al*. 2009; Bazarian *et al*. 2007).

The electroencephalogram (EEG) can be useful in differentiating other causes of loss of consciousness besides head injury in the unconscious patient, but on the whole is of limited value in identifying outcome after brain injury. Indeed, a normal EEG can be associated with worse outcome in those whose symptoms persist after milder injuries. The EEG also cannot be relied on for identifying the risk of post-traumatic epilepsy with around 50% of brain-injured patients who do develop seizures having a normal EEG previously.

5. Common aetiological factors in neuropsychiatric presentations after Traumatic Brain Injury

Alongside injury severity, it is important to consider other factors in the aetiology of neuropsychiatric symptoms after brain injury. These factors are considered in more detail in the following discussion of specific disorders, although common features are considered here.

Preinjury constitutional factors found to have an impact on psychiatric outcome that have been investigated include socioeconomic status, psychiatric history, forensic history, alcohol misuse and length of education. The findings are, however, not consistent and other studies have failed to replicate convincing effects.

Premorbid personality traits are often noted in clinical assessment to be exaggerated or magnified after TBI, however the evidence for this is lacking in the literature (Tate 1998; Hall *et al*. 1998; Corrigan *et al.* 1998). Explanations for this apparent discrepancy include the retrospective assessment of premorbid personality being biased, poor measures of premorbid traits and the possibility that the clinically apparent effects in a few patients are too small to be replicated in the evaluation of large research cohorts.

More reliably, age at the time of injury is an important variable associated with increasing disability and cognitive impairment. Mortality rates increase (Kerr et al. 1971), physical comorbidity such as cerebrovascular disease becomes more prevalent and older patients have longer PTA regardless of injury severity (Katz & Alexander, 1994).

The psychological effects of the trauma are important and how patients feel as a result of their injury and its circumstances have been shown to have an impact on neuropsychiatric outcomes. The perception of fault has been shown to be important here, where those who blame a person or organization for their TBI are more likely to have psychiatric symptoms than those who perceive the injury as 'an Act of God' (Wood, 2004). However, it is also important to consider that the risk factors for violence overlap with important variables that may affect the psychiatric outcome of TBI such as alcohol use and socioeconomic class (Machamer *et al*. 2003).

Post-injury factors including environmental and social difficulties are also important in developing psychological sequelae. In particular, in those who have cognitive impairments, financial difficulties, occupational problems and threats to personal and family safety are considerably more difficult to cope with. Unstable domestic circumstances, a risky workplace or dangerous job, particularly when the accident occurred at work, can result in protracted disability. Changes in the family hierarchy and structure may be difficult to adjust to.

Ongoing personal injury claims and seeking compensation have been associated with prolonged disability. In a meta-analysis comparing 17 studies, symptom severity in those seeking compensation was worse by, on average, half a standard deviation than in those who were not. It was also suggested that the effect of compensation is greater for those with milder injuries (Binder & Rohling, 1996).

6. Long-term neuropsychiatric syndromes after Traumatic Brain Injury

6.1 Changes in personality

6.1.1 Prevalence

Clinicians have known for more than a century that TBI can result in significant changes in personality. The first widely recognized case was that of Phineas Gage, a 25-year old construction worker, who in 1848 survived an accident in which an iron rod entered through his left cheek, traversed the anterior portion of his brain and exited through the top of his skull (Lux, 2007). Whereas previously he was described as responsible, honest and capable, after the head injury he was childish and inconsiderate, with poor judgment (Reeves & Panguluri, 2011; Vaishnavi *et al*. 2009).

TBI can result in a variety of changes in personality and emotional regulation, from the most minor to striking. Preexisting personality traits can become more pronounced, or the personality can be drastically altered. The most frequent changes cannot easily be described by standard personality disorder classifications, although when such criteria are applied the most common categories identified are avoidant, borderline and paranoid (Hibbard *et al.* 2000; Koponen *et al*. 2002).

Pelegrin-Valero and colleagues (2001) evaluated 55 patients one year after severe TBI. The DSM IV criteria for personality change due to head injury were fulfilled in 60% of the patients and the most prevalent types were apathetic, unstable, disinhibited and aggressive. Apathy was the most prevalent symptom occurring in 34.5% of the sample. Kant and colleagues (1998) utilized the Apathy Evaluation Scale in a sample of 83 TBI survivors and found that apathy alone was present in 10.8% and apathy associated with depressive symptoms in up to 60%. Younger patients were more likely to be apathetic than older patients who were more likely to be depressed and apathetic.

6.1.2 Clinical presentation

The severity of the brain injury usually correlates reasonably well with the development of personality and behavioural changes. Common symptoms include apathy, loss of spontaneity and drive, labile mood, self-centred behaviour, disinhibition, irritability and reduced control over aggressive impulses. Personality changes are frequently associated with cognitive impairment and accompanied by a lack of insight and poor awareness of safety and personal hygiene. Symptoms of an altered personality can overlap with those of comorbid psychiatric problems, for instance those of a mood disorder (Fleminger, 2008).

Personality changes are one of the most distressing consequences of TBI for families and carers. In some instances spouses have described how their relationships have changed from one of equal partners to one more like that of a parent and child.

6.1.3 Aetiology

Personality changes may in some cases be attributed to the psychological reaction to the trauma. In others a discrete brain injury may cause isolated changes in social behaviour with little or no effect on neuropsychological testing (Fleminger, 2008).

During TBI the medial orbital surface of the frontal lobes and the anterior, inferior surface of the temporal lobes are particularly vulnerable to developing contusions. These regions play a major role in social behaviour with injury resulting in changes in personality.

Studies of patients acquiring open head trauma in war have demonstrated that frontal lobe injuries are in particular associated with personality changes. Feuchtwanger (1923) compared 200 patients with frontal wounds with 200 cases with injury to other parts of the skull. They found that those with frontal injury were more prone to exhibit euphoria, irritability, apathy and tactless, disinhibited behaviour. It has been suggested that convexity lesions over the lateral surface of the frontal lobe might produce a pseudodepressive clinical syndrome with apathy and indifference while medial and orbital frontal lesions produce a pseudopsychopathic syndrome with antisocial, tactless, impulsive and irritable behaviour.

Apathy has been associated with subcortical and right hemisphere injuries (Andersson *et al.* 1999). Cortico-striatal-pallidal-thalamic pathways, enclosing the anterior cingulate cortex, nucleus accumbens, ventral pallidum, and medial dorsal thalamic nucleus, are considered mediators of motivation and damage to these circuits can produce apathy. Dopamine is

associated with apathy, with dopaminergic antagonists increasing apathy, and agonists reducing it (Schwarzbold *et al.* 2008).

6.1.4 Treatment

Appropriate treatment includes providing emotional support and education for the patient and family members (Shawn *et al.* 2007; Vaishnavi *et al.* 2009). A cognitive behavioural approach to the symptoms may also be useful (Schwarzbold *et al.* 2008). Medication regimes should be simplified and drugs worsening the troublesome personality symptoms withdrawn. Pharmacological interventions, such as selective serotonin reuptake inhibitors (SSRI's) and mood stabilizers, can be used to target specific symptoms, including aggression and emotional instability (Shawn *et al.* 2007). Drugs improving motivation such as stimulants, activating antidepressants, dopaminergic agonists and cholinesterase inhibitors have been used in the treatment of apathy (Rao & Lyketsos, 2000). Co-morbid psychiatric disorders should be identified and treated as appropriate.

6.2 Cognitive disorders

6.2.1 Prevalence

Transient and persistent cognitive deficits are the most common complaints after TBI and are a major hindrance to recovery in areas of independent living, social re-adaptation, family life and vocational endeavors (McAllister, 2008). Cognitive impairment has been described at prevalence rates of 25-70% post-TBI (Vaishnavi *et al.* 2009).

6.2.2 Clinical presentation

Immediately after TBI, loss of consciousness or coma may ensue, followed by a variety of cognitive and behavioural abnormalities including agitation, confusion, disorientation, altered psychomotor activity and both retrograde and anterograde amnesia. This post-traumatic delirium can last from a few days to one month. Over the following 6-12 months cognitive function recovers to a variable extent, followed by a plateauing over the subsequent 12-24 months post-injury. In some cases permanent cognitive deficits result which typically include difficulties with attention, concentration, memory, language, executive functions and reduced speed of information processing (Rao & Lyketsos, 2000; Konrad *et al*. 2010). Long-term studies have shown that, in a proportion of patients, cognitive functions continue to improve or deteriorate for many years after the injury (Hammond *et al*. 2004; Millar *et al.* 2003). TBI may increase the risk of disinhibition in patients with dementia (Rao *et al.* 2010).

6.2.3 Aetiology

Cognitive deficits are caused by the cumulative effects of focal and diffuse brain damage. Focal injuries can cause corresponding impairments in selective functioning and the frontal and temporal lobes are particularly vulnerable to head injury. Clinical outcome depends upon the degree of diffuse injury, the presence and size of focal injury, the duration of LOC and PTA and clinical evidence of brain stem dysfunction at the time of injury (Rao & Lyketsos, 2000). The severity of the brain injury usually correlates reasonably well with the development of cognitive impairment (Fleminger, 2008).

The relationship between TBI and the development of dementia in later life remains a matter of debate. It has become clear that TBI can lead to a progressive neurodegeneration known

as chronic traumatic encephalopathy (dementia pugilistica / punch drunk syndrome) (Gavett *et al.* 2010). This may develop years after repeated head injury, especially in boxers. The fully developed syndrome includes cerebellar, pyramidal and extrapyramidal features, mixed cortical and subcortical cognitive deficits and a variety of behavioural manifestations. Chronic traumatic encephalopathy can produce cognitive symptoms alone or in conjunction with other neurodegenerative processes such as Alzheimer's disease (Gavett *et al*. 2010). The cytoskeletal lesions found in dementia pugilistica suggest strong pathogenetical relations with Alzheimer's disease (Jellinger, 2004).

Following a systematic review of 15 case control studies Fleminger and colleagues (2003) found an association between a history of previous head injury and the risk of developing Alzheimer's disease (OR 1.58, 95% CI 1.21 to 2.06). This association was only found in males. This finding was supported by research following up head injured World War II veterans (Plassman *et al*. 2000). TBI may reduce the time to onset of Alzheimer's disease amongst those at risk of developing the disease (Nemetz *et al*. 1999).

Epidemiological studies and human autopsy data in small cohorts of patients with TBI and Alzheimer's disease indicate an increased risk of dementia after severe TBI compared with the general population (Jellinger, 2004). The accumulation of amyloid b peptide and tau pathology seen in Alzheimer's disease has been observed after experimental head trauma in animal models and demonstrated in some head injury patients who died several years after their injury.

The role of apolipoprotein E genotype for the prognosis of TBI and the later development of dementia is a matter of discussion. Although apolipoprotein Ee4 is suggested as a negative prognostic factor in TBI, with a possible neuroprotective effect of apolipoprotein Ee3, research studies have revealed variable results and convincing associations have not yet emerged (Verghese *et al*. 2011).

6.2.4 Treatment

Cognitive disorders are treated through a multidisciplinary approach focusing on neurorehabilitation. Specific cognitive deficits may improve through occupational therapy, physiotherapy, speech therapy, vocational training, cognitive rehabilitation and pharmacological interventions (Arciniegas *et al*. 2010).

TBI is associated with decreased dopaminergic activity and a hypocholinergic state (Writer & Schillerstrom, 2009). Agents increasing dopamine are reported to have positive effects on various domains of cognitive functioning. Methylphenidate has been shown to improve speed of cognitive processing and sustained attention (Neurobehavioural Guidelines Working Group, 2006; Shawn *et al*. 2007). It has been safely used in adults and children with TBI of all severities. Nonstimulant dopamine enhancers, including bromocriptine, amantadine, pramipexole and L-dopa, improve post-TBI cognitive impairments. Bromocriptine is recommended particularly for deficits in executive function, while amantadine is recommended for deficits of general cognitive function. Acetylcholinesterase inhibitors may help improve memory and attention.

6.3 Aggression

6.3.1 Prevalence

Post-TBI aggression is poorly defined and associated terms such as irritability, anger and agitation are often used in this context (Schwarzbold *et al*. 2008). As such it is difficult to

makes comparisons between studies and therefore to determine its true epidemiology. It has been suggested that post-traumatic agitation is a subtype of delirium, occurring during the period of post-traumatic amnesia, with specific behavioural and cognitive characteristics, whereas aggression indicates damaging, threatening or intimidating behaviour (Sandel & Mysiw, 1996).

Between 35 and 96% of post-TBI patients are reported to have exhibited agitated behaviour during the acute recovery period (Reeves & Panguluri, 2011). Although in many cases this behaviour resolves, it may also continue into the chronic phase and long term aggression is a common behavioural consequence of TBI (Fleminger, 2010). Tateno and colleagues (2003) studied 89 consecutive inpatients with moderate to severe TBI using the Overt Aggression Scale and found that 33.7% exhibited aggressive behaviour within the first six months of injury. 25% of TBI patients at six, 24 and 60 months post-discharge from an inpatient rehabilitation unit were still found to be displaying aggressive behaviour (Baguley *et al*. 2006). One large military study found that TBI increases the risk of discharge from military service for behavioural reasons four times compared with a non-TBI population (Hesdorffer *et al*. 2009).

6.3.2 Clinical presentation

Displays of aggression are somewhat varied among patients with TBI but are often consistent for an individual patient (Reeves & Panguluri, 2011). Aggression is usually impulsive, out of proportion to the stimulus and short lived (known as Episodic Dyscontrol Syndrome). Anger and impulsive verbal outbursts seem to be the main characteristics of aggression post-TBI (Dyer *et al.* 2006). Aggression is associated with the presence of major depression and is also more frequently encountered in post-TBI mania (Kim, 2006; Tateno *et al.* 2003). post-TBI aggression can pose a serious challenge to long term rehabilitation and is a major cause of disability to individuals and a source of stress to their families (Wood & Liossi, 2006).

6.3.3 Aetiology

Emotion is normally regulated in the human brain through a complex circuit consisting of the orbital frontal cortex, amygdala, anterior cingulate cortex, and several other interconnected regions (Davidson *et al.* 2000). It is hypothesized that damage to the prefrontal cortex affects its regulatory role in controlling behaviour resulting in a loss of self-control with spontaneous aggressive and violent behaviours (Grafman *et al.* 1996). Studies on Vietnamese War veterans have shown an association between frontal ventromedial lesions and higher aggressive/violent behaviours. Serotonin is the most widely studied neurotransmitter in aggressive behaviour and the prefrontal cortex receives a major serotinergic projection which is dysfunctional in individuals who show impulsive violence.

Other risk factors for post-TBI aggression include a history of antisocial behaviour, arrest, poor premorbid functioning and substance misuse (Greve *et al.* 2001; Kolakowsky-Hayner & Kreutzer, 2001; Tateno *et al.* 2003). There is inconsistent evidence relating the impact of socioeconomic status and severity of the injury to the development of post-traumatic aggression (Kim *et al.* 2007).

6.3.4 Treatment

Environmental interventions rather than drug therapies are often the preferred means of managing agitation in the acute post-TBI phase (Fleminger *et al.* 2006). However, in the

absence of response to behavioural and environmental modification, and in the later stages of recovery, pharmacology is frequently used (Lombard & Zafonte, 2005). There is limited evidence regarding the most effective drug treatment for aggression post-TBI. Randomised controlled trials have demonstrated the effectiveness of beta-blockers such as propanolol and pindolol. Anticonvulsants such as carbamazepine and valproate have been reported to be effective in clinical practice. Atypical antipsychotics, antidepressants, buspirone, lithium and amantadine have also been used to manage post-traumatic aggression.

6.4 Mood disorders

6.4.1 Depression

6.4.1.1 Prevalence

Depression is recognized as a common complication of TBI but estimations of its frequency vary [13]. Prevalence rates for major depressive disorder have been described between 15 to 61% (Kim *et al*. 2007; Jorge *et al*. 2004). This high variability in findings is largely due to differences in methodology for defining and measuring depression.

An association has been identified between a history of TBI and an increased lifetime prevalence of major depression. Holsinger and colleagues (2002) found that the lifetime prevalence of major depression among men who sustained a head injury during World War II was 18.5% compared to 13.4% in those without a head injury.

6.4.1.2 Clinical presentation

Diagnosing depression is complicated because the cognitive, emotional and somatic symptoms of depression can overlap with direct symptoms of TBI. For example, sleep disturbance, concentration difficulties and apathy are common symptoms in TBI survivors both with and without mood disorders. The symptoms of post-TBI depression do not differ from those with depression without associated head injury although they are more frequently characterized by irritability, anger and aggression than by sadness (Reeves & Panguluri, 2011). Psychiatric comorbidity is common in patients with depression after TBI.

Studies have shown an association between TBI and suicidality. In a retrospective study of 5,034 patients Silver and colleagues (2001) reported that patients with a history of TBI were four times more likely to attempt suicide than those without previous head injury. This risk remained even after they controlled for demographics, quality of life variables, alcohol abuse and comorbid psychiatric disorders. A study of suicidality after TBI found that 35% of individuals had clinically significant levels of hopelessness, 23% had suicidal ideation and 17% had attempted suicide in the five years since their injury (Dilley & Fleminger, 2006).

6.4.1.3 Aetiology

Risk factors for the development of post-TBI depression include stress, social isolation and maladaptive coping styles, suggesting that personal reactions to TBI deficits influence depressive symptomatology. Jorge and colleagues (2004) identified that patients with TBI with major depression were more likely to have a personal history of mood and anxiety disorders than patients who did not have major depression. No relationship was identified between development of post-TBI depression and with head injury associated loss of consciousness, skull fracture or accompanying physical and cognitive impairments (Malaspina *et al*. 2001).

Depression may be seen after TBI of any severity, but the correlation between head injury severity and the degree of depression is controversial, with studies giving conflicting results. However, a moderately strong association has been found between patient self-assessment of post-TBI ability and depression (Malec *et al*. 2010). Psychosocial factors have a major impact on depression rates at longer post-injury intervals whereas early post-traumatic depression may be more strongly related to a host-injury interaction (Jorge *et al*. 1993a; Silver *et al*. 2009).

Investigations determining the relationship between specific regional brain injury and depressive symptoms have proven inconsistent. Studies have shown an association between post-TBI depression and lesions in the left dorsolateral prefrontal cortex and left basal ganglia in the acute phase of TBI (Fedoroff *et al*. 1992). Jorge and colleagues (2004) found a reduction in the left prefrontal grey matter volume on MRI scanning, especially in the ventrolateral and dorsolateral regions, in patients with post-TBI depression. Lateral frontal lesion locations are associated with an increased risk of developing depression compared to medial lesions, with right lateral lesions increasing the risk of anxious depression and left anterior lesions increasing the risk of major depression (Paradiso *et al*. 1999; Jorge *et al*. 1993b).

It has been proposed that damage to the neural circuits involving the prefrontal cortex, amygdala, hippocampus, basal ganglia and thalamus may be related to the development of depression after TBI. During trauma diffuse axonal damage is common in the frontal and anterior temporal lobes providing an explanation for the high rate of mood disorders in this group. Rupture of the biogenic amine containing neurons, as they pass through the basal ganglia or frontal-subcortical white matter, may be related to the development of depression due to TBI.

Saran (1985) found that depression after minor closed head injury was not correlated to abnormal dexamethasone suppression test results, suggesting that depression post-TBI is not associated with hypothalamic pituitary adrenal axis dysfunction. However this study was limited by its small sample size.

Disruption in hippocampal functioning and morphology has been described in cognitive and depressive disorders (Campbell & Macqueen, 2004). Jorge and colleagues (2007) measured hippocampal volume through MRI in a sample of 37 TBI survivors and found lower bilateral hippocampal volume and reduced left frontal grey matter in patients who developed depression.

6.4.1.4 Treatment

The treatment of post-TBI depression is similar to that of depression in primary psychiatric practice and includes psychological interventions, antidepressants and ECT. SSRI's are considered first line as they are usually safe and well tolerated (Fann *et al*. 2009). Tricyclic antidepressants have a lesser role both because of the higher incidence of anticholinergic side effects that can adversely affect cognition and due to evidence of possible reduced efficacy. MAOI's are not recommended due to lack of efficacy data and potentially serious side effects, particularly when dietary restrictions are not adhered to in a population with a high rate of cognitive difficulties. All antidepressant drugs lower the threshold for seizures, which is a particular concern in TBI patients, but it must be remembered that a lower threshold does not necessarily imply increased seizure frequency (Turner-Stokes & MacWalter, 2005). ECT appears a viable option for treatment in refractory patients. Psychotherapy, in particular CBT, can also be used if the patient's cognitive status does not preclude it.

6.4.2 Mania

6.4.2.1 Prevalence

There is evidence that TBI is a risk factor for bipolar disorder (Mortensen *et al*. 2003). Both unipolar mania and bipolar disorder have been observed after TBI. However, studies are rare and often hampered by small sample sizes. These disorders do not present a problem of the same degree of magnitude as that presented by post-TBI depression (Lux, 2007).
Mortensen and colleagues (2003) found that head injury is a risk factor for bipolar disorder and that TBI survivors are 1.5 times more likely to develop this than those without TBI. Van Reekum and colleagues (2000) reviewed the literature and found a prevalence of 4.2% for mania probably caused directly by TBI. There is evidence that secondary mania is more prevalent in males.

6.4.2.2 Clinical presentation

It is difficult to differentiate between mania directly attributable to TBI and mania simply observed following TBI. Likely indicators include a close temporal association in the absence of other aetiological factors (such as a lack of previous psychiatric history or negative family history) and atypical presentations such as unusual age of onset (Schwazbold *et al*. 2008).
Diagnosis can additionally be complicated as symptoms of mania can be confused with changes in personality associated with frontal lobe syndrome, such as tactless, impulsive and irritable behaviour. Mania due to TBI may present with more aggression, irritability and less euphoria (Shukla *et al*. 1987).

6.4.2.3 Aetiology

It has been suggested that a correlation exists between the severity of the TBI and severity of post-TBI mania. Hypomania and bipolar II disorder have been associated with milder trauma (briefer durations of post-traumatic amnesia), whereas chronic hypomania, bipolar I and schizoaffective disorder were associated with more severe trauma. However, these results have not been consistently replicated. Jorge and colleagues (1993) found that post-traumatic mania was not associated with the severity of brain injury, degree of physical or cognitive impairment, level of social functioning or previous family or personal history of psychiatric disorder. Robinson and colleagues identified an association between secondary mania and a family history of affective disorder (Robinson *et al*. 1988).
An association has been shown between post-TBI mania and multifocal brain lesions, primarily in temporal basal poles (Jorge et al. 1993b). Starkstein and colleagues (1987) suggested that the confluence of either anterior subcortical atrophy and a focal lesion of a limbic or limbic-connected region of the right hemisphere, or a genetic predisposition and a limbic-connected right hemisphere lesion may account for the necessary factors to produce secondary mania.

6.4.2.4 Treatment

There is limited evidence in the literature about specific treatments for mania post-TBI. Mood-stabilizing antiepileptic drugs have proved effective, in particular valproate and carbamazepine (Shawn *et al*. 2007). Atypical antipsychotics are another treatment option, especially in patients who have manic symptoms accompanied by psychotic features. Lithium carbonate should be avoided as it lowers the seizure threshold, may worsen cognitive impairment and has a low therapeutic index.

6.5 Anxiety disorders (including Post Traumatic Stress Disorder)

6.5.1 Prevalence

Anxiety disorders are common after TBI and have been reported at rates as high as 70% (Moore *et al*. 2006). All variants are seen including GAD, panic disorder, phobic disorders, PTSD and OCD. Research indicates that the prevalence rates of anxiety disorders amongst patients with TBI are: 3-28% for GAD, 4-17% for panic disorder, 1-10% for phobic disorders, 2-15% for OCD and 3-27% for PTSD. Anxiety disorders are frequently comorbid and are also associated with depression.

6.5.2 Clinical presentation

The most frequently studied anxiety disorder associated with TBI is PTSD. This is characterized by the re-experiencing of the traumatic event through nightmares and intrusive thoughts, associated with symptoms of hyperarousal and avoidance behaviours. The possibility that PTSD can develop following TBI has been an area of controversy and debate, with some authors considering mild TBI and PTSD mutually exclusive (Sbordone & Liter, 1995). The traditional view held that impaired consciousness, typically associated with TBI, precludes encoding the traumatic experience and that this prevents subsequent re-experiencing symptoms (Bryant, 2001; Sbordone & Liter, 1995). However, research has increasingly indicated that PTSD may manifest even when memories of the incident are limited by loss of consciousness (Greenspan *et al*. 2006). In these cases flashbacks are either absent or their content is thematically related to the trauma sustained.

6.5.3 Aetiology

Research has not produced consistent findings with regards to identification of specific brain lesions in the development of PTSD after TBI. Sojka and colleagues (2006) investigated serum levels of cortisol (a biochemical marker of stress), S-100B and neuron-specific enolase (two biochemical markers of brain tissue injury) in the acute phase in mild traumatic brain injury patients and in the occurrence of post-traumatic stress-related symptoms one year after the trauma. There was a positive correlation between the levels of S-100B in the TBI acute phase and the presence of PTSD one year later. This may reflect the complexity of interactions between brain tissue injury and the ensemble of stress reactions.

Many of the studies examining the relationship between PTSD and TBI have focused on the association between post-traumatic amnesia and PTSD. Bryant has suggested that patients amnesic for the trauma can re-experience vivid pseudomemories of the event generated through a combination of imagination and information learnt following the trauma (Bryant, 1996). There is evidence that memories can be encoded outside of awareness and these memories can influence ongoing emotions and behaviours. Therefore, it is possible that in PTSD some of the traumatic event is coded even during the periods of consciousness disturbances. Subsequently, exposure to similar situations could reactivate these memories. King (1997) has proposed that patients may re-experience fragments (or islands) of memory preserved within the amnestic period. Alternatively, Bryant and colleagues (2004) have shown an association between higher heart rates in the TBI acute phase and subsequent development of PTSD and hypothesized that fear conditioning occurring outside the level of awareness could contribute to PTSD development.

Acute stress disorder has been shown to be a reasonable predictor for the subsequent development of PTSD (Harvey & Bryant, 2000). Avoidant coping style, behavioural coping

style (versus a cognitive coping style), and a history of prior unemployment (an indicator of the premorbid level of functioning) are predictors of PTSD severity (Bryant *et al*. 2000). In addition the severity of PTSD symptoms is also associated with external attributions to others of causality for the event (Williams *et al.* 2002).
Gil and colleagues (2005) followed a cohort of 120 subjects for six months after mild TBI and found that memory of a traumatic event within the first 24 hours is a strong predictor and a potential risk factor for subsequent development of PTSD (Gil *et al*. 2005). Turnbull and colleagues showed that although amnesia for the traumatic event did not protect against PTSD it did protect against the severity of symptoms and was specifically protective against intrusive symptoms (Turnbull *et al*. 2001). Longer post-traumatic amnesia appears to be protective against selected re-experiencing symptoms and patients unconscious during the trauma may have less re-experiencing symptoms (Bryant *et al*. 2009; Glaesser *et al*. 2004).

6.5.4 Treatment

Limited data exists regarding the effectiveness of psychopharmacological agents for the treatment of anxiety disorders in patients with TBI. However, case reports support the use of SSRI's and venlafaxine. Buspirone is another reasonable treatment option.
Benzodiazepines and antipsychotics should largely be avoided as they cause memory impairment, disinhibition and delayed neuronal recovery. If benzodiazepines are required in the short term, cautious dosing with longer acting agents such as clonazepam is recommended.
Cognitive behavioural therapy, neurorehabilitation and psychotherapy are important in treatment (Soo & Tate, 2007).

6.6 Mild Traumatic Brain Injury and Postconcussional Syndrome

6.6.1 Prevalence

Mild Traumatic Brain Injury (mTBI) is classically defined as an essentially reversible syndrome without detectable pathology. Around 80% of all TBI's are mild and 15% are associated with persisting symptoms. Postconcussional syndrome (PCS) is poorly defined, but is generally understood to refer to those who have persisting symptoms. PCS has been a source of controversy for many years. Understanding the true scale and scope of the problem has been complicated by lack of specificity of symptoms, disagreement between diagnostic systems on key criteria and lack of clarity over pathogenesis (Williams *et al*. 2010). PCS can occur with head injury of any severity but more often follows mTBI.

6.6.2 Clinical presentation

The immediate symptoms of mTBI include headache, nausea, dizziness, unsteady gait, slurred speech, poor concentration and slowness in answering questions. Speed of recovery is variable but reports of those who have sustained sports injuries reveal a rapid resolution, with the majority being free of symptoms at two weeks. At six weeks, emotional symptoms such as irritability and anxiety may predominate over more physical and cognitive features. Headaches are more commonly reported at follow-up.
Although the duration and severity of mTBI symptoms are highly variable amongst individuals, they are usually self-limiting and permanent cognitive, psychological or psychosocial problems are uncommon (Iverson, 2005). Belanger and Vanderploeg (2005) carried out a meta-analysis of the literature to determine the impact of TBI sports-related

concussion. They reported that the acute effects of concussion were greatest on global measures of cognitive functioning and memory. No residual neuropsychological impairments were found beyond seven days post-injury. Most patients with TBI will have fully recovered three to six months post-injury but 15% will have symptoms lasting longer than 1 year (Rutherford *et al*. 1979).

PCS refers to a cluster of somatic, mood and cognitive symptoms that persist for weeks, months or even years. These include headache, dizziness, memory loss, problems with concentration and attention, irritability, hyperactivity, sleep disturbance and emotional lability. Loss of consciousness is not necessary for its development. These symptoms are not specific to PCS and can occur in both TBI and non-brain injured patients (Meares *et al*. 2011). Overlap of PCS symptoms with other populations is marked, including individuals with depression, chronic fatigue, whiplash and pain.

6.6.3 Aetiology

There is much debate over whether the symptoms of PCS are neurologically or psychologically driven and how premorbid factors may influence the presentation. Current evidence supports the hypothesis that in the early phases of the syndrome neurological factors play a greater role but that over time psychological issues appear to become particularly relevant.

The physiological changes following mTBI at the cellular level have been extensively examined through animal and *in-vitro* modeling. From a neurological perspective it is assumed that most of the pathophysiology of concussion occurs following acceleration and deceleration forces which render neurons and neural systems dysfunctional but not destroyed.

At the time of the TBI, in the majority of cases, neurological examination and testing reveal either no abnormalities or minimal deficits. However, there is emerging evidence in certain cases linking neurocognitive dysfunction to neuroimaging findings post-TBI (Williams *et al*. 2010). Subsets of patients with presumed PCS have been shown to have abnormalities on positron emission tomography (PET) and single-photon emission computed tomography (SPECT) (Chen *et al*. 2003; Abu-Judeh *et al*. 1999). Functional imaging studies (fMRI) have indicated differential patterns of activity on working memory tasks following concussion (McAllister *et al*. 2001).

There are elevated rates of psychiatric comorbidity in patients with PCS. This may represent a response to persisting effects of brain injury on cognition and associated limitations in functioning. Alternatively, patients with chronic fatigue syndrome, chronic pain, depression or PTSD are likely to exhibit many post-concussion-like symptoms making misdiagnosis easy. Patients who experience mTBI complicated by depression report more post-concussional symptoms and more severe symptoms than patients with head injury without depression (Lange *et al.* 2011). Patients with symptoms of depression, anxiety and PTSD at seven to ten days post-mild-TBI predict post-concussional symptoms three to six months later. Symptom reporting is believed to be associated with premorbid personality characteristics and patients' negative perceptions of their illness early after head injury plays a role in the persistence of post-consussional symptoms (Whittaker *et al.* 2007). It has been suggested that in some patients with long-standing post-concussional symptoms, the extent and severity of the symptoms suggest that the illness is a form of somatization disorder (Fleminger, 2010).

Risk factors for development of PCS include female gender, previous psychiatric history and previous head injury (Meares *et al*. 2008). There remains a consistent association with involvement in medicolegal action and poorer outcomes (Belanger *et al*. 2005).

6.6.4 Treatment

Early educational information about PCS has been shown to be effective in reducing the number and severity of symptoms in the initial weeks (Borg *et al*. 2004). Longer term psychotherapy, occupational and vocational intervention and social skills training are used as necessary. A recent systematic review of psychological approaches to PCS identified that CBT may be effective (Sayegh *et al*. 2010) and an, as yet unpublished, randomized controlled trial of cognitive therapy has also shown a positive outcome from this intervention (Fleminger & Potter, personal correspondence).

6.7 Psychosis

6.7.1 Prevalence

Definitions of post-traumatic psychosis vary considerably in the literature with corresponding wide ranges of prevalence rates described. Transient psychotic symptoms are not uncommon after head injury, especially during a period of delirium immediately after TBI. Psychotic symptoms can occur as a complication of post-traumatic epilepsy, in the context of TBI related mood disorders or associated with a clinically problematic chronic schizophrenia-like condition.

The association between TBI and schizophrenia remains a subject of debate and controversy. Davidson and Bagley (1969) concluded that between 0.07% and 9.8% of patients with TBI develop a post-traumatic schizophrenia-like psychosis, with prevalence rates increasing over time. The authors concluded that TBI increases the prevalence of schizophrenia by two to threefold over 10-20 years. Most of these patients did not have a family history of schizophrenia. Van Reekum and colleagues (2000) reviewed data from more recent studies and found a prevalence of post-traumatic schizophrenia of 0.7%. Men appear to be more frequently affected by post-head injury psychosis than women (Fujii *et al*. 2002).

David and Prince (2005) appraised the literature to identify a causal role of TBI in schizophrenia and concluded that the evidence for such an association does not exist. They suggest that any association may be the result of reverse causality. It is clear that large scale epidemiological studies are needed to determine if head injury can be considered to be causally implicated as a risk factor for schizophrenia.

6.7.2 Clinical presentation

Psychotic features can be transient or persistent and may follow either an acute or chronic course. Following head injury the clinical features of delirium include confusion, inattention, cerebral disorganization and psychotic symptoms incorporated into this context. When the patient emerges from delirium, more discrete psychotic features might become evident and characteristic symptoms include delusional disorientation, delusional misidentification and confabulation. Confabulations may become chronic, especially in the context of associated global cognitive impairment and lack of insight.

The longer term clinical presentation has considerable overlap with primary schizophrenic disorder, with a prominence of persecutory and other delusions and auditory hallucinations. The onset is often gradual, with a subacute or chronic course (Zhang &

Sachdev, 2003). Prodromal symptoms are common and they include depression, antisocial and inappropriate social behaviour, social withdrawal and deterioration at work. Negative and catatonic features are unusual (Sachdev *et al*. 2001; Fujii & Ahmed, 2002).
Sachdev and colleagues (2001) reported a mean latency of 54.7 months between head injury and onset of psychosis, with the minimum being two weeks and the maximum 17 years. This study also noted a mean age of onset of 26.3 years.

6.7.3 Aetiology

Establishing a direct causal association between TBI and psychosis is difficult and consequentially differentiating patients with psychosis attributable to TBI from patients with primary psychosis who have suffered a head injury in the past is complicated. A genetic predisposition to schizophrenia may be a vulnerability factor for TBI psychosis. However schizophrenia commonly presents in men in their late teens / early 20's and this population are also at a high risk for suffering a head injury. TBI might be more common in families with a proband with schizophrenia and the trauma might increase the risk of manifesting the disorder.
Patients with psychosis secondary to TBI are more likely to have had a previous congenital neurological disorder or to have sustained a head injury prior to adolescence than TBI patients without psychosis (Fujii *et al*. 2001). Reports vary with regards to the severity of TBI required to trigger a psychosis. Some studies suggest that individuals who develop a psychosis after TBI had generally sustained moderate to severe head injuries. This contrasts with case studies reporting the development of a psychosis after mild brain injuries with no loss of consciousness.
Patients with psychosis following TBI have demonstrated more impairment on neuropsychological testing compared to those with TBI but without psychosis. Specific cognitive areas included deficits in general intelligence, verbal memory, executive functioning and vocabulary. The first three deficits are similar to those found in schizophrenic patients (Fujii *et al*. 2004).
Smeltzer and colleagues (1994) reviewed the evidence related to an anatomical localization of brain injury and relationship to psychosis. They found the evidence to be sparse, inconsistent and flawed. Some studies suggest that psychosis is related to left sided and temporal injuries but others find no relationship to the type or location of the injury.
Fujii and Ahmed (2002) analysed data from 69 published case studies of psychotic disorder due to TBI in order to describe common characteristics. They found abnormalities on EEGs in 70% of cases, especially within the temporal lobes and almost 30% had seizures. About 65% of the cases reported positive findings on MRI/CT which included focal lesions and atrophy in equal quantities and the most common location of findings was in the frontal lobes. These findings occurred in equal occurrence in the left and right hemispheres.

6.7.4 Treatment

Treatment with typical antipsychotics may cause a functional decline in patients with TBI who already have diminished dopaminergic circuits as a result of frontal brain injury. Therefore atypical agents, with less dopamine antagonism and greater serotinergic properties are preferred. Atypical antipsychotics, particularly olanzapine, are considered to be first line treatment of TBI psychosis. Initial doses should start low, at one third to one half

the usual starting dose, as individuals are particularly susceptible to side effects. The full range of psychotropic medication side effects are seen in individuals with TBI.
Clozapine can lower the seizure threshold, which can be problematic in TBI, and also has anticholinergic properties that can further impair cognitive function and may provoke delirium.

7. Summary of pharmacological treatment guidelines

The evidence for pharmacological and psychological treatment strategies for neuropsychiatric disorders is limited, as has been discussed. Two recent reviews of pharmacological management have identified the best evidence available, targets for future research and attempted to recommend best practice guidelines. Reference to these reviews is recommended (Warden *et al*. 2006; Chew & Zafonte, 2009).
Careful neuropsychiatric assessment needs to precede the development of the treatment plan. Making sure that the diagnosis is correct, that treatment is being taken and whether the dose of treatment is effective or has been given for an adequate trial period all need to be considered. When reviewing medications, it is important to ask oneself repeatedly what the drug is being given for and where there is no effect or benefit, stop it.
Practically speaking, when managing the neuropsychiatric sequelae of brain injury there are a number of principles that should be borne in mind. Wherever possible, the psychiatrist should wait to see how symptoms evolve and whether they remit spontaneously. Drug treatments should be started at lower doses and gradually titrated, avoiding polypharmacy wherever possible. Particular care about drug-drug interactions, and particularly interactions with antiepileptics and warfarin, should be taken. The iatrogenic effects of some agents in worsening cognitive impairment, for example through anticholinergic effects or causing akathisia and worsened agitation, should be taken into account when choosing appropriate agents.
The following treatments are recommended in the clinical management of neuropsychiatric disorders with the caveat that further research is required to ascertain effectiveness in the brain injured patient:
Long-term Aggression: Valproate or Carbamazepine or Sertraline
Cognitive Dysfunction: (Impaired Attention) Methylphenidate or Cholinesterase Inhibitors; (Memory) Cholinesterase Inhibitors; (Executive Dysfunction) Bromocriptine
Depression and Anxiety: Sertraline
Mania: Valproate or Carbamazepine or Olanzapine
Psychosis: Olanzapine

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14

Are Teachers Aware of the Potential Consequences of Their Work-Related-Stress Such as Burnout and Other Main Pathologies?

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1. Introduction

Since the first half of the 1980's, several investigators have focused their attention on the so-called 'burnout syndrome' among teachers (17). By definition, burnout syndrome is the psychological response of vulnerable individuals to stressors occurring in the work environment (18). The personal characteristics/variables that can make a person more vulnerable – or more resilient – to work-related-stress include personality, sex, age, tolerance, professional expectations, susceptibility, cognitive manner, cultural background, race, religion, temper, tenacity, flexibility, resistance, social-economic level, life style, family situation, life-events etc (17).

Burnout syndrome is characterized by four principal elements (17):

- physical and emotional fatigue (emotional exhaustion and fatigue);
- detached and apathetic attitude towards students, colleagues, and in interpersonal relations (depersonalisation and cynical attitude);
- feeling of frustration due to lack of personal accomplishment;
- reduced self-control.

Stressors occurring in the work environment of teachers include the following (14):

- distinctive characteristics of the profession (relationship with students and parents, numerous classes, insufficient pay, lack of resources, temporary employment, conflicts among colleagues, need for constant professional updating);
- social transformation towards a multi-ethnic and multi-cultural reality as a result of globalization (increased number of foreign students);
- continually evolving social values (introduction of new politics in favour of the handicapped and consequent introduction of disabled students in the classes, educational delegation by families to cope with absence of working parents or single-parent families; parent-child alliances damaging the parent-teacher relationship).
- advances in technology (introduction of computer sciences and new technologies of electronic communication);
- constant reform (scholastic autonomy, team work, elevation of the level of compulsory education, younger entrance age to school);

- stress for the loss of retirement privileges (until 1992 – before the so-called 'baby retirement reform' – an Italian teacher could retire with only 15 years of seniority);
- little appreciation of teachers' work in the public opinion.

According to newly introduced Italian legislation on workers' health protection (art. 28 Decree 81/08), and particularly on work-related-stress in the helping professions (2; 4; 6; 12; 13; 14; 15; 16; 17; 23; 24; 25; 26; 27; 29), schoolmasters are required to: (a) analyze teachers' stress, (b) prevent their mental damage and (c) counteract any kind of professional disease – including cancer – that may occur to the teachers. The law clearly states that worker's sex and age must be taken into account while devising prevention plans to minimize and prevent work-related-stress disorders. This is particularly important for teachers who have a median age of 50 years because the 82% of them are female (15) (the two data mean "menopause period" which enhances 5 fold the risk of depressive disorders) (7-8-9-10-11-22).

Psychologists (4) have addressed the 'burnout syndrome' several years before physicians had recognized the medical implications of the syndrome (1; 17; 30). Only recently, physicians are slowly starting to recognize and treat teachers' mental disorders, even those initially diagnosed as "burnout syndrome". This despite the fact that the "burnout syndrome" is not mentioned in the American DSM IV TR or in the European ICD 10. Moreover, further elements on teachers' health condition are pointed out in a newer study (15).

The high prevalence of psychological distress among teachers is an international problem. France (5; 12; 20; 29) and Japan (13) have respectively launched a suicide warning among teachers and have registered a dramatic increase of absence due to psychiatric problems. In Bavaria, Germany, the majority of teachers who retired for health reasons had a psychiatric diagnosis (2).

A further warning is given by the greater incidence and prevalence of cancer among teachers compared to the general population (3, 17). The 80% of tumours, according to the prevalent women population, were obviously breast cancers. Studies recently performed in Italy (17) as well as in California on 133.479 teachers (3) came to the same dramatic conclusion.

2. Study rationale

Considering the increasing prevalence of work-related-stress disorders among teachers – including burnout syndrome – we conducted a study to assess the level of awareness of burnout syndrome among Italian teachers. The study had two specific aims. First, to assess the level of awareness, experiences and perceptions of Italian teachers in regards to the risk of developing work-related-stress disorders. Second, to devise prevention programs designed to protect the health of Italian teachers within a new national body of legislation on work-related-stress.

3. Methods and analysis

The two aims of the study were explored with the use of a semi-structured questionnaire specifically developed for the current investigation **(Table 1)**. The questionnaire consisted of 15 open-ended questions. Questions 1 to 8 directly dealt with psychological distress and burnout. Question 9 explored the teacher's perception of the most important source of education for students. Questions 10 and 11 focused on teachers' opinion and knowledge on legislation. Questions 12 to 15 dealt with teachers' medical knowledge, prevention practices

and their thoughts about the awareness of health-care professionals in regards to work-related stress among teachers.

1. Have you ever dealt – in your career – with colleagues affected by psychiatric disorders?
2. Do you think your job may lead to psychophysical stress, mental disorders, cancer?
3. Did you ever lose self control at school with your students?
4. What is the main cause of your work-related-stress?
5. What relationship is the most stressful in your job? Students, parents, schoolmaster?
6. Do you generally feel comfortable when you start your lessons?
7. Do you generally share your problems with colleagues/friends or you prefer to face them on your own?
8. Have you ever been victim of mobbing by students, schoolmaster, colleagues or others?
9. Among family, friends, school and technologies which are, in your opinion, the most important sources of education for students?
10. Are you aware of the rights and duties the new legislation gives you to protect workers' health?
11. What do you think about the proposed increase of the retirement age of female teachers to 65 years?
12. Do you think depressive disorders arise much easier during menopause?
13. Do you regularly undergo screening tests for cancer?
14. Do you think general practitioners (GPs), psychiatrists and other physicians are aware of burnout, psychophysical stress, mental disorders and cancer in teachers?
15. Have you ever given days off and/or psychoactive drugs by your GP for health reasons?
Procedure: Teachers participating on compulsory seminars on burnout syndrome throughout Italy were asked to fill out the semi-structured questionnaire before the start of the seminar. A total of 85 seminars were held in 14 of the 20 Italian region[1] (Piemonte, Lombardia, Friuli Venezia Giulia, Emilia Romagna, Veneto, Toscana, Lazio, Puglia, Sardegna, Abruzzo, Sicilia, Campania, Calabria, Liguria).

Table 1. Semi-structured questionnaire

4. Results

Participants: The study was conducted from October 2008 up to March 2011. A total of 6.132 grade school to high school teachers (4.998 female and 1.134 male teachers) were invited to complete the questionnaire. 6.022 teachers answered to at least 10 out of 15 questions. These 6.022 questionnaires were considered valid for final assessment.

[1] The burnout seminars took place in the following cities/town: *Padova, Biassono, Pontassieve, Caserta, Pozzuoli, Pula, Sarroch, Domusnovas, Dolianova, Cagliari (8), Bari, Trani, Villanova d'Asti, Milano (5), Legnano (3), Rho, Bergamo, Brescia, Mortara, Torino, Darfo, Pontevico, Ariccia, Cerveteri, Sabina, Roma (8), Civita Castellana, Francavilla a Mare; Reggio Emilia, Palermo (2), Altofonte, Cefalù, Vicenza, Udine, Poggio Mirteto, Arpino, Barletta, Falcone di Acri, Vibo Valentia, Acri, Oppido Mamertina, Catania (2), Oliena, Ozieri, Pattada, Buddusò, Villamar, Milazzo, Abbiategrasso, Belgioioso, Alessandria,Tivoli, Subiaco, Altamura, Grottaglie, Rimini, Biella, Porto Torres, Enna, La Spezia, Genova, Sesto Fiorentino, Campi Bisenzio.*

Eighty one point five percent of participants were female – a figure that is superimposable (82%) to the sex distribution among Italian teachers (15). The mean age of female teachers was 46.5 years and that of male teachers was 46.9. Forty percent of female participants were in the perimenopausal period (45-55 years). Forty six point five percent of participants had been teachers for more than 20 years; 29.3% had been teachers for 10-to-20 years and 24.2% had been teachers for less than 10 years.

Responses to questions 1 to 8: Psychological distress and burnout

- **Q1**: 42.5% of responders had met colleagues affected by mental disorders.
- **Q2:** Most participants (84%) had heard of teachers' burnout during their career, yet only 19% was aware that work-related-stress could cause burnout and it can increase the risk of mental disorders and cancer; 8% thought that teaching was associated with no health risks. Seventeen percent of participants was convinced that burnout is the only work-related health risk for teachers and 38% was convinced that burnout plus mental disorders are the only two work-related health risks for teachers. Both groups were unaware of the risk of cancer. Finally, 18% did not answer the question.
- **Q3***:* 27% of responders admitted to have lost self-control while teaching in at least one occasion.
- **Q4***:* 73% of participants stated that work-related-stress was severely (50%) or moderately (23%) worse than stress experienced in their private life. The remaining participants (27%) thought that stress in their private life was severely (13%) or moderately (14%) worse than work-related-stress.
- **Q5***:* The major perceived sources of stress were the students (26%), their parents (20%), colleagues (20%) and the schoolmasters (2%). A substantial minority of responders (32%) stated that students and their parents, colleagues and schoolmasters were all equally responsible for causing stress.
- **Q6:** 27% of responders felts comfortable with their job; 59% felt concerned and 13% reported high levels of anxiety. Only 1% reported no concerns whatsoever.
- **Q7:** 65% of responders stated that they shared their problems with their colleagues; 35% preferred to face their problems on their own.
- **Q8:** 22% of responders was convinced that they had been victims of mobbing by the hands of colleagues or schoolmaster in the past; 1% was convinced to be victims of mobbing at present.

Responses to question 9: Most important sources of education

- **Q9:** The vast majority of responders (84%) considered the family as the students' most important source of education. This was followed by technologies (12%) and friendships (3%). Surprisingly, only 1% of responders considered school as the students' most important source of education.

Responses to questions 10 and 11: Teachers' opinion and knowledge of legislation

- **Q10:** The large majority of teachers (98%) – and schoolmasters[2] – were completely unaware of the legislation that mandates teachers' evaluation by government medical commission in case of health concerns.

[2] In a study conducted by the author in 2008 on 1.452 schoolmaster (16) showed that less than 1% perfectly knew the legislation on appealing to the Medical Commission to protect workers' health. The research was presented on the 21st May 2008 in the Italian Parliament.

- **Q11:** 48% of respondents were against the increase of the retiring age for women to up to 65 years; 38% were ready to consider the reform only if the health risks of the category were assessed beforehand. Only a minority (6%) of responders agreed to the increase in the retirement age with no preconditions. Finally, 8% suggested that it should be left to the teachers the decision whether to work until age 65 or not.

Responses to questions 12 to 15: Teachers' medical knowledge, prevention practices and thoughts about the awareness of health-care professionals in regards to the work-related-stress of teachers

- **Q12:** Only 35% of responders knew that compared to the fertile period the risk of depressive disorders increases 5 fold during menopause; 42% did not know of this risk and 22% denied any association between menopause and depression.
- **Q13:** 58% of female responders reported undergoing screening for cervical cancer (Pap smear) and 52% of them reported undergoing screening for breast cancer (mammogram); 27% of male responders reported to undergo screening for prostate cancer and 32% of them reported to undergo screening for colon cancer. The 13% of male and 12% of female responders stated that they were not old enough to require cancer screening.
- **Q14:** 40% of responders thought that general practitioners are totally unaware of teachers' burnout; 8% thought that general practitioners are aware of it and 13% did not answer the question. A total of 39% of responders thought that only psychiatrists are aware of the psychiatric risks associated with the teaching profession.
- **Q15:** 51% of responders stated that they felt no need to take days off for health reasons. A conspicuous minority (36%) declared they had taken no days off for health reasons, yet they thought it would have been useful to do so. Few teachers reported having taken days off for health reasons 'periodically' (1%), 'rarely' (4%) or 'one time only' (8%). Female responders reported more absences for health reasons than male responders (14% versus 9%). Most male and female responders (75%) denied taking any psychoactive medication for mental disorders; 17% reported taking psychoactive medication only 'as needed' and 7% reported taking psychoactive medications daily. Female responders used more psychoactive medications than male responders (25% vs. 23%).

5. Discussion

This is the first large cross-sectional investigation focused on the perception and understanding of work-related-stress and comorbidities among Italian teachers. The study has five major findings. First, a large proportion of teachers were aware of burnout and experienced work-related-stress, but only few of them knew that work-related-stress could cause mental disorders and could increase the risk of cancer. Second, nearly one fourth of teachers felt mobbed at work. Third, most participants were not aware of the legislation regulating workers' health care (including the psychological well-being of teachers). Fourth, most participants did not recognize the association between menopause and increased risk of developing depression. Fifth, despite of stress related work increases burnout, cancer and mental disorders in teachers, retiring age is going to be moved to 65 years of age (apparently against the new law protecting workers' health). Sixth, many participants rightly thought that physicians are totally unaware of teachers' burnout.

6. Conclusions

The teaching profession is associated with increased risks for the physical and psychological well being of teachers. Unfortunately, despite these increased health risks, a pervasive misconception in the public opinion is that teachers have a pampered (part time) work, peppered with many more holidays than in any other profession. Few comparative studies on workers' health, conducted among different professions, demonstrate a higher prevalence of mental disorders and cancer among teachers (1; 2; 3; 13; 15; 17). A worrisome trend in this regard is the worsening of teachers' health reported in last few decades in many countries including France (5), Japan (13), Germany (2) and Italy (1-17-30). Factors that may be responsible for this disturbing trend include the weakness of the family as educational agency and the ageing of teachers: the median age of teachers is approximately 50 years. In female teachers – which represents the overwhelming majority of teachers – this is a particularly vulnerable period as a result of physiological changes (menopause) which have been associated with depression.

This study, as well as other recent investigations conducted in Italy (15; 16; 17;30), shows the critical need of educating teachers about the health risks (including mental disorders and cancer) associated with their profession. This objective can be reached by fostering the participation of teachers to "damage prevention" seminars and workshops. These "damage prevention" programs should be focused on specific issues such as:

- work-related-stress in "helping professions";
- increased risk of depression in menopause;
- cancer risks and cofactors (genetic, diet, etc);
- importance of screening-test in cancer prevention;
- positive and negative coping strategies for mental disorders;
- appropriate legal knowledge (rights and obligations) of laws designed to protect workers' health.

"Damage prevention" seminars and workshops, should be followed by two additional initiatives namely: "damage repair" and "damage management". "Damage repair" consists in the care of teachers, who are victims of work-related-stress and allied conditions, by physicians who are conversant with the diagnosis and treatment of work-related-stress in helping professions. "Damage management", consists of supporting and advising schoolmasters faced with teachers suspected to be victims of work-related-stress disorders. According to the current Italian law, schoolmasters are mandated to refer these teachers to an ad-hoc medical commission. This commission, in turn, has to visit the worker to assess if the teacher is able to continue his job or has to stop for a while or forever. If considered "not able" the worker has to be assigned to another office in his/her school.

The results of this study suggest that it is critical to assess the real health condition of the teacher population, on national basis. Such assessment is the necessary foundation needed by those health-care professionals who are interested in designing programs that address teachers' risks of mental disorders and cancer. For their part, legislators must understand that increasing the retirement age of (female) teachers to 65 years is a mistake unless specific steps are taken to prevent the negative health consequences associated with this helping profession. In the absence of those specific steps, any increase in retirement age would be at odds with the recent Italian law focused on the protection of workers' health (Decree 81/08).

Finally, an effort should be made to inform physicians on the risks of helping professions and to restore the teacher's image and dignity in the public's opinion eyes through adequate mass media campaign.
July 7, 2011

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A psychiatric disorder is defined as any complex condition that involves the impairment of cognitive, emotional, or behavioral functioning. Aside from knowing the physical organic factors, its causal pathology has remained a mystery. Regarding recent advances in psychiatry and neurosciences, psychiatric disorders have been closely associated with socio-cultural, psychological, biochemical, epigenetic or neural-networking factors. A need for diverse approaches or support strategies is present, which should serve as common knowledge, empathetic views or useful skills for specialists in the filed. This book contains multifarious and powerful papers from all over the world, addressing themes such as the neurosciences, psychosocial interventions, medical factors, possible vulnerability and traumatic events. Doubtlessly, this book will be fruitful for future development and collaboration in "world psychiatry".

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