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Autism Spectrum Disorder

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AUTISM SPECTRUM DISORDER - RECENT ADVANCES

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Notice

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Meet the editor

Prof. Michael Fitzgerald - First Professor of Child and Adolescent Psychiatry in Ireland, specialising in Autism, Aspergers Syndrome and ADHD. He has a large number of peer reviewed publications and 25 books written, co-written or co-edited. Simon Baron-Cohen described his book 'Autism and Creativity' as "is the best book on autism". He has diagnosed over 3,000 persons with Autism and Aspergers Syndrome. Dr. Fitzgerald has a number of foreign language publications in Japanese and Polish. He has lectured extensively throughout the world including The Royal Society in London and China, Korea, Hawaii, New York, Buenos Aires, Tbilisi, Melbourne and many European countries. Recent books include 'Recent Advances in Autism Spectrum Disorders' INTECH Volume I & II. For further information, visit www.professormichaelfitzgerald.eu

Contents

Preface

Autism Spectrum Disorder is a neurodevelopment disorder. Neurodevelopment disorders are among the most important disorders in psychiatry and now also include Intellectual Disability, ADHD, Bipolar Disorder and Schizophrenia. There is a great deal of overlap between these disorders and not surprisingly, these often co-occur or are co-morbid. Indeed ASD was originally called Autistic Psychopathy and the first chapter of this new book suggests that this should be brought back under the title of Criminal Autistic Psychopathy for the small group of persons with Autism that commit crimes. While the global number of school shootings, mass killers or serial killers is relatively small compared to the total global population, the effect of some of these events on any one country or a number of countries can be significant. In many of these situations warning signs have been missed. Hopefully with the material on this book, this will happen less often in future.

Autism Spectrum Disorder is an extraordinarily complex disorder from almost every perspective with more than one neurodevelopment disorder, occurring at the same time in the same person. Unfortunately, often only one disorder is identified and the other disorders are missed, which leads to poor treatment and poor outcome, as each disorder needs to be treated in its own right. There are also overlapping and distinct aetiological factors occurring between the neurodevelopment disorders, which greatly complicates research. Identifying genuinely discreet diagnostic categories which is necessary for research is becoming more difficult and complexity of this is well illustrated in this book. Because of the current problems with diagnostic categories American Psychiatric Association DSM V and indeed the proposed classification for ICD XI means that alternative criteria are being put forward called the Research Domain Criteria. No quick research breakthrough is likely on a par with the Higgs Bosum research breakthrough recently. Nevertheless, progress can be expected on some aspects of the ASD spectrum issues. Despite a lack of major breakthrough at present, at the research level, progress continues to be made at the therapeutic level and particularly for children under the age of 2 and in the immediate years following.

There is no doubt that the best outcome comes where the research described in this book is initiated as early as possible. While there is no prospect of a “miracle cure” and discussions of this idea occur at a religious level and are most unhelpful from a professional psychiatric scientific level, very good progress has been made with persons with autism and in general as described in this book. This book describes issues in relation to Autism from the research level, the intervention level and the parents level. This book will bring the reader up-to-date in relation to the current status of Autism Spectrum Disorders at this point in time.

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New Diagnostic Subcategory - Criminal Autistic Psychopathy

Chapter 1

Autism and School Shootings — Overlap of Autism (Asperger's Syndrome) and General Psychopathy

Michael Fitzgerald

Additional information is available at the end of the chapter

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1. Introduction

The vast majority of persons with Autism Spectrum Disorders are highly moral but can show aggression of a non-lethal severity. Nevertheless there are a small number of persons with Autism or Asperger's Syndrome who do show lethal violence. I have described these as Criminal Autistic Psychopathy [11]. The rate of these problems in special hospitals and prisons is almost twice the general population prevalence of Autism and Asperger's Syndrome. Originally, these conditions were called Autistic Psychopathy by Hans Asperger 1938 and 1944. [9] I am suggesting that we bring back the diagnosis of Autistic Psychopathy for those persons with Autism and Asperger's Syndrome who engage in criminal activities with the new diagnosis Criminal Autistic Psychopathy. These persons have the dual features of Autism and Psychopathy. The seriousness of this condition is often missed with the sole diagnosis of Autism or Asperger's Syndrome. There are overlapping features but also differences from General Psychopathy as described in these examples of school killers in the literature.

In relation to the school shooting at Sandyhook School, Solomon (214) noted that from his conversation with Peter Lanza that his son Adam who shot 26 people at his school showed poor eye contact, problems with social relationships, preservation of sameness, narrow interests, poor communication skills and sensory issues. These are the classic features of Asperger's Syndrome DSM IV or the sub group of Asperger's Syndrome called Criminal Autistic Psychopathy [11].

2. Social relationship problems

Father [16] p.38) described him as showing "social awkwardness" and one of his psychiatrists Robert King [16] p.39) noted that he declined "to shake hands" when he met him. Adam was extremely controlling and dominating and had very little capacity for social reciprocity. He became very withdrawn and isolated as he grew up. Father said [16] p.40) that his son "was not open to therapy" and "did not want to talk about problems". Poor concentration is central to Asperger's Syndrome and Criminal Autistic Psychopathy. He showed problems in that area. He had major empathy deficits in relation to other people. According to [16] when his mother "asked Adam whether he would feel sad if anything happened to her, he replied "no". He found it much easier to communicate online. It's online that the true state of affairs of people with dangerous thoughts and fantasies particularly those with Asperger's Syndrome, Criminal Autistic Psychopathy sub type can be noticed. He felt hostile to people particularly females. On his computer he wrote "why females are inherently selfish" [16] misogynism is very common in these conditions. Father [16] states that "Adam would have killed me in a heartbeat, if he'd had the chance". He shot his mother "four times". [16].

In relation to social relationships the State Attorney [16] stated that he "was more likely to be victimised than to act in violence against another". This is usually what happens to people with Asperger's Syndrome. He once asked his father "why do you need friends?" [16].

2.1. Preservation of sameness

[16] describes him as showing "sclerotic orderliness". He found changing classes during the school day very stressful. His psychiatrist King also noted that "if mother walks in front of him in the kitchen, he would insist she re-do it" [16]. He had evidence of OCD and according to [16] "washed his hands excessively".

2.2. Narrow interests

He would spend hours playing with lego with his brother [16] and indeed "invented his own board games". [16]. He wrote violent stories. [16]. He was "fascinated with guns and with the second world war, and showed an interest in joining the military". [16]. He became pre-occupied with "mass murder". [16] and "left a photograph of himself with a gun to his head". [16]. He created his own private autistic world. He loved hi-tech matters and "was a member of his school hi-tech club". [16]. Mother tried to fit in with his special interests for example taking him to the shooting range. She did her best. His interest in violence was best seen in his essays and online.

2.3. Non-verbal behaviour

He showed poor eye contact and the psychiatrist Robert King described him as "pale, gaunt, awkward, young, adolescent standing rigidly with downcast gaze". [16].

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2.4. Sensory issues and motor issues

He suffered from sensory overload, which of course made school much more difficult for him. [16] noted that he "showed hyper-sensitivity to physical touch that tags had to be removed from his clothing and "sometimes he smelled things that weren't there". I don't agree with this as he had hyper-sensitivity to smell and could smell things that the average person would be unable to do so. In relation to visual hyper-sensitivity "colour graphics" upset him. [16]. He probably also had clumsiness with a "stiff lumbering gait" [16]. His father stated that he had an "awkward walk" [16] pointed out that he was "intolerant of his mother brushing by his chair and objected to her new high heels, high heel boots, because they were "too loud". This was according to psychiatrist King.

2.5. Verbal communication

King [16] also noted that he "had relatively little spontaneous speech but he responded in a flat tone with little inflection and almost mechanical prosody". And when King asked about his three wishes he replied "that whatever was granting the wishes would not exist".

2.6. Anxiety and depression

He suffered from anxiety and depression and was prescribed Lexopro an anti-depressant but got side effects and stopped it. Father described him as suffering from "uncomfortable anxiety" [16]. He had negative thinking, low self-esteem and mother noticed that "he was exhausted and lethargic all day" and had a "sense of hopelessness". [16]. He was tearful and his mother described his "escalating misery". [16].

2.7. School

He was a bright boy nevertheless school was experienced as a challenge for him both socially and academically which led to some home schooling. He was an autodidact. There was evidence of symptoms of Attention Deficit Disorder in terms of poor concentration. He showed poor school progress and his mother reported that he was in despair "when faced with some course work in German" [16]. Nevertheless he set himself very high standards.

3. Eric Harris: Columbine

Eric had Criminal Autistic Psychopathy with a Narcissistic Personality and Depression.

3.1. Early years

He was a highly intelligent child. He loved fishing with his father and loved the quietness of the mountains and lake. He was very visual and had a keen appreciation of landscape and appreciated the effect of light on water and in particular loved "water". [5]. [5] describes a neighbour's comment on Eric that he was "nice, polite, preppy, and a dork". [5] noted that "his

hand was always shooting up in a class and he always had the right answer". Page 9. He was highly intelligent and of course in the long term this increased his dangerousness. He was also described as being "painfully shy". [5]. He had surgery for "pectus excabatum, an abnormally sunken sternum". [5]. This was a narcissistic wound for him as a child. Eric was "gifted analytically, excellent at maths, a technology expert and into "gadgets, computers, video games". [5]. Here again we see some overlap between General Psychopathy and Criminal Autistic Psychopathy. Cullen notes that a Little League Team mate described Eric as the "shyest out of everybody" and was restricted in what he said. His coach [5] noted that "he didn't want to miss (a ball). He didn't want to fail" and therefore he was very slow to swing a bat. This again shows his narcissistic vulnerability and his fear of missing which he found humiliating. In a way according to [5] Eric "scripted Columbine, as a made for TV murder". [5]. This is further evidence of his narcissism and in fantasy he re-enacted the pleasure of the massacre endlessly in the long period leading up to it. In his own mind he was the superior one, the man who was awesome and frightened the world.

[5] noted that "Eric wanted to be remembered". He certainly left his mark on the sands of time. He wanted to be feared and wanted to be in a position where nobody ever looked down on him again.

3.2. Narcissism

The FBI analyst who examined his motives suggested that Harris was a classical psychopath and had a "messianic level superiority complex and hoped to illustrate his massive superiority to the world". Immelmann (2009) described Eric as possessing a "malignant narcissism… a Pathological Narcissistic Personality Disorder with borderline and anti-social features, also with some paranoid traits and unconstrained aggression". Eric wrote according to [5] that "my belief is that if I say something, it goes. I am the law. If you don't like it, you die". [5] summarised Fuseliers opinion that "Eric had a preposterously grand superiority complex, a revulsion for authority, an excruciating need for control". This was largely inherent in Eric with huge innate factors and again we see the overlap with Criminal Autistic Psychopathy. Eric also stated "I feel like God and I am higher than almost anyone in the fucking world in terms of universal intelligence". [5]. This was not psychosis but it is close to psychosis.

Eric also said that "Zeus and I also get angry easily and punish people in unusual ways". [5]. In a way Zeus was one of the superior Gods. After Eric was arrested for the breaking into the car he switched from being an "observer to enforcer". [5]. This was a critical life event and even though he was the perpetrator he understood it himself as that he was the victim and how dare they arrest him and put him in handcuffs. This speeded up his sense of injustice, his hatred of humanity and simply accelerated his wish to do the massacre. Of course he was on that path before he was arrested. Eric "fancied himself as a non-conformist, but he craved approval and fumed over the neighbour's disrespect". [5]. Eric was hypersensitive to any rejection or criticism and [5] noted that Eric had "a long list of betrayals, an actual "shit list" on his computer of despicable young girls". He talked a lot about people who "knifed… him in the back". Most of this was more imaginary than real. Nevertheless it was psychologically very real to him.

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3.3. Attitude to other people

Eric stated on one occasion "I hate almost everyone" and ah yes "I wanna rip his head off and eat it" in a "flat voice". [5]. After a fishing trip he talked about going back to "shithead society populated by automatons too dense to comprehend what was out there". [5]. Eric also wrote "if you have a problem with my thoughts, come and tell me and I'll kill you" [5]. Another one of his rants was "I hate". [5]. According to [5] p.216 Eric's "only internal struggle concerned which stupid bastards was more deserving of his wrath". He saw himself as an avenging God. Before the massacre of course he was a petty criminal. [5]) noted that Eric "savoured the idea (of) heroic opportunities to obliterate alien hoards. His dreams were riddled with gunfire and explosions" and "he was always dazzled by fire". Eric made "death threats" to another student. [5] p.88. Eric wrote on his website that he wanted to "mow down" the people of his area and that "I don't care if I live or die in the shootout..."all I want to do is kill and injure as many of you pricks as I can". [5] p.216. [5] p. 219 notes that Eric "described going to some random downtown area....and blowing up and shooting up everything he could. He assured us he would feel no remorse, no sorrow, no shame. He would make them pay". This shows an incredibly deep hatred of the human race and he did not have a traumatic childhood. Again we are dealing with a personality and with problems largely coming from inside him.

In 1998 he wrote in a notebook "I hate the fucking world" and that "I am not respected". [5]. This was a largely paranoid thought and not based on reality. Eric also stated that "human beings were pathetic fuckheads too dense to perceive their lifeless existence...automatons" and people were "assembly-line robots". In a way Eric wanted to destroy humanity in the world. In addition Eric "had a grander vision. All his writing alluded to a wider slaughter; killing everything, destroying the human race" and he also wrote "kill them all. Well if you have not figured it out yet, I'd say "kill mankind". [5].

3.4. Eric's description of himself and description of him by others

[5] states that girls found him "cute" and that "he'd always hated his appearance". Eric also could be charming and told a great deal of lies. He did not suffer from guilt for his actions. [5] noted that his Principal in college Frank de Angelis noted that Harris was "the type of kid who, when he was in front of adults, he'd tell you what you wanted to hear". Cullen also noted that a classmate had "the impression... (that Eric) wanted to be an outcast. He was also described as "moody and aggressive". P. 140. He suffered from depression. Eric was "egotistical, empathy-free". [5]. When Eric was asked to describe himself in filing out a questionnaire which focused on distrust etc., he described himself as agreeing with some of the following descriptions: jealous "anxiety, suspiciousness, temper, obsessive thoughts, mood swings, disorganised thoughts, homicidal thoughts" [5]. When mental health professionals assessed him he seethed "as he scrawled out his answers" and he considered "the nerve of these low lifes judging him" and how he "hated fools telling him what to do." [5]. In addition, Eric was "a dreamer" of "a world where the rest of us had been removed". [5]. [5] described Harris as a "cold-blooded, predatory psychopath". Fusilier [5] noted that Eric showed "cold rational calculation-(was) charming, callous, cunning, manipulative, comically grandiose, egocentric, with appalling failures of empathy". He had the capacity when he wanted to to fool people and deceive people

and was a superb liar and he was also a sensation seeker and novelty seeker. Therapy for persons with psychopathy often makes them better at psychopathy and improves their destructive social skills. He was in therapy but only pretended to engage himself from it. He was "unemotional" and was extremely dominating and controlling. [5].

He was well able to manage adults and to tell adults what they wanted to know and what they wanted to hear. His parents described him earlier as "getting angry all the time.at almost anything he didn't like" and he would "punch a wall" [5].

3.5. Interests

Eric wrote [5] that "guns! boy, I loved playing guns". He was also superb at violent video games. He used to sketch "medieval armour and sub-machine guns" and would draw "victims (who) were frequently on fire and freshly decapitated" as well as he showed a great interest in the Nazis and their activities. [5], p.81. Another great interest was in "explosives". [5]. He loved to make home made bombs. Other interests included "Nietzsche, Freud, Hitler" and he used to say "Sich Heil" or "Heil Hitler". He was obsessed with massacres and mayhem on television.

3.6. Relationship with girls and other adults

Eric was a boy who "smoked, drank, dated" (page 6 [5] and he would walk up to "hotties in the Mall". "He won them over with quick wit, dazzling dimples and a disarming smile". [5]. Nothing could be further from Asperger's Syndrome than this. This was his genuine evidence of an element of General Psychopathy.

3.7. Control and domination

[5] stated that when "somebody needed to take control. Eric was your man. He was like a robot under pressure". The local Pizza Store where he worked had a particularly good opinion of his capabilities and put him "in charge when he left". [5]. He had excellent management skills and found it very easy to manage his co-killer Dylan Klebold.

3.8. Conclusion

In writing there was often contradictions and Eric's writing wasn't always logical. Eric had excellent social know how compared to Dylan. Dylan and Eric had major empathy deficits and were both hostile and somewhat paranoid people. Both suffered from depression. They became a most dangerous murderous couple. Eric was the active one the leader and Dylan was the follower the passive one. They played out their killing in fantasy many times before they carried it out. The warning signs were mainly in their writings and on their website. Nevertheless they both had contact with the police. Clearly if teachers read the kind of essays that they write and their pre-occupations from now on they should take these writings very seriously and take action on them.

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4. Dylan Klebold

4.1. Childhood

Dylan was described by his parents as an "introverted and has grown up isolated" and is "often angry or sullen and his behaviours seemed disrespectful to and intolerant of others". [5]. Dylan [5] was "born brilliant" and went to school "a year early" and was sent to a gifted child programme because he was "a maths prodigy". Everybody said he was extremely shy. He was extremely sensitive to criticism and could have meltdowns that could take quite a while for him to recover from. He had very vulnerable self-esteem and criticism would easily lead to a meltdown.

4.2. Social relationships

[5] points out that Dylan Klebold was "meek, self-conscious and shy. He could barely speak in front of a stranger, especially a girl. He'd follow quietly after Eric (co-mass killer) on the Mall conquests attempting to appear invisible". Eric flattered "girls" with compliments; "Dylan passed them chips, cookies to let them know he liked them. Dylan's friends said he had never been on a date; he may never have asked a girl out". Not surprising Dylan wrote in 1997 "I feel so lonely without a friend". [5]. Dylan was a loner, which caused him pain and "felt cut off from humanity". [5] Dylan described himself as someone who had "no girl (friends)/not even platonic, no other friends, nobody accepting him, doing badly in sports, looking ugly and acting shy, getting bad grades, having no friends in life". [5]. Dylan did at times regard other humans as "zombies" and wrote about himself "I am God compared to some of these un-existable brainless zombies". [5]. This was projection and shows that he had some grandiosity as well which is often hidden behind low self-esteem.

He was very naive and tended to be caught if he did anything wrong. This is typical of persons with Autism. He was caught when he broke into a car and stole stuff with his friend Eric Harris (co-mass killer). According to [5] "Dylan Klebold was not a man of action. He was conscripted by a boy who was". Persons with Asperger's Syndrome are very easily led. They are often led into serious crime by other people particularly persons with psychopathy like Eric Harris. He shared talents with Eric Harris including great mathematical ability, technological expertise and in particular Dylan was excellent at "analysing, inventing, deconstructing". [5]. Dylan would hammer at "ideas relentlessly". [5]. Dylan wanted to become a specialist in computing technology and there was no doubt he would have achieved that if he hadn't met Eric Harris.

4.3. Interests

Dylan was very interested in "classical philosophers and renaissance literature". [5]. Dylan was into polarities and felt himself to be split in his mind. One of the polarities that fascinated him was "good and bad". This was a major focus for him [5]. [5] that "Dr Fuselier from the FBI stated that "both boys fantasised about murder, but Dylan focused on a single attack".

4.4. Sense of self

[5] points out that Dylan did believe in God but that he would "cry out, cursing God for making him a modern Job, demanding an explanation for the divine brutality of his faithful servant. It's hardly surprising he considered suicide as a way out. Dylan wrote that "God had chosen him" as someone "in search of answers, never finding them, yet in hopelessness understands things. He seeks knowledge of the unthinkable, of the undefinable, of the unknown. He explores everything/using his mind, the most powerful tool known to him". [5].

4.5. Depression

Dylan had fantasies about relationships with a girl which were very powerful. He suffered from depression which is very typical with Autism indeed he wrote "good God I hate my life, I want to die really bad right now". [5]. He also had preservation of sameness and was very much a routine driven boy.

4.6. Naivety

When Dylan hacked into the school computer he was caught and reprimanded. [5] wrote that when Dylan was "caught scratching obscenities into a freshman's locker, he was called before the school Dean and went ballistic. He cussed the Dean and bounced off the walls" and acted bizzarely.

4.7. Home movies

Dylan had acting potential which was really one area where he was superior to Eric Harris his leader. It is well known [11] that many great actors had Autism or Asperger's Syndrome. [5] noted that on film Dylan "unleashed his anger and he was that crazy man disintegrating in front of the camera. His eyes bulged out". It was also noticed that in life generally he was not very capable and was not given complex tasks to do.

Overall he had no ability to plan an operation on his own like the massacre and was simply led in a very naive way by a person with psychopathy Eric Harris.

5. Virginia tech shootings

Cho Seung-Hui the mass killer at Virginia Tech also had a diagnosis of Autism. He was a shy, withdrawn child who had problems with social know how and social cop on. He hated hugging as a child and was very violent. He was clingy to his mother. He showed poor communication and often gave one word answers to questions. He great aunt [2] stated that "when others called his name he just answered yes or no but never showed any feelings or emotions. We started to worry he was autistic". Later he was formally diagnosed with Autism. He was bullied within the educational system.

A Professor Lucinda Roy complained to the campus police about him and she also gave him "individual lessons" and said to him: "You seem so lonely"-"Do you have any friends?". "I am

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lonely". Cho replied. "I don't have any friends". A student at Virginia Tech Karen Grewal [17] noted that "he was so quiet, it was almost as if he wasn't there and was invisible. He must have been worried that he'd would be found out".

[3] noted that there were "college girls who reported him to the police for stalking and got him carted off to a mental hospital after he sent them shy love messages full of meaning". Cho [3] also wrote "by a name, I know not how to tell who I am". This is typical of the identity diffusion of autism. He was unable to get a girlfriend and "he had to make up with a fantasy girlfriend". [3]. He was a loner as a child. [2] notes that a fellow student noted he was "obsessed with violence and with serious personal problems". He admired the Columbine killers. Professor Nikki Giovanni one of his teachers at Virginia Tech was concerned about his writing i.e. "your bra is torn and I am looking at your flesh". [3]. He'd never speak but he frightened everyone. According to [17] "he insisted on wearing sunglasses and pulling his baseball cap low on his forehead" and that neighbours "described him as a surly youth who did not communicate and ignored them in the street". He was a major mathematical talent like many with Autism. [9]. Professor Louis Schlesginger a Professor of Forensic Psychology states that "mass killers tend to be aggrieved, hurt, clinically depressed, socially isolated and above all paranoid". (Begley 2007).

In the psychiatric hospital in 2007 a psychiatrist noted his "affect is flat and mood is depressed". (Begley 2007).

6. Conclusion

School shootings and mass killings are not uncommonly committed by persons with neurodevelopmental disorders i.e. Criminal Autistic Psychopathy/Asperger's Syndrome with often a good deal of warning based on writings on the internet and elsewhere.

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Section 2

Psychological and Biological Assessment

Chapter 2

Neurotransmitter Systems in Autism Spectrum Disorder

Fatih Hilmi Cetin, Huseyin Tunca, Esra Guney and Elvan Iseri

Additional information is available at the end of the chapter

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1. Introduction

Neurotransmitters, which connect neurons with each other, have key roles in normal development of brain, memory, motor activity and behavior regulation [1]. Based on these knowledge, neurotransmitter system dysfunction thought to be the cause of Autism Spectrum Disorder (ASD), by affecting neuronal cell migration, differentiation and synaptogenesis and eventually developmental processes of the brain [2, 3]. In pathophysiology of ASD many neurotransmitter systems has been investigated and dysfunction of these systems has been shown to be responsible. In the literature, neurotransmitters that are most commonly associated with the pathogenesis of ASD are, GABAergic, glutamatergic and serotonergic systems [4].

2. GABA

In order to maintain function and homeostasis of Central Nervous System (CNS) the balance between excitation and inhibition of neurons is very important. Main inhibitory neurotransmitter in the brain is gamma amino butyric acid (GABA) [5]. GABA is synthesized from glutamate by the enzyme glutamic acid decarbosilase (GAD) [6]. This enzyme has two isoforms known as GAD67 and GAD65, these are encoded by GAD1 and GAD2 gene. These enzymes different from each other in terms of the intracellular localization, expression, and enzymatic activity [7]. After GABA sythesized, it is taken to the vesicle by vesicular GABA transporter (VGATs) [8]. GABA is released to synaptic space under influence of Action Potential (AP) and binds to the $GABA_A$ and $GABA_C$ iyonotrophic receptors or metabotropic $GABA_B$ receptors [9]. The activity of GABA that is released to the synaptic space is ended by GABA transporters which are located at cell membrane (GAT) [10]. Finally GABA that

is taken to the inside cell furtherly degrades by the transaminase or succinate semialdehide dehidrogenase enzymes [9].

GABA has a key role in the regulation of early developmental stages of cell migration, neuronal differentiation and stages of maturation [11]. Besides, formation of GABAergic system has a critical role in migration of GABAergic neurons and formation of glutamergic system mediated excitatory processes that regulate cortical inhibitory system [12]. Therefore, it is not suprising that especially in ASD and in many neurodevelopmental disorders GABAergic system is the main responsible [13, 14]. In addition, the high prevalence of epilepsy in patients with autism have made it worth to investigate GABA neurotransmitter system in individuals who has ASD [15].

Neurochemical abnormality that postulated to be associated with pathophysiology of ASD is the reduction in the expression of GAD65 and GAD67 which cause suppression of GABAergic inhibition [16]. Fatemi and his colleagues [17], in the cerebellum and parietal cortex of patients has shown significantly decrease in two isoforms of the rate-limiting enzyme which are responsible for the conversion of glutamate to GABA. Detection of low platelet GABA levels in children with ASD [18] and postmortem studies that illustrtaed significant reduction in $GABA_A$ and $GABA_B$ receptor subunit in various brain regions [19, 20] support the widespread dysfunction of GABAergic system in patients with ASD. Reduced production or signaling of GABA cause hyperexcitability state and leads to cognitive dysfunction [21]. Deletional mutations of genes encoded by chromosome 15q11-q13 which is some of the GABAA receptor subtype unites (GABRB3, GABRA5 and GABRG3) might be cause of reduction in GABAergic transmission, and these mutations have been suggested to be a risk factor ASD [14]. Also, many of the candidate genes associated with ASD are expressed in interneurons [22]. Antiepileptic agents, especially benzodiazepines has been used in ASD and epilepsy coexisted patients and they have shown to improve socialization and communication skills, though, in some cases, they lead to increased anxiety and aggression, because of this, the information mentioned above is not clear yet [23,24]. Lemonier and Ben-Ari [25] sugeested that the inhibition of Na / K / Cl transporter (NKCC1) lead intracellular increased Cl levels, so the GABAergic transmission will change depolarization to the hyperpolarization and in five ASD cases they get positive results after the treatment with NKCC1 inihbitor bumetanide. Then they carried out double blind randomized controlled clinical trial of bumetanide for treatment of ASD for 3 months of period in 54 patients, the results has shown to provide a significant improvement of ASD symptoms [26]. In utero exposure to valproate in mice model, has caused dissappearance of swicth between GABA excitation / inhibition and this problem has shown to lead the development of chronic chlorine deficits and autistic-like behavior [27]. Ion channels mutated mouse model which led to the reduced GABAergic transmission, and the corelation between ASD symptoms and reduced GABAergic transmission level and with benzodiazepine treatment autistic-like behavior to has shown to decrease [28].

As a result of animal model publications and studies conducted in patients with ASD has confirmed the hypothesis of "decreased GABAergic transmission in ASD patients". In future studies, to develop a new therapeutic agents, and to even prevent the disease focus should be directed on the GABA neurotransmitter system.

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3. Glutamate

Glutamate is essential excitatory neurotransmitter of the central nervous system. It is synthesized from glutamine via glutaminase enzyme. There are two types which are iyontropic and metabotropic receptors. Metabotropic receptors (mGluR) are coupled with G protein and within the cell according to signaling pathways they divided 3 into subtypes: Group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3), Group III (mGluR4 and mGluR6-8). Group I works through activation of phospholipase C whereas Group II and Group III works through decreasing cyclic AMP level [29]. Ionotropic receptors which are coupled with ion-channel, have 3 sub-types: N-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and kainate receptors. Kainat receptors located presynaptically at the hippocampus, stimulation of them reduce glutamatergic transmission [30]. Induction of AMPA receptors, these are associated with learning and memory, lead to the long-term potentiatio (LTP) and long-term depressio of (LTD) [31]. High levels of glutamate leading to overstimulation of NMDA receptors and cause a high amount of calcium influx, which is main responsible for excitotoxicity lead to the neuronal damage. Therefore, optimization of the level of glutamate in the synaptic cleft is critical. To protect post-synaptic neurons from excitotoxic effect the neuronal glutamate transporters which reside at the presynaptic membrane take back glutamate into cell from synaptic cleft. In final stage, glutamate is destroyed with GAD [1]. Balance between excitation / inhibition is crucial for synaptogenesis and plasticity, especially in first 3 years of life [32]. Blockade of NMDA receptors in the prenatal period initiates apoptosis in neurons [1].

From this point, glutamate plays a central role in shaping the architecture of the brain. Cell migration, maturation and developmental stages, such as synaptogenesis and neuroplastisicity is accomplished with the optimum glutamat transmission level [33, 34]. At the same time it is directly associated with cognitive processes such as memory and learning [35].

Glutamate receptors associated with ASD are highly expressed in the hippocampus and cerebellum [36]. For these reasons, the role of glutamatergic system in patiets with ASD has been substantially investigated, two opposite hypotheses regarding the role of this system have been proposed [37]. First hypotheses of ASD has been proposed hypoglutamatergic state [38, 39, 40], the second postulated the depletion of GABAergic inhibition excitation / inhibition rate which eventually lead to the hyperglutamatergic state [41, 42, 43]. Consistent with the hypothesis suggested that ASD is hypoglutamatergic disorder, in 1998 Carlsson has postulated decrease in glutamate signaling lead to activation of receptors at the cortical GABA interneurons and this state cause significant depression in excitator glutamate circuit [38, 44].

Other supportive evidence is hypoglutamatergic state in mouse models caused similiar presentation to ASD including inability to change behavior paradigm, limitation in habits and behavior [45] In a postmortem study patients with ASD has shown significant decrease in AMPA type 2 and 3 in cerebellum tissue [40].

Another hypothesis that might be surrogate to explain ASD is hypoglutamatergic state and associated cortical tissue hyperexcitability in spesific cortical areas. Some studies has demon-

strated higher serum glutamate levels in individuals with autism [46]. Increased glutamate level probably connected with diminished GAD enzyme level [47, 48, 49]. This diminish also explain reduction in GABA transmission [50]. First study was done by Shimmura has illustrated higher serum glutamate levels and lower glutamine levels [51]. Secondly Shimmura et al. [52] has done another study they researched brain tissue from 7 postmortem ASD patients, they found higher levels of glutamate and glutamine levels at anterior cingulate cortex, interstingly levlels of glutaminase, glutamine synthase, and GAD were normal. As mentioned above ASD patients have high incidence of epilepsy, this is due to increase in glutamatergic activity [53, 54].

Animal models and conducted clinical studies in ASD subjects support hyperglutamatergic hypothesis. Silverman et al. [55] is conducted a study on ASD core symptoms observed mice model and found that GRN-529 (allosteric modulators of mGluR5 receptor) ameliorated all core symptoms of ASD. Another study conducted with AMPA receptor agonist (Ampakin) relieved symptoms of respiratory system on mice model with Rett syndrome [56]. Lamotrigine, which reduce glutamate transmission, has improved communication skills, socialization and behavior problems in 28 children diagnosed with ASD [57]. Ketamine, an NMDA receptor antagonist, has been shown to have a positive impact on focused attention in ASD cases [58].

Another NMDA receptor antagonist, memantine, significant improvement was observed on learning, language skills and in the areas of socialization in patients with ASD [59]. Recently, a randomized controlled study carried out, the memantine and risperidone receiving group were compared to placebo and risperidone receiving group, at the 10th week of treatment, memantine and risperidone received group better recovered compared to only risperidone received group in terms of the irritability, stereotypies and hyperactivity symptoms [60]. Recently, non-invasive brain imaging techniques such as magnetic resonance spectroscopy has enabled measurment of glutamate levels in brain tissue. Since first study was published in 2006 to date there were 15 studies done and conflicting results have been obtained [37]. In some studies, the anterior cingulate cortex [61] and auditory cortex [62] areas glutamate levels was increased compared to healthy controls, while in others there was no difference, and in the rest lower glutamate levels was observed [63, 64].

Some researchers thought these two hypotheses related to glutamatergic system are not completely opposite, some spesific cortical areas has increased excitatory / inhibitory ratio whereas in other regions, this ratio could turn opposite [44].

As a result, it is not clear yet whether the ASD individuals hyper or hypoglutamatergic, but it is clear that there is dysfunction in the glutamatergic system. New investigations has focused more in hyper-glutamatergic state and efforts are directed at glutamate receptor antagonismin order to develop new therapeutic agents. A better understanding of the glutamatergic system agents in the future will contribute to enlight ASD pathogenesis.

4. Serotonin

Serotonin is a neuromodulator which acts as a developmental signal [65]. Serotonin is synthesized by the enzyme triptophanhidroksilase which convert triptpohan to 5-hydroxy-

tryptophan, and decarboksilation at the end [66]. Serotonin neurotransmitter system has critical role in the regulation of crucial steps of neuronal development such as cell proliferation, differentiation, migration, apoptosis synaptogenesis, neuronal and glial development [67, 68]. Serotonin system in the prefrontal cortex and temporal cortex regulates GABAergic inhibition, therefore it has played a role in the regulation of many aspects of cognitive functions [69].

Serotonin plays an important role in the development of social skills during gestational period and early childhood. Inadequate stimulation of serotonin in the early stages of life, can lead to the unpreventable abnormalities in serotonin metabolism in subsequent period of life. These defect may cause permanent problems in serotonin metabolism in people who have been deprived serotonin effects necessary for the brains especially early developmental stages of life. This is why, adequate levels of serotonin are necessary for the development of close relationships and social skills in the early stages of life [70]. Social skills and behavior have been shown to be associated with hippocampal neurogenesis in ASD individuals and because of that hippocampal abnormalities are found frequently [71]. Serotonin play a central regulating role in serotonin dependent neurogenesis activity in the hippocampus [72].

Pathophysiology of ASD has two main hypothesis for serotonin neurotransmitter systems, just like glutamate hypothesis. One widely accepted for a long time and confirmed for many times is hyperserotonin state and while the other one is hyposerotonin hypothesis which became prominent in recent years [66]. Two main findings of hyperserotonin hypothesis in patients with ASD are increased blood serotonin levels (my hiperserotone) and decreased brain serotonin levels [66]. The presence of hyperserotonemia in 25 to 50% of individuals with ASD is important to showing they may have abnormalities in the serotonergic pathway [73, 74,75].

Furthermore, first-degree relatives of individuals with ASD found to have hyperserotonemia, as well as parents of these kids more often showed the presence of serotonin associated psychiatric disorders, such as depression and obsessive-compulsive disorder [74, 76]. Other supportive evidence, brain serotonin level decreased and exacerbation of many repetitive behavior was observed (such as spinning, stepping, self-hit and shoot) with tryptophan poor diet (low-tryptophan diet) [77]. Serum levels of tryptophan to large neutral amino acid ratio was shown to be decreased in children with ASD. This rate is an indicative of presence of tryptophan for serotonin synthesis in the brain and this lower ratio demonstrate low tryptophan usability which might suggest one of the mechanisms associated with serotonergic dysfunction in ASD [78]. Another study demonstrated, after L-5-hydroxytryptophan administration young people with ASD, their blood serotonin levels increased, whereas in control group no difference was seen [79].

Severity of at least one specific behavioral problem in ASD is reported to be associated with 5HT1D receptor sensitivity [80]. Various studies have reported controversial results regarding association of serotonin transporter gene in ASD. In contrast, in accordance with the data regarding the transfer of serotonin transporter gene polymorphic alleles associated with the findings of the degree of the social and communicative deficits, these alleles instead of being risk factor for ASD they might change the severity of clinical presentation in autistic children [75].

Shown correlation between ASD and serotonin transporter gene and found mutations in genes encode rate-limiting enzyme in the catabolism of L-tryptophan such as 2,3 dioxygenase gene is thought to be responsible for increased serotonin levels [81]. There might be defect in the development of the serotonergic system in patients with ASD. Normally, the serotonin neurotransmitter system follows a pattern of age-related development, for example, developmental studies of serotonin receptor binding in monkeys showed that increment during infancy and throughout childhood, a prepubertal peak, and eventually slowly reduction during adolescence and early adulthood [82]. In humans at 6 year of age serotonin receptor binding is higher than neonatal period or 13-14 year of age [83]. This dynamic changes are impaired in ASD, at the beginning of childhood low serotonin levels are observed compared to normal baseline, but steadily increased from 2 to 15 years of age and reaches higher than adult levels [84, 85]. In various animal models when effect of higher levels of serotonin investigated particılarly in the development of somatosensory system, the deterioration in the formation of thalamo-cortical sensory circuits were observed [86]. Recently "ASD is a hyposerotonergic condition" hypothesis is worth to discuss. In a study of volunteer postmortem brain tissue of ASD patients examined, and the increase in number of serotonergic axons were observed [87].

This situation cannot be explained by the hypothesis of compensatory mechanisms which expected to result reduction of serotonergic axons in hyperserotonergic state [88]. In men with ASD, in one side of the brain of frontal region and thalamus, typically synthesis of serotonin was reduced, in opposite side of the brain of cerebellum, and dentate nucleus serotonin has been shown to be increased [70].

Several PET and SPECT studies in individuals with ASD has shown serotonin transporter binding amount decreased significantly in various brain regions (frontal cortex, cingulate, thalamus, etc..) [89, 90]. Other study was exhibited that low levels of blood serotonin in mothers of children with ASD compared to normal developing children's mother [91]. In another study, individuals with ASD were shown to have low levels of gene responsible for synthesis of serotonin [92]. Serotonergic drugs, the main symptoms of ASD respond less to treatment, but some are partially effective in the symptomatic treatment of patients with autism. These drugs include selective serotonin reuptake inhibitors (selective serotonin reuptake inhibitör=SSRI), 5-HT 2A receptor antagonists, tricyclic antidepressants and receptor antagonists (dopamin/5-HT) mix.

Mechanism of action of these treatments are unknown, but they are thought to act on the developmental defects in serotonergic pathways such as serotonin synthesis, catabolism, and transport-related dynamic abnormalities [93, 94].

As a result, the highest level of evidence for ASD relationship with monoamines is the serotonergic system. Hyperserotonemia in peripheral blood in individuals with ASD, despite the presence of opposite results, has been shown to be present in many studies. Low levels of serotonin in the brain tissue is the common finding of hyposerotonergic and hyperserotonergic hypothesis. Future studies will enlight reson for lower serotonin levels in the brain tissue and will open new horizons both for diagnosis and treatment.

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5. Catecholamines

Evidence for the relationship of dopamine and norepinephrine with ASD was gathered from the studies reported decrease in DBH (Dopamine B Hydroxilase) activity and increased serum norepinephrine levels in children with autism and in their parents [95]. Findings increased catecholamine levels of the blood, urine, and cerebrospinal fluid in children with ASD [96, 97] as well as evidences sugested abnormal dopaminergic activity in the medial prefrontal cortex proposed abnormal cathecolaminergic activity [98]. Another supportive study has shown that, patients with ASD have increased urinary homovalinic acid level which is a degradation product of dopamine [99].

Robinson et al [100] demonstrated, mothers of children with ASD has low serum DBH levels and this interpreted to cause possible risk factor for ASD by creating a non-ideal intrauterine environment (leading to reduced norepinephrine and increased levels of dopamine). Study was done by using positron emission tomography (PET) in high-functioning ASD individuals has enligthened that increased activity of dopamine transporter (DAT) at the orbitofontal cortex region [89]. In a more detail study, Neale BM and his colleagues have found a de novo mutation of DAT gene (SLC6A3] in individuals with ASD [101].

6. Acetylcholine

Chemical and histochemical studies in the brains of individuals with ASD has shown loss of nicotinic receptors, in addition to that basal forebrain cholinergic neurons have been reported to be abnormally large and surplus [102]. A postmortem investigation of parietal neocortex showed reduced number of neuronal α-4 and β-2 nicotinic acetylcholine receptor (nAChR) subunit [103]. A while decreased cerebellar α-3/α-4 / β-2 nAChR ligand binding was detected, α-7 receptor subunit was exhibited compensatory increase [104].

Another study showed reduction in the expression of α-4 nAChR subunit in the frontal cortex whereas expression of α-4 nAChR subunit was found to increase in the cerebellum [105]. In another study, the α-7 nAChR subunit was determined to decreas especially in paraventricular nucleus and nucleus reuniens [106]. Postmortem samples taken from ASD individuals demonstrated significantly decreased α-7 receptor mRNA levels in frontal cortex [107]

Brain samples of cerebral cortex and basal forebrain choline acetyltransferase and acetylcholinesterase enzyme activity was measured, but no significant relationship was found with ASD. However, increased BDNF levels were detected which has affect on development and functions of cholinergic neurons in the basal forebrain [103]. Evidence of relationship between ASD and cholinergic circuits is still weak. Therefore extensive research in this area are needed.

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Chapter 3

Structural and Functional Brain Imaging in Autism Spectrum Disorders

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Additional information is available at the end of the chapter

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1. Introduction

Damasio and Maurer (1978) proposed that autism occurs due to structural and functional abnormalities at mesolimbic (dopaminergic) brain areas (ventromedial prefrontal cortex, medial temporal lobes, limbic striatum and thalamus), as damage to these brain regions can cause features of autism (impaired social and emotional functioning, stereotyped behaviours, mannerisms and obsessionality) [1]. This hypothesis is supported by studies in animals and human [2]. Areas outside the limbic system, such as the parietal lobes, are associated with autism. The lack of attention about understanding significant social cues in autism is similar to negligence and attention deficiency in the parietal lobe damage [3]. In addition to structural abnormalities in the cerebellum, another aetiological factor associated with autism is functional deterioration in cerebellar-cortical serotonergic pathways due to acquired cerebellar lesions, which can lead to impairment in social and emotional behaviour and impairment in executive functions and obsessions [4]. Brain imaging techniques are used in the investigation of these proposed structural and functional changes within autistic spectrum disorders.

2. Magnetic Resonance Imaging (MRI) studies

2.1. Head circumference and total brain volume

Atypical head circumference growth curve in the first two years of life is a phenotypical risk indicator for autism [5, 6]. In the case of autism, head circumference that is normal or near normal size at birth follows an accelerated growth pattern at about four months [7, 8]. It has been shown that 37% of autistic children between the ages of two and four meet the criteria for developmental macrocephaly [9].

In a follow-up study by Dawson et al. [2007], involving 28 children with autism from birth up to 36 months, has been shown accelerated growth of head circumference and previous studies have indicated that repeatedly [7]. This head circumference growth pattern occurs independently from autistic regression [10]. In autism, head circumference growth rate has been compared to the period from birth to 12 months; after the 12th month, these findings shows that unusually rapid head growth is limited to the 1st year of life [11]. Many studies have shown that the behavioural symptoms of autism become easily understandable during the first eight- to 12 months. [12, 13]. Therefore, the onset of accelerated head circumference growth between four- and 12 months partially leads to significant behavioural symptoms and an overlap between these symptoms. Interestingly, Dawson et al. reported a slowdown in the rate of head circumference growth in the next 12 months to be associated with a loss of or deceleration in the acquisition of new skills. Another study [7] reported that rapid growth in head circumference between birth and the 12-month period, followed by a slowdown in growth after 12 months to be a risk indicator for the development of autism symptoms at 24. months [14].

Magnetic resonance imaging (MRI) is used in order to measure the size and shape of brain structures. The results of research conducted using the MRI method has been consistent with results yielded by head circumference studies in terms of autism. Sparks et al. (2002) reported that children aged three to four with autism had a significantly larger total brain volume compared to normally developing peers or developmental delayed peers [15]. Another study [16] showed that 90% of children with autism spectrum disorders aged between two and four had larger brain volumes than usual. Using the MRI method, the size of the brain among autistic children aged between one-and-a-half and four years old was shown to be abnormally increased (about 5-10%) [8, 15, 16]. Courchesne et al. [16] proposed that an increase in brain volume among children with autism in younger age groups tended to decrease front-to-back (maximum at the frontal lobe, with the occipital lobe growth showing the least). However, it has not been clearly determined whether the growth pattern of young children (four years old) is permanent or not among older children and adolescents [16, 17]. It has been found that brain size in autistic children at birth was 13% smaller than the control group, reached a 10% larger size at the age of one and was at the onset of puberty only 2% larger than the control group; these results were obtained by Redcay and Courchesne [6] following the evaluation of head circumference and brain weight using MRI brain volume and autopsy studies. It has been reported that in a large proportion of individuals with autism in adulthood, the brain volume did not differ from healthy controls [6].

The hypothesis has been put forward that unusual brain growth curves lead to an abnormal pattern of changes in cortico-cortical connections. Changes in the brain during development adversely affect the development and persistence of growth curves among short-and long-haul connections. It has been suggested that the growth rate of brain size is less than the normal rate where developmental disorders are concerned, which leads to an increase in long-haul connections. Moreover, if brain size is larger than normal in developmental disorders such as autism, leads to a reduction in long-distance structural and functional connections [18].

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2.2. White and grey matter changes

Abnormal brain growth in autistic children primarily stems from cerebral white and grey matter. However, Herbert and colleagues asserted that this growth originates from the disproportionate increase of white matter, not grey matter [19]. Abnormalities in white matter volume can be linked to differences in axonal density and organization, myelination abnormalities or the abnormal proliferation of glial cells [20]. In two different studies with autistic children (between one-and-a-half and four years old) has been shown to significantly increase white matter rather than grey matter [8, 16]. However, it is not clear whether this increase in older children and adolescents is permanent or not [21, 22]. Even though the growth rate of grey matter has been shown to be smaller than that of white matter in early life, it is reported to be persistent in adulthood [16, 21].

Diffusion tensor imaging (DTI), also called diffusion tensor magnetic resonance imaging (DT-MRI) is a method used to assess the integrity of white brain matter. One of the parameters determined by this method, which identifies the movement of water molecules in the brain, is fractional anisotropy, which reflects asymmetry in fluid movement [23]. High fractional anisotropy values reflect a more intense or more proper structure of the brain. Two separate studies in children and adults with autism have shown a decrease in cerebral white matter using fractional anisotropy. A decrease in the temporal cortex among adults with autism has also been indicated using fractional anisotropy [24], as well as on the ventromedial prefrontal cortex, anterior cingulate, temporal lobe, amygdala and cortical and along subcortical regions containing the corpus callosum in autistic children and adolescents [25]. The most consistent findings concerning decreases in the brain using fractional anisotropy has been found for the corpus callosum [25, 26]. In another study, a 14% reduction in the size of the corpus callosum was shown, which is associated with decreased fractional anisotropy on genu and splenium [27]. In contrast to these findings, Ben-Bashat et al. [28] observed an association between increased fractional anisotropy values and white matter maturity in autistic children at younger ages. These findings have been associated with abnormal increases in brain volume during the early ages of children with autism [28].

A reduction in fractional anisotropy alongside an increase in white matter volume may reflect abnormal connections in the form of increased non-myelinated white matter connectivity. Extremism in the weak links due to the activity of immature myelination may adversely affect information processing. A decrease in white matter integrity reduces the brain's functional integration, a factor that has served as a basis of current theories about abnormal connections [20].

Recently, corpus callosum abnormalities have been associated with the theory of insufficient common functional connectivity (underconnectivity) in adults with autism [29]. Functional brain imaging studies have shown a decrease in the activation of the synchronization of many brain regions concerning different functions like social content interpretation [30], working memory [31], executive functions [29] and visual imagery [32]. These findings have led to the hypothesis that insufficient cortical connections may be associated with autistic disorders [33]. The reduction of white matter structural integrity in the context of autism may cause differences in functional connectivity, while theory of mind deficits [34] within the autism context can potentially be responsible for weak central coherence as well as social and cognitive symptoms [26].

2.3. Cerebral cortex

The largest and most consistent increase has been reported for the frontal lobe, despite a grey and white matter increase having been in the frontal, temporal and parietal lobes in several studies [21, 35, 36]. In autism, there exists an opposite growth rate from the norm following the period of accelerated growth in cerebral and cerebellar regions. For example, it has been shown that frontal lobe grey and white matter volume increase by 19% at two- and four years of age and 46% between the ages of nine and 12 in normal children, while in autistic children, these rates are 1% and 14%, respectively [36, 37].

In autism, abnormal asymmetry patterns in the frontal and temporal regions associated with language have been observed. Herbert et al. has shown that lateral inferior frontal cortex language (Broca's area is associated with pars opercularis) has reverse asymmetry in children with autism. It has also been shown that autistic men have a 27% larger volume in the right side of the frontal language region, compared to controls' 17% larger volume on the left side of the frontal language region. In addition to these findings, planum temporal asymmetry has been reported to be fairly different between the two groups; autistic males showed a 25% left dominance, while this rate was only 5% for the control group. Differences in terms of right-sided symmetry at the supramarginal posterior gyrus have been identified between autistic (39% greater) and control groups (greater than 2%). Another asymmetry region is the posterior superior temporal cortex (greater at the right in controls) associated with Wernicke's area, although this is not statistically significant. Structural abnormalities like abnormal asymmetry observed in autistic males in language regions may be associated with abnormalities in language skills [38].

2.4. Cerebellum

The cerebellum plays a role on coordination between voluntary movements and complex movements. Data obtained from animal and human studies have shown that the cerebellum may play a role in cognitive processes, in language use and emotion [39, 40]. Several MRI studies have determined that when autistic patients in different age groups are compared with a control group, there is a significant increase in cerebellar volume. This increase in cerebellar volume function is usually proportional to the total brain volume [41]. Different from other studies, in a study with autistic children below the age of three (18-35 months), there was no difference in terms of cerebellum size [8]. In contrast to the increase in the total volume of the cerebellum, some autistic children showed a relatively small volume vermis [42, 43]. Specifically cerebellum region is vermian lobules VI-VII that reported about volume reduction in autism [16]. Vermis hypoplasia in autism is associated with deficits in automatically attention directing and research behaviour. [37]. Courchesne et al. [44] suggest that autistic disorders have two subtypes associated with cerebellum pathology: [1] vermis hypoplasia and [2] vermis hyperplasia [44]. However, no differences have been reported concerning IQ levels being affected by vermal volume in different study groups matched for intelligence quotient (IQ) [45]. In addition, it has been suggested that increases in the volume of the frontal lobe is associated with a reduction in cerebellar vermis volume. It has been shown that patients with normal vermis volume have normal frontal cortex volume, while patients with vermis

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hypoplasia have greater frontal cortex volume. Abnormal neuronal signals from subcortical structures can affect the development of the cerebral cortex and increased neuronal activity can in this way lead to growth among neuronal elements. Therefore, it has been claimed that abnormal neuronal activity in the cerebelloretinal-thalamocortical projections (possibly associated with a reduction in inhibitor signals as a result of the premature reduction in the number of cerebellar Purkinje cells) can lead to developmental failure in the frontal lobe and in the other input regions [37]. These volume changes are not specific to autism and are also commonly found in various developmental and psychiatric disorders [43, 46]. In autism, hypoplasia at the structure of the brain stem has been identified by Hashimoto et al. [47] in a study that evaluated cerebellum and brain stem structures.

2.5. Amygdala

Amygdala volume shows an increase in proportion to the total cerebral volume in children with autism. Sparks et al. [15] found that autistic children (aged between 36-56 months) had an abnormal amygdala growth rate (13-16%). It has been reported that an increased amygdala volume (without increasing total cerebral volume) at three years of age is associated with severe progress in children aged between three and six years old [48]. An increase in amygdala volume has been associated with more severe anxiety [49] and with poor communication skills and social skills [48]. In a study with autistic males aged between the eight and 18 compared with a healthy control group, , it was found that amygdala volume had grown up to 15% between 8-12 age period, but in the period between the ages of 13-18 were found to be any difference at the amygdale volume. Amygdala volume among men with healthy development increased by about 40% between the ages of eight and 18; however, this was not the same for males with autism. These findings are important for the realization of amygdala volume initially being larger than normal in autistic children, and also important for indicate that autistic children have not age-related increase at amydala volume in the preadolescence period like healthy controls [50]. These findings are supported by some MRI studies, including those pertaining to autistic adolescents and adults where results showed an amygdala volume not significantly different or smaller [51] than those in control groups. It has been suggested that amygdala abnormalities in autism spectrum disorders play a central role in social symptoms [52].

2.6. Hippocampus

In autism, findings are contradictory regarding hippocampal volume. A MRI study by Schumann et al [50] showed that autistic children had an increase of hippocampal volume and this increase persisted during adolescence. A study that included autistic adolescents and young adults reported a decrease in hippocampal volume [51]. Where autism is concerned, various studies have shown no significant differences in hippocampal volume [53, 54].

2.7. Corpus callosum

The corpus callosum is responsible for transferring cortical and subcortical information between homologous regions of the cerebral hemisphere. It is associated with bilateral sensory

and motor integration such as bimanual motor coordination, visual attention scrolling and procedural memory processes. In autism, especially in the posterior region of the corpus callosum, a volume decline was noted in [55]. These findings are associated with interhemispheric weakness in autism [20].

2.8. Caudate nucleus

It has been shown that the caudate nucleus volume is increased in autism. This increase may be associated with observed repetitive and ritualistic behaviour in adolescents and adults with autism [56, 57].

3. MR Spectroscopy (MRS) studies

MRS techniques are used to distinguish between patients with active neurodegenerative process. N-acetyl groups, bearing phospholipids, choline, creatine (Cr), phosphocreatine, lipid and lactate levels can be measured by proton MRS. N-acetyl aspartate (NAA) is a marker of neuronal integrity and lower NAA/Cr ratio is associated with neuronal loss or damage. Choline reflects the integrity of cell membranes and increased levels of choline or choline/Cr ratio indicate increased cell destruction, the destruction of myelin, gliosis or inflammation. Creatine is sometimes used as a standard for relatively fixed elements of cellular energy metabolism in the brain. Creatine signals reflect glial and neuronal cell density. Myo-inositol plays a role in neuronal homeostasis [58].

It has been determined that NAA, creatine and myo-inositol concentration decrease significantly in children with autism spectrum disorders between the ages of three and four [59]. In several studies, it has been shown that NAA concentrations significantly decreased in the amygdaloid-hippocampal region, cerebellum and Brodmann's [41-42] areas (primary auditory area) in children and adults with autism [60, 61]. These findings can be associated with neuronal loss or functional immaturity in these regions, which play an important role in cognitive and emotional processes [60].

Levitt and colleagues [62], in a study involving autistic children, showed that choline and creatine levels increased in the head of the right caudate nucleus, while choline levels decreased in the left inferior anterior cingulate cortex. In the same study, decreased levels of creatine were found in the left body portion of the nucleus caudatus and right occipital cortex. These findings were associated with changes in membrane metabolism and energy metabolism in these regions. In a different study, NAA and glutamate/glutamine (Glx) levels were found to be significantly decreased on the grey matter which involves many cerebral lobes in a common area. at children with autism. These findings have been associated with neuronal integrity and dysfunction, which spreads over a wide area at glutamatergic neurons in autistic children [63]. In some MRS studies, no significant changes have been found in metabolite levels in white matter [63, 64].

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Vasconcelos et al. [65] reported that myo-inositol and choline levels were increased in the anterior cingulate cortex and left striatum, in contrast with previous studies that reported no significant changes in NAA levels.

When evaluated, these molecular indicators, amendments and increased white and grey matter volume have been believed to reflect changes in a) the number and size of neurons and glia; b) in the development of axons, dendrites and synapses; c) axodendritic pruning; d) programmed cell death; e) the occurrence of the cortical column; f) changes in myelination [66].

4. PET and SPECT studies

In the context of autism, functional neuroimaging studies were performed at rest or during various activities. Injected or inhaled radiopharmaceuticals were applied in positron emission tomography (PET) methods. Dissolved radioactive isotopes emit positrons that are detected by the PET camera. Some PET methods measure blood flow, while others measure cerebral metabolic rate [67].

In PET studies performed with autistic children at rest it has been determined that a decrease in blood flow occurred in the temporal lobes. Functional dysfunction in the temporal lobe was concentrated within the auditory associative cortex and superior temporal sulcus. Functional impairment in the auditory cortex of autistic children may explain initial diagnoses of going deaf and experiencing serious deterioration in communication. It has been suggested that functional deterioration in the superior temporal sulcus might explain emotional and cognitive components of autistic symptoms indirectly, due to these being closely linked with the frontoparietal and limbic regions of the multimodal association [68].

A PET scan study conducted with autistic adults found a wide increase in glucose utilization in the brain at rest [69]. Despite these findings, different results during the performance of different tasks have also been found. Haznedar et al. [70] reported a decrease in glucose metabolism in the anterior and posterior cingulate gyrus during a verbal learning test for autism and Asperger's syndrome [70]. Similarly, in a different PET study, it a decrease in relative glucose metabolism was determined for frontal lobe medial/cingulate areas during verbal memory operations. The same study showed an increase in relative glucose metabolism for the occipital and parietal regions [71].

Neuronal activation areas associated with auditory cortical processing was also examined using the PET method. In a study by Boddaert et al. [72], activation in the superior temporal gyrus was observed while listening to the complex speech-like sounds of adults with autism, which was similar to the control group [72]. However, while this activation was observed for the right superior temporal gyrus in the autistic group, the opposite pattern was observed in the control group. It has been shown that although there is less activation at the left temporal areas, there is pronounced activation patterns at the right middle frontal gyrus among autistic individuals [73]. In a different study involving children with autism, lower activation patterns in the left superior temporal gyrus (in fields related with auditory) have been identified when

listening to speech-like sounds, similar to what was found for adults. According to these findings, it is suggested that abnormalities in auditory cortical processing are associated with defects in language skills and that they result in a poor response to the voice among those with autism [72].

A PET scan study with high functioning autistic adults which practiced during instruction the tasks of theory of mind identified decreased activity in the medial prefrontal cortex, bilateral superior temporal sulcus and basal temporal area (right temporal tip and left fusiform gyrus adjacent to the amygdala), which are components of the mentalization network [30].

In several PET studies, the association between neurotransmitter systems and autism has been investigated. In a PET study with autistic children, Nakamura et al. [74] showed a reduction in the binding capacity of serotonin transporter protein throughout the entire brain. In autistic individuals, decreased serotonin transporter protein binding capacity in the anterior and posterior cingulate cortex has been associated with deterioration in social cognition, similar to decreased serotonin transporter protein binding capacity in the thalamus being associated with recurrent and obsessive behaviours. It has also been reported that dopamine transporter protein (the dopamine transporter = DAT) binding correlates in the opposite direction with serotonin transporter binding protein in the orbitofrontal cortex. These findings support the relationship between autism and serotonergic/dopaminergic systems.

The single-photon emission tomography (SPECT) method provides information on regional cerebral blood flow and provides a cerebral blood flow map according to the regional cerebral glucose metabolism of the brain. A decrease in regional cerebral blood flow reflects hypometabolism and consequently reflects damage in brain functions [75].

In accordance with several PET studies, reduced regional blood flow in the temporal cortex [76, 77, 78], frontal cortex [76], parietal cortex [77], occipital cortex, thalamus, basal ganglia [79] and cerebellar hemisphere [80] has been observed in SPECT studies with autistic children and adults. In a study of children and adolescents with high-functioning autism, evidence has been provided that the presence of abnormal neuronal network lateralization. In this study, it has been found lower blood flow at the right angular region than left angular region and also lower blood flow at left pericallosal, thalamic and hippocampal regions than right pericallosal, thalamic and hippocampal regions [81].

A decrease in regional cerebral blood flow in the bilateral insula, superior temporal gyrus and left prefrontal cortex has been reported by Ohnishi et al. in a SPECT study with autistic children. Autistic symptoms are associated with perfusion patterns at the limbic system and the medial prefrontal cortex. In this SPECT study by Ohnishi et al., support is provided for impairments in communication and social interaction that is thought to be related to the theory of mind deficits associated with perfusion changes in the medial prefrontal cortex and anterior cingulate gyrus, as well as the obsessive desire for sameness, which is associated with the right medial temporal lobe. Regional blood flow patterns are important in terms of indicating the possible location of abnormalities in brain function that underlie abnormal behaviour within the context of autism [82].

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A SPECT study that investigated the relationship between neurotransmitter systems and autism showed a reduction of serotonin transporter protein binding capacity in the medial frontal cortex in accordance with PET studies in this area; however, DAT binding capacity did not differ in autistic individuals [83].

5. Functional MRI (fMRI) studies

According to the SPECT and PET methods, the fMRI method has superior spatial and temporal resolution, is not an invasive procedure and does not involve ionizing radiation [67].

Autistic individuals have corrupted cognitive processing, both in a self-referential and other-referential context. Lombardo et al. recently conducted an fMRI study focusing on when autistic disorder adults made reflective "mentalizing" (reflective mentalizing) or physical judgments about themselves or the Queen of England. In another recent study, healthy individuals were compared to autistic patients for self-other reference tasking. The results revealed that autistic patients responded more to other mentalization as opposed to self-referential mentalization at the middle cingulate cortex, while these two operations respond equally at the ventromedial prefrontal cortex [84]. This finding is consistent with earlier study results that reported decreased activity in the middle cingulate cortex while high-functioning autism making their decisions the social condition [85]. These atypical responses only occur in areas that primarily process self-knowledge and do not affect the area that primarily responds to other-referential information. The neural self-other distinction at the ventromedial prefrontal cortex is closely associated with the degree of social impairment in autism in early childhood. It has been shown that individuals whose ventromedial prefrontal cortex can make the obvious distinction between self- and other mentalizing have had the least social disruption during early childhood, while individuals whose ventromedial prefrontal cortex makes little/any distinction between self- and other mentalizing are more likely to have experienced maximum social disruption during early childhood. These findings are important in terms of showing the atypical organization of neural circuits, primarily in self-information encoding, in the context of autism [84].

Brain regions such as the medial prefrontal cortex, rostral anterior cingulate, posterior cingulate and the precuneus have high metabolic activity during resting states. Internally managed processes (self-trial thought and higher-level social and emotional processes) continuously activate the medial cortical network, which includes the medial prefrontal cortex, rostral anterior cingulate, posterior cingulate and precuneus. This metabolic activity is suppressed during tasks that require cognitive effort. The suppression during activity, which is observed as "deactivations" using the fMRI method, is indicative of interrupted mental activity during rest. Kennedy et al. [86] showed that this deactivation does not appear in autistic individuals. These findings have been associated with the absence or abnormal mental processes in autism. The absence of this deactivation in autism has shown abnormalities in internally managed process and these findings have been suggested to be associated with social and emotional deficits regarding autism.

Individuals with autistic disorders and Asperger's syndrome experience abnormalities in the perception of faces. It has been shown that healthy individuals have increased activation in the fusiform gyrus during face processing and increased activation in the inferior temporal gyrus during processing object activation, while individuals with autistic disorders or Asperger's syndrome have less activation in the right fusiform gyrus and more activation during face discrimination (this is not the case for objects). The autism group tends to use more of the inferior temporal gyrus during face processing when compared to controls. This finding shows that they process faces like objects [87]. The basic zone associated with face processing in healthy individuals is the lateral fusiform gyrus (called as "fusiform face area"). It has been reported to decrease activation in the fusiform gyrus and other areas associated with processing face detection such as the inferior occipital gyrus, superior temporal gyrus and amygdala in individuals with autism during face detection tasks. It has also been reported that autistic individuals use different neuronal systems for seeing faces and have individual-specific, scattered activation patterns when compared to normal individuals [88].

In a fMRI study with high-function autistic adults, detected decreased activation in the fusiform gyrus during the identification of the person who has been seen before, in contrast to previous studies. Social dysfunction in autism has been associated with common abnormalities observed in the social brain network. The severity of impairment in social functioning is associated with a reduction in the connections between fusiform face area and amygdala and also increment in the connections between fusiform face area and right inferior frontal cortex.. This result indicates neuronal abnormalities in the limbic system to be associated with a prevalence of poor social impairment in autism [89].

Neuronal activation fields associated with working memory have been studied using fMRI methods. Luna et al. [90] reported lower activation in the dorsolateral prefrontal cortex and posterior cingulate regions during spatial working memory. Koshino et al. [91] showed that autistic individuals had lower activation in the inferior left prefrontal area (verbal processing and working memory-related) and right posterior temporal area (associated with theory of mind) during a working memory task that used photographic facial stimuli. The same study noted activation in the different division of the fusiform area in autistic individuals. It has also been shown that fusiform activation is in the lower and lateral division and also displaced from the typical region activated during face detection, compared to the region activated during object detection in an autistic group. These findings support the notion that face processing in autism analyse face characteristics as an object in terms of humanitarian significance. Abnormal fusiform activation showing a lower-level link with the frontal area is associated with the presence of the neuronal communication network, which has reduced synchronization [91].

A study conducted by Müller et al. [92] determined activation on opposite sides of the primary sensorimotor (the most powerful) cortex, premotor and/or supplementary motor areas during a simple finger movement task completed by healthy individuals in contrast, autistic groups showed no significant activation. [92]. Autistic individuals showed activation in regions that are not associated with these tasks, e.g., the superior parietal lobe and posterior neuronal precuneus.

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Over time, neural outputs decrease in response to recurrent stimuli. This adaptation is believed to be associated with plasticity and learning. In the case of autism, it has been shown that there is no neural adaptation in the amygdala in response to neutral facial stimuli. In the case of autism, abnormal sustained amygdala stimulation in response to social stimuli is believed to be associated with social disruption, as observed in [89] (activation levels in the amygdala never reach the maximum level in healthy individuals).

The mirror neuron system (the pars opercularis in the inferior frontal gyrus) is active during observation, imitation and understanding the actions of others. Therefore, it is considered to provide a neuronal mechanism for a complete understanding of the purpose and actions of others. When on the move, along with the limbic system, it is thought to mediate an understanding of emotions or facilitating sympathy with someone else's feelings. Thus, the feelings of others are perceived as real and not simply at a cognitive level, but understood at an emotional level (empathy). It has been shown that there is no activation of mirror neurons on the pars opercularis during the observation or imitation of emotional expression in children with autism. Activation in this region is inversely proportional to the severity of the symptoms shown. Early functional defects that emerge in the mirror neuron system have been suggested as the primary cause of social and emotional deficits in autistic disorders [93].

In FMRI studies with autistic individuals, a significant reduction has been revealed in the timing of the activation or synchronization between cortical areas associated with memory functioning, language, problem solving and social cognition. These findings support the hypothesis referred to as "insufficient functional connectivity" (underconnectivity) within and between neocortical systems [93].

6. Conclusion

In autism, common neuroanatomical defects in the early stages of brain development such as hypoplasia at specific areas and excessive cerebral growth leads to abnormalities in the development of functional systems. If the developing brain is traumatized by genetic or environmental factors, the functional organization and hence, functional activities, are disrupted. Abnormal functional activity and organization affect different structures in different ways, because autism is associated with neural defects in many types and locations. Many structures that have been shown as affected by autism can in turn affect the different functional areas of cerebral and cerebellar organization, as these structures function as intermediaries for the development of different types of neural defects. Therefore, more obvious abnormalities have been observed in some functions [94].

Functional imaging studies pose various limitations, for example, these studies include patients with autism and Asperger's syndrome together so study groups have heterogeneous diagnostic measurement. It is proposed that in future studies, working groups can be created to be a homogeneous diagnostic measurement comprised of different age groups and different levels of mental development when testing different tasks.

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Chapter 4

Coping Strategies and Parents' Positive Perceptions of Raising a Child with Autism Spectrum Disorders

Encarnación Sarriá and Pilar Pozo

Additional information is available at the end of the chapter

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1. Introduction

Autism spectrum disorder (ASD) is a developmental disorder of organic origin characterised by impairment and deficits in social interaction and communication as well as repetitive and restricted patterns of behaviour [1]. ASD can manifest with very different degrees of severity, but most children with autism have special needs in all aspects of their development and in all contexts. Associated problems such as intellectual deficit, sensory issues, problems with eating and sleeping and behavioural problems are also common in ASD and may cause as much impairment as the core features of the disorder [2-5].

Therefore, autism is considered one of the developmental disorders that has the greatest impact on the family. Raising and caring for a child with autism is a daunting and permanent challenge for parents and primary caregivers. Parents often need to adapt their professional lives and relationships in order to find appropriate solutions that are suited to the specific needs of their child [6]. A large number of studies have consistently found that parents of children with ASD have higher levels of stress, anxiety and depression than parents of typically developed children or children with other disorders [7-13].

However, previous research also reports large differences in the adaptation of families to ASD. Despite the difficulties of caring for a child with ASD, many families demonstrate resilience and achieve a good fit between the needs of the child with ASD and the needs of the other family members [14, 15]. Various factors, including social support, the characteristics of the child with ASD, coping strategies and the perception of the problem may be involved in the family's adaptation to ASD and could explain the differences in degree of resilience. Social support (both formal and informal) appears to be a protective factor that relieves parental stress [16-19] and increases personal well-being and family quality of life [20-22]. With regard to the characteristics of children with ASD that relate to family stress, many studies suggest that behaviour

problems are the main predictor of parental stress rather than the severity of the disorder [23-28]. Parents' coping strategies also prove relevant. Parents who adopt coping strategies of active avoidance (denial, distraction and guilt) report more stress than do those who adopt positive and problem-focused strategies [29-32]. Parents' perceptions of the problem and how they define for themselves the state of their lives also appear to be significant predictors of parents' adaptation. A negative perception of the situation as a catastrophe and feelings of guilt about having caused their child's problems are main predictors of stress for parents of children with intellectual disabilities [33] and mothers with children with ASD [34], whereas positive perceptions or definitions of the situation as manageable, understandable and meaningful seem to protect families from stress and improve their welfare [7, 10, 22, 31, 35, 36].

However, very little is known about the nature and impact of positive perceptions of the situation, because of the dominance of research focused on the negative consequences of ASD. The positive orientation of research on the impact of disability on families with children with ASD and the study of the factors that explain parents' psychological well-being are very new and are progressing only slowly.

A review of the studies on this subject suggests that most research on the situation of parents of children with intellectual disabilities has focused on the analysis of the negative aspects (such as stress, anxiety or depression) and possible related factors [37, 38]. This negative perspective is even more evident in research focused on parents of children with ASD [39]. The idea that caring for a disabled child may have a positive influence on parents and families is not incorporated into the dominant trend in research.

Helf and Glidden [37] conducted a review of published research (between 1970 and 1990) on the adaptation of families of children with intellectual disabilities. Independent judges rated the degree of negativity or positivity reflected in the approach, method and discussion of research. They considered any reference to benefits the family or any of its members had experienced as a result of having a child with disabilities as positivity. Indicating that the family or its members had suffered negative consequences such as anxiety, depression, frustration, loss, illness, neuroticism, stress and others was considered an expression of negativity, particularly when these references were not balanced by the inclusion of positive concepts or reactions such as adequate coping, family strength, positive adjustment, recovery or reward. The study concluded that although there has been some decrease in the negativity in the study of family adjustment over the past 20 years of research (e.g., terms such as "disaster" or "permanent damage" present in the findings of studies in 1970s disappear in studies of 1980s and 1990s), this decrease has not been accompanied by a concomitant increase in positivity. The negative approach in studies on adjustment of families with a member with intellectual disabilities still dominated in the 1990s. According to Helfin and Glidden, "In the overwhelming majority of the articles reviewed, the authors failed to mention any positive outcomes of having a child with a developmental disability" [37, p. 461].

As these authors point out in the introduction to their work [37], and others [14, 40] also assume, various reasons may explain the predominance of studying the negative effects of

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having a child with a developmental disability. The influence of researchers with a clinical orientation whose fundamental experience is related to families with difficulties who look for their assistance, coupled with the challenges of applied research that must evaluate and justify an investment in resources and specific supports for these families, is strong. All of these reasons are honest and understandable, and the results of these studies have certainly provided great help in the form of psychological interventions and support for these families; however, these lines of research have also had some less-than-positive effects.

Research paradigms and interventions both reflect and influence each other. If we only focus on risks and problems and do not formulate hypotheses about family strengths and if we do not develop sensitive instruments for measuring positive experiences of families, we will hardly detect the existence of these strengths. As Antonovsky [40] stated over 20 years ago, if our research questions are formulated negatively and only ask about the negative, we are not very likely to find positive answers.

When research provides an opportunity to make the positive aspects of these situations manifest, those positive aspects become clear. Parents of children with disabilities do not dwell only on difficulties of caring for their children with special needs, but they also speak of the positive impact that having a child with a disability has on their personal growth and family cohesion [14, 41-48].

As Hastings and Taunt [42] reported in their review of research on positive perceptions of disability in the family, one of the first and most relevant documents in this regard is the report by Mullins [49]. Mullins analysed the content of 60 books written by parents of children with different disabilities. He found that parents report that their child's disability involves both strong demands and stress and enrichment and expansion of the meaning of their lives. These conclusions are borne out by a further analysis of texts produced by parents of children with disabilities by Hornby [50].

One of the most important studies on the positive contributions of children with disabilities to the family was conducted by Behr, Murphy and Summers [51]. This research was the basis for the construction of the four scales that make up the Kansas Inventory of Parental Perceptions (KIPP), which includes the specific assessment of positive contributions (Positive Contribution Survey). A qualitative analysis of interviews with 28 families led the researchers to generate a database of 206 items related to the perception of positive contributions that they pooled into 16 categories and five factors. A validation study with 1,262 families with disabled children showed new factors that were not identified in the previous phase. Thus, the Positive Contributions scale was formed, comprising 52 items corresponding to eight dimensions. Positive contributions were defined as a) learning through experience with special problems in life; b) happiness and fulfilment; c) personal strength and family closeness; d) understanding life's purposes; e) personal growth and maturity; f) awareness of future issues; g) expanded social network; g) career or job growth; and h) pride and cooperation. In a subsequent study that factor analysed this scale [52], these dimensions were grouped into three distinct factors of positive contributions that

have become a benchmark for future research: 1) happiness and fulfilment, 2) strength and family closeness, and 3) personal growth and maturity.

Kausar, Jevne and Sobsey [44] conducted a qualitative study of interviews with 19 parents of children with developmental disorders. Most parents reported that accompanying their disabled child throughout their life became a positive and empowering experience for their own lives. Parents reported that the birth of their child with disabilities led them to redefine their role as parents, giving them a new sense of strength and meaning. They also reported that having a positive approach (e.g., addressing their child's achievements and abilities rather than disabilities) increased their hope and determination to seek and find resources and solutions to better meet the needs of their child. The initial experience was described as a frustrating blow, but parents also described how, over time, this experience evolves into a fortress of personal growth and a new meaning of life. Hope appeared linked to a realistic acceptance of the conditions of their disabled child.

These findings about the positive evolution of parents in their perception of the impact of disability on themselves and their family are reaffirmed in the results of a longitudinal study [48]. This study found that while positive perceptions appeared earlier in mothers than in fathers, both parents converged over time in recognition of the positive impact of childhood disability on family life. Additionally, the study of Bayat [14] on the resilience of families with children with autism reported a positive evolution among most parents. This study suggested that a positive change of perspective occurs among parents two years after receiving their child's diagnosis of autism. This change makes them recognise within themselves a new sense of life and makes them more aware of difficulties and differences, stronger and more patient, and more appreciative of small pleasures in their life. The stories of parents in this study further demonstrate that they consider their child with disabilities to have been a source of cohesion and family unity.

This transformation of initial negative reactions into feelings of acceptance and strength and the joy and satisfaction that accompany witnessing their child's accomplishments [43] have been shown in other studies to support parents for the exercise of their role as caregivers Hastings et al. [52] found that positive perceptions of mothers of children with intellectual disabilities were associated with a restructuring of their coping strategies. The authors concluded that the perception of positive contributions can functions as a mechanism to cope with stress and the demands of raising a child with intellectual disabilities. Werner and Shulman [53] reported that giving a positive meaning to the care that parents give to their children, along with self-esteem and psychosocial support, plays a moderating role in the effect of the stigma of disability on psychological well-being for mothers of children with intellectual disability.

Although the findings are still scarce, the few studies we could find on the role of the perception of positive contributions to the psychological adaptation of parents of children with ASD also present suggestive evidence of the protective role of positive perceptions.

Kayfith, Gragg and Orr [54] analysed the relationship between positive experiences and parental stress in 23 pairs of mothers and fathers with school-aged children with ASD.

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While mothers reported more positive perceptions than fathers, these perceptions were negatively related to stress for both mothers and fathers. Data suggesting greater perceived positive contributions among mothers also appeared in a study using a sample from the Spanish population (24 fathers and 33 mothers of children with ASD) [55]. This study reported a negative relationship between perceived positive contributions and anxiety in mothers. Mothers who perceived more positive contributions of their child with ASD had lower levels of anxiety than did mothers who reported fewer perceived positive contributions.

Hastings et al. [56] attempted to identify possible predictors of perceived positive contributions in 41 pairs of parents of preschool children with autism. Their results indicated that mothers reported greater perceived positive contributions than fathers, and none of the characteristics of children evaluated in the study (symptoms of autism, behaviour problems and adaptive behaviours) proved to be a significant predictor of perceptions of positive contributions in fathers or mothers.

In summary, review of the literature allows us to state that research on the positive aspects of living with a child with intellectual disabilities in the family is still in the minority compared to the predominance of research focusing on the negative impact of disabilities. This shortage is even more striking in the case of specific studies on the impact of ASD and points to significant gaps in our knowledge about the role that positive contributions can play in supporting the psychological adjustment and emotional well-being of parents who face the challenge of living with a child with autism.

Another feature of the research in this area is that most of the studies are based on the responses of mothers, both because of mothers' greater availability and because mothers are often assumed to be the primary caregiver for children with disabilities [57]. While we accept that this assumption might be largely true, it is also necessary to note that fathers are generally more involved in raising their children in recent years than they were in previous generations. Many studies found that mothers have higher levels of stress than fathers [3, 58-61], but some recent studies have detected comparable levels of anxiety [30] and no differences in family quality of life [62, 63] among mothers and fathers of children with intellectual disabilities.

We consider it important to include fathers as participants in studies on the impact of ASD in the family and recommend that they be represented with appropriately sized samples. As noted by other authors [64], possible discrepancies in the results from different studies comparing the psychological adjustment of mothers and fathers may be related not only to the historical timing of the research but also to methodological variability. In most comparative research, the number of fathers in the study is usually very small, both in absolute terms and in relative terms compared with the number of mothers.

Research on factors related to the psychological well-being of parents (mothers and fathers) who face the challenge of caring for a child with developmental disabilities is doubly important. A better understanding of the factors related to psychological well-being among parents would allow us to design guidelines for psychological support for families and

orientation guidelines for the different professionals involved in the care of the child. Parents themselves are worthy of the best and most effective psychological support that professionals can provide to promote parents' quality of life and well-being. Research has shown that parents can obtain significant benefit from psychological support to face the challenge of caring for their child with special needs [65-70]. It is also important to remember that the psychological well-being of parents affects the exercise of their parental role and, therefore, contributes to conditions that support the child's development and welfare [71, 72].

This review allows us to justify the pertinence of a study with the primary aim of analysing the relationship between parents' perceived positive contributions of raising a child with ASD and their psychological well-being and perception of family quality of life. The complexity of parents' psychological adaptation processes leads us to propose a complex design that include other variables to obtain the most comprehensive information about possible intervening factors, the relationship among these factors, and the relative position that positive contributions could have on predictive models of parental well-being. An *ex post facto* design was applied with a wide sample of parents of children diagnosed with ASD (127 mothers and 90 fathers) and the following study variables:

- Predictor variables: age of the child with ASD, behaviour problems, family income, parents' coping strategies, social support and perception of positive contributions
- Criterion variables: parents' psychological well-being and family quality of life.

Considering the results of the research reviewed above, the following hypotheses are formulated:

1. We expect some differences between mothers and fathers. Mothers will have higher levels of perceived positive contributions than fathers.

2. The perception of positive contributions will be related to psychological well-being and perceived family quality of life among the parents in the study. Higher levels of perceived positive contributions would correspond with higher levels of psychological well-being and family quality of life.

3. The perception of positive contributions will be a relevant predictor of the two criterion variables: psychological well-being and family quality of life.

2. Method

2.1. Participants

The sample used this research was composed of 217 parents of children diagnosed with ASD (127 mothers and 90 fathers). All of the parents spoke Spanish as their primary language. Participation was voluntary and kept confidential. The data presented in Table 1 indicate that mothers and fathers were similar in age, marital status and educational level.

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	% (n)	Mean (Standard Deviation)
Mothers (n = 127)		
Age (years) range 28-73		44.03 (8.5)
Education level		
Primary school	18.9 (24)	
Secondary school	29.9 (38)	
University	51.2 (65)	
Marital status		
Married	88.2 (112)	
Stabled couple	3.1 (4)	
Divorced	5.5 (7)	
Windowed	3.1 (4)	
Employment status		
Unemployed	43.3 (55)	
Employed	53.8 (67)	
Retired	3.9 (5)	
Fathers (n = 90)		
Age (years) range 32-78		46.05 (9.1)
Education level		
Primary school	17.8 (16)	
Secondary school	34.4 (31)	
University	47.8 (43)	
Marital status		
Married	94.4 (85)	
Stable couple	2.2 (2)	
Divorced	3.3 (3)	
Employment status		
Unemployed	2.2 (2)	
Employed	89.0 (81)	
Retired	7.8 (7)	

Table 1. Demographic information for parents

A significant difference appeared in employment (*chi square*=54.89, *p*=0.01), with 54% of the mothers and 89% of the fathers gainfully employed. Data on family composition with the frequency distribution according to number of members and household income are presented in Table 2.

Families (n = 137)	% (n)
Family composition	
2 members	4.4 (6)
3 members	25.5 (35)
4 members	51.8 (71)
5 members	15.6 (20)
6 members or more	3.7 (5)
Family incomes	
< 500 euros	10.9 (15)
500-850 euros	30.7 (42)
850-1200 euros	29.2 (40)
1200-1800 euros	18.2 (25)
1800-2000 euros	2.9 (4)
> 2000 euros	8.0 (11)

Table 2. Family composition and family income

Individuals with ASD (n = 137)	% (n)	Mean (SD)
Age (years) range 3-37		11.72 (8.36)
Gender		
Men	79.6 (109)	
Female	20.4 (28)	
Type ASD		
Autistic disorder	59.9 (82)	
Asperger's syndrome	4.4 (6)	
Rett's syndrome	5.8 (8)	
Disintegrative disorder	1.5 (2)	
PDD-NOS	27.7 (38)	
Education centre		
Ordinary school	43.0 (59)	
Special-education school	5.1 (7)	
Autism-specific school	38.0 (52)	
Day centre	13.9 (19)	

Note. SD=Standard Deviation; ASD=Autism Spectrum Disorders

PDD-NOS=Pervasive Developmental Disorder – Not Otherwise Specified

Table 3. Demographic information for individuals with ASD

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With regard to the characteristics of the individuals with ASD (N=137), it is important to note (see Table 3) the wide age range (3-37 years); the average of age was *M*=11.7 years, *SD*=8.36; 109 of the individuals with ASD were male and 28 were female. The main category of ASD among participants was Autistic Disorder (82), followed by PDD-NOS (38), Rett's Syndrome (8), Asperger's Syndrome (6) and Disintegrative Disorder (2). The criteria diagnoses correspond to the categories of DSM-IV-TR because the diagnoses were made before publication DSM-V (APA, 2013).

2.2. Procedure

Initially, the heads of schools were contacted and informed of the aims of the research through the psychologist responsible for the school counselling in the case of ordinary schools and through the Spanish Professional Association of Autism in the case of specific centres. Parents received a letter inviting them to participate in the study. Further instructions were sent with the questionnaires to the voluntary participants. Instructions highlighted the confidential nature of the data, the participants' right to abandon the research if desired and the requirement that questionnaires be completed individually, without discussion with their spouse. We relied on a non-probability sampling based on schools' accessibility to the researcher and individuals´ availability for participation (convenience sample). Parents participated by individually completing a set of questionnaires that they received either through the school or by e-mail, depending on their preference. A total of 217 parents (127 mothers and 90 fathers) completed the questionnaires.

2.3. Measures

Demographic information describing the parents, individuals with ASD and families was obtained through a brief questionnaire designed by the research team. Six questionnaires administered in Spanish evaluated the study variables. Two questionnaires—the *Brief Psychological Well-being* and the *Family Quality of Life Scale*—were previously adapted for Spanish by other authors. We translated the following measures into Spanish: the *Behaviour Problems Inventory,* the *Checklist of Support for Parents of the Handicapped,* the *Positive Contributions Scale* and the *Brief Coping Orientation of Problems Experienced.* We adopted the backtranslation technique to ensure translation accuracy. Two bilingual experts were invited to translate the Spanish versions back to English to correct differences between the two versions.

The *Behaviour Problems Inventory* (BPI; [73]), a 52-item scale, was used to assess the behaviour problems of individuals with ASD. Each item is scored on a 4-point severity scale ranging from 0 (no problem) to 3 (a severe problem). The BPI has three subscales: self-injurious, stereotyped and aggressive/destructive behaviour. The BPI has been found to be a reliable and valid rating instrument for behaviour problems in individuals with mental retardation and developmental disabilities [73]. The reliability in the original scale is high, with a Cronbach's alpha of.83 for the total scale. The internal consistency of the total scale in the present study was also high, with α=.89.

The *Checklist of Supports for Parents of the Handicapped* (CSPH; [74]) was used to evaluate the social support available to parents caring for a child with ASD. It is a 23-item rating scale that uses a 5-point item scale ranging from 0 (nothing useful) to 4 (very useful). The total score of the measure was used in this study. There is no information regarding the internal consistency of the original scale, but in the present study, Cronbach's alpha was.82.

The *Positive Contribution Scale of the Kansas Inventory of Parental Perceptions* (KIPP; [51]) was chosen to evaluate the positive feelings of parents towards the child with ASD. The KIPP is a 50-item rating scale that ranges from 1 (strongly disagree) to 4 (strongly agree). Higher scores are associated with greater awareness of the positive perceptions. We also used measures of three subscales: a) source of happiness and fulfilment subscale (six items) to represent positive feelings towards the child; b) source of personal growth and maturity subscale (seven items) to indicate positive impact upon the respondent; and c) source of strength and family closeness (seven items) to represent the positive impact upon the family. The alpha reliability for the original Positive Contribution Scale was.80. For the subscales, the alpha reliability ranged from.84 and.86, indicating good psychometric characteristics. In the present study, Cronbach's alpha for the total scale was.91, and for the subscales, the alpha ranged from.68 to.81.

The *Brief Coping Orientation of Problems Experienced* (Brief-COPE; [75]; adapted to Spanish by [76]) was used to obtain information on coping strategies used by parents raising an individual with ASD. The Brief-COPE has 14 two-item subscales. Each item is rated in terms of how often the responder utilises a particular coping strategy as measured on a 4-point scale, where 0 represents "I have not been doing this at all" and 3 represents "I've been doing this a lot".

To reduce the number of strategies, we performed a principal component factor analysis following the methodology used by Hastings et al. [30]. The results showed that two factors explained 28% of the variance; the two factors included items from the original Brief-COPE sub-scales. Factor 1, which is named "positive and problem-focused coping strategies", includes thirteen items for active coping, planning, seeking instrumental and emotional social support, positive reframing, and humour (items 2, 5, 7, 10, 12, 14, 15, 17, 18, 19, 21, 23 and 28). Factor 2, which is named "active avoidance coping strategies", includes nine items (items 1, 3, 6, 8, 9, 16, 20(-), 24(-) and 26). Only the scores for these two factors were used in the current study. Reliability was good for the total scale (α=.77), positive and problem-focused coping strategies (α=.79), and active avoidance coping strategies (α=.71).

The *Brief Psychological Well-being Spanish Version* [77] is a brief version of the original Psychological Well-being Scale [78]. It is a 29-item scale with a 4-point item scale ranging from 1 (completely disagree) to 4 (completely agree). The 29 items are organised into six dimensions (self-acceptance, positive relations, autonomy, environmental mastery, purpose in life and personal growth). The measure of psychological well-being used in this study was the total score. The internal consistency of the brief version of the scale in the original study was good (α=.84). In the present study, Cronbach's alpha was.91.

The *Family Quality of Life Scale* (FQOL [79]; adapted for Spanish by [80] was used to assess parents' satisfaction with their family quality of life. This is a 25-item scale with five sub-scales (family interaction, emotional well-being, parenting, physical/material well-being and

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disability-related support). This scale has two different response formats: satisfaction and importance. We used the total score of satisfaction format in this study. The items are rated on a 5-point scale ranging from 1 (very dissatisfied) to 5 (very satisfied). Cronbach's alpha for the FQOL subscale rating of satisfaction was.94 in the original study and.95 in this study.

There were no missing values for the total scores of any of the scales. Missing values were limited to specific items of the questionnaires and were not always the same. The rates for all missing data were less than 1%. We applied average values derived from the existing values to fill in missing items. Comparative analysis between mothers and fathers were applied. Bivariate correlations and multiple regression analysis were performed separately for mothers and fathers. Data analysis was conducted using the SPSS 15 Program. The G* Power 3.1 program [81] was used to calculate the effect size.

3. Results

3.1. Comparative analysis between fathers and mothers

First, we were interested in exploring the data to know the average values of the variables that made up the study among both fathers and mothers. T-tests were applied to examine whether there were significant differences in the values of the variables between the two groups. The results of the comparisons of mean values are shown in Table 4.

As shown by the data in the table, we did not find significant differences between fathers and mothers in the perception of the severity of the behaviour problems presented by children with ASD. The same pattern was found with the social support total score and subscale scores (informal, formal, and informational). None of the criterion variables (psychological well-being and family quality of life) was found to be significantly different between the groups.

The study variables that showed significant differences between fathers and mothers were the positive contributions and coping strategies. In relation to the positive contributions that the child of ASD brings to the family, the data indicated that mothers perceive a higher amount of positive contributions than fathers (t (1, 215)=-2.97, p=.003; M=134.94, M=126.76, respectively). The same results were found with the subscale of strength and family closeness (t *(1, 215)*=-3.18; p=.002; M=21.84 for mothers, M=20.20 for fathers). The effect sizes of the differences were Cohen's d=.41, and.44 for the total scale and subscale scores, respectively.

With regard to coping strategies, t-tests showed that mothers reported higher use of both strategies: positive and problem-focused coping strategies (t (1, 215)=-3.50; p=.001; M=17.76 for mothers, M=15.14 for fathers; Cohen's d*=.49*) and active avoidance coping (t (1, 215)=-3.18; p=. 05; M=3.67 for mothers, M=2.87 for fathers; Cohen's d=.27).

Another aspect of active avoidance strategies to note is that the average value obtained in both groups is very small (M=3.67 for mothers, M=2.87 for fathers) because the potential range that this variable can reach is 0-21. These data indicate the limited use of this type of strategy for dealing with situations that arise in everyday life.

Variables	Fathers (n = 90)		Mothers (n = 127)			
	Mean	*SD*	Mean	*SD*	*t (1, 215)*	Effect size (Cohen' d)
Behaviour problems	18.79	15.16	18.65	13.89	.68	
Social support	49.03	15.22	49.80	14.81	-.37	
Informal support	20.48	6.32	19.07	6.80	1.54	
Formal support	17.80	6.73	18.35	6.73	-.60	
Informational support	10.76	5.97	12.37	6.51	-1.86	
Positive contributions	126.76	20.47	134.94	19.53	-2.97**	.41
Happiness and fulfilment	17.53	3.69	18.35	3.60	-1.64	
Personal growth and maturity	17.69	4.60	18.54	4.56	-1.36	
Strength and family closeness	20.20	4.13	21.84	3.43	-3.18**	.44
Positive and problem-focused coping	15.14	4.96	17.76	5.71	-3.50**	.49
Active avoidance coping	2.87	2.76	3.67	3.07	-1.97*	.27
Psychological well-being	124.34	22.52	122.63	18.91	.61	
Family quality of life	85.97	18.12	87.60	15.75	-.71	

** $P < 0.01$, * $P < 0.05$

Table 4. Results of the comparisons of fathers and mothers' mean values on study variables

3.2. Correlations

Pearson correlations were used to explore bivariate associations between all of the variables considered. Correlations were calculated separately for fathers and mothers (see Tables 5a and 5b, respectively). The correlations results are described below.

The table data show that psychological well-being has a significant positive relationship with family quality of life in both parents (r=.49 for fathers; r=.54 for mothers). For both parents, psychological well-being was negatively associated with behaviour problems (r=-.38 for fathers; r=-.20 for mothers) and with active avoidance coping (r=-.51 for fathers; r=-.33 for mothers), and positively correlated with positive contributions (r=.27 for fathers; r=.37 for mothers). For fathers, we also found a positive relationship with family income (r=.21). In the case of mothers, psychological well-being was positively correlated with social support (r=.24) and positive and problem-focused coping strategies (r=.19).

For fathers and mothers, the family quality of life was negatively associated with behaviour problems (r=-.29, r=-.21, respectively) and active avoidance coping (r=-.23, r=-.33, respectively). Additionally, for both parents, family quality of life was positively associated with social support (r=.23, r=.23, respectively). Only in the case of mothers was family quality of life

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	1	2	3	4	5	6	7	8	9
1. Age of individuals with ASD	---								
2. Educational level	-.02	—							
3. Family income	.17	.29**	—						
4. Behaviour problems	-.11	-.11	-.17	—					
5. Social support	-.03	-.02	-.09	-.02	—				
6. Positive contributions	-.04	.01	.24*	-.22*	.25*	—			
7. Positive and problem-focused coping	-.28*	.22*	.12	.11	.17	.19	—		
8. Active avoidance coping	-.02	-.15	-.16	.33**	-.07	- .01	.10	—	
9. Psychological well-being	.06	.13	.21*	-.38**	.08	.27*	.02	-.51**	—
10 Family quality of life	.11	.15	.03	-.29**	.23*	.20	-.04	-.23*	.49**

(a)

	1	2	3	4	5	6	7	8	9
1. Age of individuals with ASD	—								
2. Educational level	-.18*	—							
3. Family income	.12	.26**	—						
4. Behaviour problems	-.12	-.12	-.22*	—					
5. Social support	.03	-.08	-.03	-.08	—				
6. Positive contributions	-.12	-.14	-.01	-.01	.24*	—			
7. Positive and problem-focused coping	-.13	.01	-.07	.22*	.11	.25**	—		
8. Active avoidance coping	.05	-.11	-.03	.23**	-.09	-.06	.10	—	
9. Psychological well-being	-.06	.12	.16	-.20*	.24**	.37**	.19*	-.38**	—
10. Family quality of life	-.09	.06	.05	-.21*	.23**	.31**	.21*	-.33**	.54**

(b)

** $P < 0.01$, * $P < 0.05$

Table 5. (a) Pearson correlation coefficients for total measures of study variables in fathers; (b) Pearson correlation coefficients for total measures of study variables in mothers

positively associated with positive contributions (*r*=.31) and positive and problem-focused coping (*r*=.21).

Next, we describe the relationship between predictor variables. Educational level was positively associated with family income (*r*=.29 for fathers; *r*=.26 for mothers), and social support was positively correlated with positive contributions (*r*=.25 for fathers; *r*=.24 for mothers). Only in mothers, the perception of severity of child's behaviour problems were negatively associated with family income (*r*=-.22) and positively associated with the two types of coping (*r*=.22 for positive and problem-focused coping; *r*=.23 for active avoidance coping). In the case of fathers, behaviour problems were negatively correlated with positive contributions (*r*=-.22), and positive contributions were positively associated with family income (*r*=.24).

We performed a more detailed analysis of the relationship between positive contributions (total and subscales) and the other variables included in the study. Correlations were calculated separately for fathers and mothers. The results are presented in Tables 6a and 6b, respectively.

	Total positive contributions	Happiness and fulfilment	Personal growth and maturity	Strength and family closeness
Age of individuals with ASD	-.04	-.31**	-.06	-.03
Educational level	.01	-.06	-.12	-.02
Family income	.24*	.23*	.25*	.23*
Behaviour problems	-.22*	-.20	-.07	-.12
Social support	.25*	.13	.06	.19
Positive and problem-focused coping	.19	.20	.17	.24*
Active avoidance coping	-.01	-.23*	-.07	-.06
Psychological well-being	.27*	.22*	.12	.29**
Family quality of life	.20	.11	-.04	.23*

(a)

	Total positive contributions	Happiness and fulfilment	Personal growth and maturity	Strength and family closeness
Age of individuals with ASD	-.12	-.32**	-.02	-.01
Educational level	-.13	-.04	-.26**	-.05
Family income	-.01	-.03	-.98	.05
Behaviour problems	-.01	-.14	.07	.04
Social support	.24**	.11	.13	.09
Positive and problem-focused coping	.25**	.18*	.22*	.25**
Active avoidance coping	-.06	-.18*	-0.12	-.16
Psychological well-being	.37**	.38**	.18*	.32**
Family quality of life	.31**	.35**	.16	.29**

(b)

** $P < 0.01$, * $P < 0.05$

Table 6. (a) Pearson correlation coefficients between positive contributions (total and subscales) and other study variables among fathers; (b) Pearson correlation coefficients between positive contributions (total and subscales) and other study variables among mothers

The correlations involving the total score on the positive contributions scale has already been described; here we describe only the findings related to the subscales. For both parents, the happiness and fulfilment subscale was positively correlated with psychological well-being (*r*=.

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22 for fathers; *r*=.38 for mothers), and negatively associated with age of the children (*r*=-.31 for fathers; *r*=-.32 for mothers) and active avoidance coping (*r*=-.23 for fathers; *r*=-.18 for mothers).

The strength and family closeness subscale was positively associated with three variables: psychological well-being (*r*=.29 for fathers; *r*=.32 for mothers), family quality of life (*r*=.23 for fathers; *r*=.29 for mothers) and positive and problem-focused coping (*r*=.24 for fathers; *r*=.25 for mothers).

In the case of fathers, family income was positively correlated with the three subscales (*r*=.23 for happiness and fulfilment; *r*=.25 personal growth and maturity; *r*=.23 for strength and family closeness). In the case of mothers, two subscales were positively associated with positive and problem-focused coping (*r*=.18 for happiness and fulfilment; *r*=.22 for personal growth and maturity), psychological well-being (*r*=.38 for happiness and fulfilment; *r*=.18 for personal growth and maturity), and family quality of life (*r*=.35 for happiness and fulfilment; *r*=.29 for strength and family closeness).

Having explored the correlation matrix of the variables, we next examined which variables predict psychological well-being and family quality of life. We performed a multiple regression analysis, as described below.

3.3. Regression

A stepwise forward selection multiple regression analysis was run to examine the predictor variables of psychological well-being and family quality of life. The analysis was carried out separately for fathers and mothers. We considered the age of children with ASD, behaviour problems, family income, social support, positive contributions and coping strategies (active avoidance coping and positive and problem-focused coping) as potential predictor variables. The null hypotheses tested were that multiple R^2 was equal to 0 and that the regression coefficients were equal to 0. The data were screened for violation of assumptions prior to analysis.

The results of the multiple regression analysis for psychological well-being are presented in Table 7. We used the adjusted R^2 index, which indicates the percentage of variation in the dependent variable explained after adjusting for sample size and the number of predictors.

The active avoidance coping strategies measure was the main explicative variable in the models for both mothers and fathers, accounting for a significant amount of the variance in psychological well-being (Δ adjusted R^2=.24 for fathers and.14 for mothers). Specifically, higher levels of active avoidance coping strategies predicted lower levels of psychological well-being (β=-.50, p <.001 for fathers and β=-.38, p <.001 for mothers). Positive contributions also accounted for a significant amount of the variance in psychological well-being (Δ adjusted R^2=.07 for fathers and.11 for mothers). In this case, higher levels of positive contributions predicted higher levels of psychological well-being (β=.26, p=.004 for fathers and β=.35, p <.001 for mothers). The regression model included a third predictive variable in the case of fathers, indicating that higher behaviour problems predicted lower fathers' psychological well-being (β=-.19, p=.049). The total adjusted R^2=.33 for the fathers' model indicated that these three variables accounted

Variables	adjusted R^2	Δ R^2	Degrees of freedom	*F*	β
Active avoidance coping	.24	.24	(1,87)	29.32**	-.50**
Positive contribution	.31	.07	(1,86)	20.47**	.26**
Behaviour problems	.33	.02	(1,85)	15.45**	-.19*
		(a)			
Variables	***adjusted R²***	**Δ R^2**	**Degrees of freedom**	***F***	**β**
Active avoidance coping	.14	.14	(1,125)	20.71**	-.38**
Positive contribution	.25	.11	(1,124)	22.00**	.35**
		(b)			

**p <.01; *p <.05

Table 7. (a) Regression analysis predicting psychological well-being in fathers' (b) Regression analysis predicting psychological well-being in mothers

for approximately 33% of the variation in psychological well-being among fathers. Interpreted according to [82], this value suggests a large effect size (^{2}=.49). In the case of mothers, the multiple adjusted R^2=.25 (^{2}=.33) indicated a medium effect size. Other variables proposed in the analysis such as age of children with ASD, family income, and social support were not included in the models, indicating that these variables do not account for a significant amount of variance in psychological well-being after including active avoidance coping strategies, positive contributions and behaviour problems.

Regression models of family quality of life are presented in Table 8. The fathers' model includes only behaviour problems and social support as predictor variables, and the total adjusted R^2=.11 (^{2}=.12) indicates a small effect size. Higher behaviour problems predicted lower perceived family quality of life (β=-.28, p=.007), and higher levels of social support predicted higher levels of family quality of life (β=.23, p=.027) among fathers.

In mothers, the regression model was more complex, with four predictors that could predict 23% of the variance of family quality of life (adjusted R^2=.23; ^{2}=.30), which suggests a medium effect size. The active avoidance coping strategies measure was the main variable explaining the variance in family quality of life among mothers (Δ adjusted R^2=.11). Behaviour problems also appeared as a predictor (Δ adjusted R^2=.02). Higher levels of active avoidance coping strategies and behaviour problems predicted lower levels of family quality of life (β=-.33, p <.001 and β=-.18, p=.027, respectively). Positive contributions and positive and problem-focused coping strategies accounted for a significant amount of the variance in mothers' reported family quality of life (Δ adjusted R^2=.04, Δ adjusted R^2=.05, respectively). Higher levels of positive contributions and positive and problem-focused coping strategies predicted higher levels of mothers' reported family quality of life (β=.29, p=.004 and β=.18, p=.011, respectively).

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Variables	*adjusted* R^2	Δ R^2	Degrees of freedom	*F*	β
Behaviour problems	.07	.07	(1,87)	7.63**	-.28**
Social support	.11	.04	(1,86)	6.53**	.23**

(a)

Variables	*adjusted* R^2	Δ R^2	Degrees of freedom	*F*	β
Active avoidance coping	.11	.11	(1,125)	15.73**	-.33**
Positive contributions	.16	.04	(1,124)	15.29**	.29**
Positive and problem-focused coping	.21	.05	(1,123)	11.98**	.18*
Behaviour problems	.23	.02	(1,122)	10.53**	-.18**

(b)

**p <.01; *p <.05

Table 8. (a) Regression analysis predicting family quality of life in fathers; (b) Regression analysis predicting family quality of life in mothers

The other variables proposed in the analysis (age of children with ASD and family income) were not included in the models.

4. Discussion

We conducted a study with the aim of analysing both the perception of positive contributions of disability in a large sample of Spanish parents with children with ASD and the impact of this positive perception on their well-being. The results confirm the relevance of the perception of positive contributions of disability for both parents and support its role as predictor of psychological well-being and family quality of life. Coping strategies also appear as a relevant factor, in relation to both the parents' well-being and their perception of positive contributions. The results also provide suggestive information on common and specific issues for fathers and mothers.

Comparative analysis of the values reported by fathers and mothers in terms of the different variables of the study inform us that both groups showed similar levels of psychological well-being, perceptions of family quality of life and social support. However, the results reported differences in coping strategies and perceptions of positive contributions, such that mothers had higher values than fathers. These results are consistent with the hypothesis that differences exist between fathers and mothers on these measures. The finding of greater perceived positive contributions among mothers is consistent with what has been detected in other studies [54-56]. However, providing an explanation for this result is not easy. One could pose an explanatory hypothesis based on gender characteristics, but one hypothesis to consider the

role of primary caregiver among mothers in most families may be more parsimonious. The role of primary caregiver can generate more everyday strain but may also provide more opportunities to experience personal growth and strength as positive contributions of their disabled child. The significant difference on the outside employment situation of fathers and mothers in our sample (89% and 54%, respectively) is a relevant fact that demonstrates the high probability that mothers were exercising the role of primary caregiver. In addition, this difference in employment status of parents of children with ASD is not unique to our sample and the social environment in which this study is carried out but instead seems to be a fairly widespread reality [83].

The results of the correlation analysis showed a positive relationship between the perception of positive contributions and psychological well-being among both fathers and mothers. That is, parents who perceived more positive contributions of their child's disability had higher levels of psychological well-being. In mothers, it also appeared that a positive relationship existed between perceived positive contributions and the perception of family quality of life. These results support the hypothesis that the positive relationship between perceived positive contributions and the perception of family quality of life exists, but it appeared only in the case of mothers. The positive relationship between positive contributions and psychological well-being found in this study is consistent with the results of other studies that found a negative relationship between perceived positive contributions and both paternal stress [54] and maternal anxiety [55] in parents of children with ASD.

It is pertinent to note the relationship between coping strategies and perceived positive contributions. More frequent use of active avoidance coping strategies had a negative relationship with the perception that the condition of their child contributed to their happiness and fulfilment among both fathers and mothers. Meanwhile, positive and problem-focused coping strategies were associated with the perception of positive contributions, particularly in the case of mothers. For fathers, only a positive relationship between positive and problem focused coping strategies and the subscale of strength and family closeness appeared, while in the case of mothers, this relationship was broader. Mothers who reported greater use of positive and problem-focused coping strategies reported also higher levels of perceived contributions not only in relation to the strength and closeness of the family but also in relation to more personal aspects such as happiness and fulfilment and personal growth and maturity.

The bidirectionality of these relationships makes it difficult to know whether the ability to perceive positive contributions has a positive effect on promoting the use of positive and problem-focused coping strategies or whether parents who resort to this type of coping strategy better perceive the positive contributions of their child to their life and the life of their family. It is also possible that a third variable, such as a psychological trait, could explain the covariation of these two factors. In any case, despite the difficulty of clarifying the direction of effects, this finding on the relationship between coping strategies and positive perceptions is important, to the extent that both factors were also expressed as predictors of psychological well-being and the family quality of life reported by parents. Both aspects could become the subject of future work in psychological intervention to support parents with potential mutual benefits and positive effects on parents' well-being.

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Active avoidance coping strategies appeared as the main predictor negatively related to psychological well-being in the regression models, both mothers and fathers. Positive and problem-focused coping strategies appeared as relevant predictor of family quality of life among mothers. This finding is consistent with the results of previous research on parental stress. Research examining the coping strategies used by parents to manage daily situations has demonstrated that parents who adopt active avoidance coping strategies report more stress than parents who adopt positive reframing coping strategies [29, 30]. Other studies show that, compared with parents of typically developing children, parents of children with ASD more frequently employ escape-avoidance coping strategies [84-86]. Therefore, it is important to help parents of children with ASD discover and implement positive coping strategies that can replace these avoidance coping strategies.

The results of the regression analyses are also consistent with the fundamental hypothesis of this study on the relevance of the perception of positive contributions as predictor of parental well-being. Another common result for both groups, mothers and fathers, was the detection of perceived positive contributions as the second most important predictor of parents' psychological well-being. The regression models of family quality of life also highlighted the role of positive contributions; however, in this case, this variable only appears as a relevant predictor in the model of mothers. Increases in the perception of positive contributions predicted increases in family quality of life. Inversely, behaviour problems of the child predicted lower family quality of life, both mothers and fathers.

Before considering the implications of the findings of this research, it is convenient to reflect on its limitations. The main limitation to note is the correlational and cross-sectional nature of the design and, therefore, the inability to determine the direction of effects in the relationships between variables. Although we assign and test the possible role of predictor variables when performing regression analysis and although some of the study results are significant and clear, we cannot rule out influences in the other direction. Perceived positive contributions appear in our results to have a predictive in increasing psychological well-being and family quality of life, but we cannot know to what extent the levels of parents' psychological well-being affect their ability to perceive positive contributions of disability. More research, especially longitudinal research, is required to advance knowledge of the direction of these effects.

In addition, it must be noted that this study is based on a sample of Spanish families. We must be aware that there are significant cultural differences in the understanding of disability and the dynamics of families and should therefore be cautious in generalising these results to other cultures.

5. Conclusions

Despite its limitations, this study contributes to a better understanding of the factors related to the psychological well-being of parents raising a child with ASD. A better understanding of these factors may guide the design of intervention strategies to promote parents' well-being. The empirical evidence supporting the importance of coping strategies and the perception of the positive contributions of disability for parental psychological well-being and their family

quality of life suggest the importance of awareness among professionals working with families. Parents of children with ASD are faced with many potential stressful situations. The challenges may change over the course of their children's lifespan. There is not only one pattern of coping that fits well for all of these stressful situations. The results of the current investigation show that active avoidance coping strategies may be maladaptative and may not contribute to parents' well-being. Professional interventions to help parents of children with ASD could include objectives oriented to provide them with a wide repertoire of emotional, cognitive and instrumental positive coping strategies and to develop the flexibility to implement the most appropriate strategy to address the situation at a given time. Moreover, helping parents in their processes of positive transformation, guiding them to pay attention to and learn to appreciate the achievements of their children and helping them discover their own personal and family strengths will contribute to their well-being.

We agree with Patterson [87] in her conclusion that clinicians who believe in the ability of the family to discover their strengths are in a much better position to enhance family resilience and facilitate the adaptive processes needed by the family to restore its functioning after a crisis situation. Believing in the ability of the family to discover their strengths and recognising their success in coping with stressful situations, whether large or small, empowers the family to cope effectively. The importance of paying attention to the positive aspects of the development of children and families it is not solely the responsibility of clinicians. Many professionals in very different roles (psychologists, medical, nurses, social workers and teachers) are involved in accompanying parents in caring for their child with ASD. In each moment of evaluation, monitoring or guidance to parents, professionals' ability to adopt, within their speciality, a perspective not only focused on the problem and the difficulties but also oriented toward the child's achievements and other positive aspects of his or her development and family's functioning can be critical to help parents develop strength and positive experiences.

Over the past few decades, we have been able to incorporate major changes related to the perception of people with disabilities. An increase in sensitivity has led to important legislative changes that recognise and promote rights aimed at improving the quality of life of people with intellectual disabilities and their families. There have been changes that affect aspects as simple as our language, such as changing the disorder-focused expression (e.g., disabled child or autistic child) to a person-focused expression (e.g., child with intellectual disabilities or child with autism or ASD) or changing patient consideration to the active participants, and some decisive other as inclusive education. Considering not only the problem and special needs of the child but also the positive contributions of people with disabilities to their environment, particularly to their family, is a necessary change in both research and practice. This change is just beginning to take hold, and much more work in practice and research is needed.

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Chapter 5

The Intertwining of Language Impairment and Autism Spectrum Disorders — Highlighting the Need of Long Term Interdisciplinary Collaboration

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Additional information is available at the end of the chapter

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1. Introduction

This chapter highlights the importance of adopting a broader as well as longer perspective in screening for problems of language and communication in children prospectively as well as in adults retrospectively. As coauthors we represent a wide range of professional experience covering different disciplines: speech and language pathology, pediatrics, child psychiatry and adult psychiatry. We have several years of experience of working in teams for assessment and diagnostics as well as of performing interventions for children, youth and adults with complex developmental disorders.

2. Language Impairment (LI) and Specific Language Impairment (SLI)

One of the most common worries in parents of young children concern their children's language and communication development and these are thus among the first aspects that parents as well as nurses at the Child Health Care (CHC) centers focus on in developmental screening procedures. Language delays are fairly common although there is a huge variation in typical early language development, in particular in expressive language, i.e. language production. Language impairment (LI) might be an early sign of a severe developmental disorder such as an intellectual disability and/or an autism spectrum disorder [36], although commonly it is only a question about problems of language development. Specific language impairment (SLI) is used as a diagnosis for markedly impaired expressive language when

nonverbal intelligence has been tested and found to be within the normal range and if there are no apparent sensory or neurological dysfunctions. As [38] points out, SLI is not used if there is an autism-related disorder, but [38] also comment on the fact that "a notable minority of individuals with SLI move across subtypes throughout development" (p. 944). These authors made a review of possible links between different language impairments and autism spectrum disorders and ended up with the recommendation to "concentrate on those aspects of language impairment that predominate in each disorder rather than on those comparatively small areas of potential overlap" (p. 944). There are also several, but rare genetic disorders that cause both problems with language acquisition and autistic traits. Therefore, children with language problems should always be evaluated broadly as [13] pointed out in his formulation of Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations, ESSENCE. The speech and language therapist have a central role in the teamwork that scaffolds families with preschool children. However, in line with the ESSENCE thinking, the team must include disciplines representing child development as well as clinical psychologists, physiotherapists and social workers. The team must have access to several other consultant services-child neurologists, child psychiatrists and sometimes even adult psychiatrists. The latter should preferably have experience of developmental disorders in adults, as parents sometimes realize that they have or have had similar problems as their children have.

In line with the ESSENCE thinking, the child is often presented to the pediatrician as a child with a delayed gross motor function, especially delayed walking ability, often before two years of age. It is of great importance for the pediatrician not only to analyze and possibly exclude any neurological pathology behind this, but also to, in collaboration with the physiotherapist, instruct the parents how to stimulate the child´s development of gross motor function during everyday activities. It is also important to assess the level of the child´s development in all aspects including language production as well as comprehension, vision and hearing ability and social interaction. As the parents often at the first visit mainly are aware of the child's gross motor function and language production, the child must be observed and the parents must be asked to describe the level of other abilities. It is highly recommended to see the child regularly during the following years in order to, by watchful expectancy, observe development in all functions and, in case of delays in any ability, to consult other specialists.

Language and communication problems occur in different disorders and vary in symptomatology. Language is a complex skill covering perception as well as production of language and comprises both structural aspects such as phonology, morphology, syntax, and functional aspects, such as use of language in different social contexts, often referred to as pragmatic skill or ability of social communication. Another language skill reflects the meaning of words, the content of language, both in order to understand and interpret, and to retrieve words in narration, a skill which has many labels, i.e. semantic, lexical or vocabulary skill. For these reasons language problems often tend to coexist and be intertwined with other problems, and furthermore they tend to be persistent over time [34] although there is a large heterogeneity of causes as well as symptomatology.

Expressive language problems often elicit early concerns in parents. One reason is that expressive language is fairly easy for parents to notice and possibly take notes of. Another

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reason is that parents tend to compare with the development of siblings and peers. However, language skills, in particular language production, not only reflect how far the child has developed language skills, but also his/her interests and personality, which all are revealed by how much s/he is engaged in a topic and talks.

Language comprehension skills, often referred to as receptive language skills, however, are most often identified indirectly, for example by misunderstandings or by the child notably not paying attention. A consequence of this might be that language comprehension problems neither early nor easily are detected in small children. Another reason why language comprehension problems tend to be ignored is that parents and those who know the child well intuitively facilitate for the child by sharing the same context with its referential objects, and thereby offer a redundancy of contextual information scaffolding the information given by words. Sometimes they almost "mind-read" the child and render the support the child needs in order to understand. This tendency to be "hidden" makes language comprehension problems particularly detrimental, especially since they are closely associated with generic learning skills with a long term negative effect on academic skills [6].

Another important aspect of language development is the ability to participate in social communication, often referred to as pragmatic skill. It is not easy for parents to neither describe nor evaluate the pragmatic skill of their children – the parents are themselves part of the communication and instinctively compensate the child in case of problems. For an early detection of pragmatic problems it is therefore necessary to ask teachers at preschool and school and use a questionnaire for example the Children's Communication Checklist [3], which focus on different aspects of social communication in a more neutral and descriptive way.

3. Autism Spectrum Disorders (ASD)

As described above, problems with social communication can, in children with language impairment, be either the main problem or a possible consequence of the weak and vulnerable language. To make the picture even more complex, communication problems are one of the core characteristics in autism spectrum disorders. Although less frequently occurring, problems with structural language, often recognized in specific language impairment, SLI, can also be seen in children with ASD, something that Williams, Botting and Boucher referred to as ASD-LI (2008). Cognitive, communication and language problems are commonly found to co-occur, although in different combinations and levels of severity, which reflects their nature of being complex and heterogeneous. Family studies that found a relation between genetic vulnerability to autism and language impairment revived the interest to more thoroughly study aspects of language in autism [35]. Diagnoses based on mainly communication and language problems are therefore difficult to discriminate and differentiate between [38]. Many trials have been performed with psychometric as well as language tests (i.e. [10]. When the concept of pragmatic language impairment was introduced [5], it became particularly tricky to delineate this kind of language impairment from autism spectrum disorder, in particular in individuals with average or high intellectual functioning. Furthermore these problems not

seldom change picture over time [11]. However, it is important to try to discriminate between different symptoms since they might require different types of intervention.

The parents may have worries and questions concerning long time prognosis for their child. When there is a severe developmental problem, as an autism spectrum disorder with intellectual disability, it is necessary to plan very well in advance for the child's transition into adulthood and adult services [17]. The complete puzzle is laid when child and youth psychiatrists, pediatricians, psychologists and speech and language therapist collaborate with adult psychiatrists. Also in adult patients it has been shown that those with developmental problems often had shown the ESSENCE deviances in childhood [31]. Persistent language problems have been shown in long-term follow-ups [12, 19, 24, 34]. [9] made a follow-up of children with developmental language disorders in later adult life and found severe literacy impairments as well as phonological processing problems. Furthermore, they reported unemployment and social problems, i.e. very few close friends.

The prognosis, or the functioning in adulthood is of course depending not only on the degree of communication difficulties, but also on several other factors. Foremost is the individual's general cognitive functioning, or IQ. An intellectual disability, at least in the range of moderate or severe, is generally accompanied by severe language and communication problems, especially in the many cases where there is also an autism spectrum disorder [29]. In these cases, the prognosis is poor, and the individual will need constant support, supervision and augmentative communication also in adult life [2, 26]. As Noens and Van Berckelaer-Onnes highlight, the comprehension problems, including the strong tendency to attend to details rather than, and instead of, "seeing the whole picture" is supposed to be at the core of the communication difficulties.

The same can be said about individuals with autism spectrum disorders and intellectual abilities within the normal range. Many authors have described the so-called weak central coherence as an autism-specific cognitive style, which causes dysfunction and impairment in most situations [15]. This is especially the case in social situations, where the quick and intuitive grasping of the whole situation and thus the meaning in the ongoing communication is essential. Even in cases with good over-all cognitive skills, adults with autism spectrum disorders find it difficult to find work and to keep up relationships [1, 14, 23] since their pragmatic communication skills are not on par with their intellectual level. It can be speculated that the communication difficulties contribute to the vulnerability to psychiatric disorder, which is often seen in these cases [16, 32]. Even when an adult with autism spectrum disorder seeks help in adult psychiatry, communication problems in association with receptive language problems [22], may be an obstacle to diagnosis and treatment.

4. Connections and coexistence between LI, SLI and ASD

In order to prevent negative – and perhaps additional and secondary-consequences of the language delay, e.g. problems with social communication and learning, it is important to identify persistent problems and differentiate them from transient ones. This requires valid

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and reliable methods of prediction, which seems to be easier at a later age when the variation is not any longer so large. Botting, Faragher, Simkin, Knox and [11] found that narrative skills and expressive syntax were the strongest predictors of future outcome.

This scenario of complexity and variability both on presentation and longitudinally highlights the importance of working in multidisciplinary teams that include professionals from different clinical disciplines and with focus on a longer perspective from childhood to adulthood. Such early soft signs or symptoms of vulnerability as are understood by the term ESSENCE might reflect developmental problems as well as persistent impairments. The symptoms vary between individuals, and dynamically shift in different contexts as well as over time, i.e. they are heterogeneous and dynamically changing. As described above, one dilemma is that comprehension problems and social communication problems are difficult to identify for parents who are part of the communication themselves. Another dilemma occurs when young children are referred to see different professionals one at a time; this practice makes it difficult to grasp the whole picture, for both the specialists and the parents.

Individuals with language and communication delays require different intervention principles in different ages and contexts. Therefore language and communication impairments as well as autism spectrum disorders can be regarded as relational and contextual.

5. Anna — A child with early identified language problems

Anna was referred to a speech and language therapist after screening at the Child Health Care center at the age of four. Her parents had elicited concern and asked for a referral to a speech and language specialist. Her preschool teachers had pointed out that Anna had difficulties when asked to tell about things that had happened at home, but also when referring to activities at preschool, telling and retelling stories. She almost never asked questions and actually did not manage to participate actively in simple everyday conversations. The CHC nurse had been a little sceptic about her having a developmental problem since Anna had for a long time demonstrated fully intelligible expressive language skills with almost perfect pronunciation. However, the nurse pointed out that she had experienced some difficulties in chatting with Anna, whose answers and comments were found to be quite odd and irrelevant. This was not something Anna herself seemed to worry about; she continued to speak even if others were not following and responding properly.

At preschool it was pointed out that it was difficult to understand what Anna wanted although her pronunciation was pretty clear. It was also difficult to calm her when she was upset. Communication with Anna was tricky and there was a feeling of frustration from both parts. Misunderstandings and conflicts were commonly occurring during play. However, the nurse at the CHC-center did not seem to find the situation problematic, she underlined that Anna since early age had a fully intelligible spoken language. Eventually the nurse also noticed that it was a little difficult to get answers from Anna to simple questions and that she sometimes gave a bit odd answers to trivial, simple questions.

When Anna was about to start preschool classes, make new friends and have a new preschool teacher, her mother was worried. She pictured Anna ending up to be excluded from the peer group, short of play mates and a lonely girl. She was also afraid that new playmates would make fun of her, tease and cheat her.

The pre-school year proved to be a challenge for Anna herself. Almost every day there were misunderstandings and conflicts. Anna was not aware of her own role in the communication problems, as is usually the case with pragmatic problems. In addition, neither preschool teachers nor parents or peers could point out or articulate what the problem was. There were often conflicts, chaos and confusion. However, it became a little easier as the months went by and everyone got to know each other. This was particularly true in structured and teacher-led activities and thematic work where the topic was well defined and known.

The first years of elementary school went quite well. The teacher got to know Anna and more or less intuitively she adapted the teaching to Anna's needs. For example, she repeated instructions, she explained with other and easier words and simplified grammar and asked for feed-back to make certain that Anna had understood. A special needs teacher gave Anna individual teaching and introduced her in a social communication-training group. In this group the communication itself was highlighted in a metacognitive way. This means that the participants of the group explicitly talked about what was said, how different conversational participants interpreted it and what the speaker intended to say. Altogether this was very helpful for Anna, who became more aware of what was going on in conversations. She also got some help in narrative skill by visualization of story grammar, which scaffolds the construction of meaning and chronology in a story. Sometimes, Anna's associations went too far away for the listener to be able to follow, i.e. topic drifts and abrupt topic shifts. Although Anna had learnt to use some communicative strategies, e.g. repetitions and reformulations, there was often a risk of misunderstanding. The time outside the classroom was much more of a challenge. All peer conversations were rapid and there were no adults participating and scaffolding.

The following years at school turned out to be an even bigger challenge for Anna-as well as for her teachers and parents who suffered seeing Anna withdrawing from active participations in social communication, predominantly at school but also after school at home. Anna became introvert and dropped her assertiveness and spontaneity and spent less time with peers. She completely avoided situations with demands on social communication, but since she had no expressive language difficulties it was not obvious for anybody that she had hidden language vulnerability with at least former language comprehension problems. Instead the teachers perceived her behavior as a teenage problem and as a sign of lack of motivation for school.

What can we learn from this story? First, developmental language problems do not necessarily involve expressive language problems. Therefore they might be more subtle and difficult for the environment to discover although they have a bad prognosis and are challenging for the child to cope with. Such problems have been referred to as pragmatic language impairment [5], but has been renamed as social communication disorder in the updated diagnostic manual DSM-5 (http://www.psychiatry.org/dsm5). The diagnosis of social communication disorder is

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hereby more precisely defined and seen as a distinct language problem rather than a variant of autism spectrum disorder [28].

In a study by [19] the symptoms of earlier diagnosed language impairment commonly persist at age 11 years, although they are no longer specific language problems, but problems of general learning skill and/or social communication. With increasing age the demands on language skills both in academic literacy and in social communication are accentuated. As a teenager and young adult one is expected to make new acquaintances, to listen, understand and respond to what people say, both in more spontaneous conversations and while reading and writing academic texts. The more one is engaged into broader perspectives and new subjects, the more ones world is widened and the more concepts and language one needs to develop. The single most important factor for school success is a wide and well organized vocabulary [37], a skill that is continously being challenged and stimulated in all contexts during a persons whole life. [33] underline the importance of teaching children wordlearning principles explicitly, stressing associations and morphologic as well as semantic relationships between known and new words with focus on meningfulness and usability. The better a person's vocabulary is organized and structured, the more fast and easy it is to retrieve words when narrating stories. This is an important argument for the need of interdisciplinary collaboration in a long time perspective [11].

One question is if Anna's language problems could have been compensated for at an early age and thereby prevented or proactively been scaffolded? A predictive symptom was her early reluctance to tell and retell stories. Narrative skill has been found to predict the later language development [8]. Story telling is an important activity that is continuously performed and thereby stimulated and challenged in preschool activities, which makes is possible to scaffold narrative skill from early childhood.

Another symptom regards language comprehension focusing the ability to engage in social communication, i.e. pragmatic skill. Can such problems be identified and compensated for at an early age? There is not one straightforward answer on this question. At an early age there is a huge tolerance for breaking social rules and expectations. Explicit comments on social behavior e.g. politeness or the absence of it, are commonly given by parents and other adults. Anna's language problems affecting the functional aspects of language rather than the structural ones, made social interactions based on verbal conversation difficult. This in turn affected her status as a playmate during childhood and she often preferred playing with adults [21]. As she grew older Anna became less and less assertive and she had few close friends of her age [5, 7]. As a child becomes older both these parameters are changed: the tolerance for differences decreases – at least in similar age groups – and explicit comments on behavior are not expected. On the other hand being practiced in a variety of contexts and social meetings pragmatic skill is developed in an emergent way [30]. One way of stimulating pragmatics is therefore to involve and engage the child during social communication with different people, possibly representing different roles in play. Such imaginative play stimulates the ability to take different perspectives from different points of view, which means a kind of decontextualisation and mindreading, often referred to as theory of mind [25].

6. Anders — A young adult diagnosed with autism spectrum disorder

Anders, 26 years old, was referred to psychiatry for depression after having tried sixteen different training jobs without success. He was living alone in his own apartment, which his mother helped him to clean every week. He had a friend, but kept in touch by e-mail and had not met the friend for 4 years. He had never had a girlfriend, and, when asked, said "I don't want a girlfriend-it would be too time-consuming since I would have to be with her in my leisure time". He had no idea why the jobs he had tried had been failures, but he remembered one of them going well for several months, whereafter he was asked to leave. He described that in the job that went well, he had a written detailed description of his assignments which he had followed precisely. However, after three months his supervisor took away the instruction, assuming that Anders now knew what he was supposed to do. But since there was no description any more, Anders did nothing. His supervisors in this and other jobs were contacted, and they described why Anders had been asked to leave. In the workplaces he had behaved oddly in many ways – not greeting his colleagues, taking the biggest pieces of cake first in the coffee room but without socializing, intruding on others' workspace and many other things. Consistently were described misunderstandings and misinterpretations – Anders had a tendency to interpret literally and to say things that were considered rude or offensive.

Anders and his parents described that he had been quite clumsy as a small child, but the parents did not worry since he started walking at 15 months of age. He was quite late to speak, but soon developed a large vocabulary that impressed the parents. He preferred to play by himself or with his 3 years younger sister, and had no special friends at school. He disliked surprises, and became upset when routines were changed, and the family had adapted to this by e. g. never going on trips overnight until Anders was 15. The teachers had expressed some worry since Anders was always by himself, but since he did not seem unhappy, and since the father thought of himself as a "happy loner", nothing was done. Anders got fairly good grades, especially in science subjects but had relatively more difficulties in subjects where more of a social or coherent understanding was required. He was never bullied, and he liked going to school. However, after finishing high school he did not know what to do. His most intense interest was in bird-watching, especially night-active birds and he had collected large amounts of facts and observations concerning these birds.

The jobs that Anders was assigned were mostly low-skilled work in offices, food shops or stockrooms. The assignments were below his intellectual skills, but he failed since he did not have any intuitive understanding of the aims, or the bigger picture of the workplace, in addition to irritating his coworkers by being socially clumsy.

The psychiatrist and a psychologist, after doing a cognitive assessment of Anders and interviewing his parents, diagnosed an autism spectrum disorder with IQ within the normal range. His depression was considered to depend on his lack of meaningful occupation, and he was referred to a job center for adults with developmental disorders and normal IQ. In the job center Anders was assigned a special job coach with experience in autism spectrum disorders, and at his last visit to the psychiatrist seemed hopeful regarding his future chances to get a part time job as an assistant in a research lab, and perhaps later study science at the university

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in a program for students with autism. Anders was also referred to the habilitation center, where he has regular visits with a social worker.

Looking backward, Anders may, or may not have been helped by an earlier recognition of his problems. After all, he managed to go through school with good grades and without emotional disturbances. His family and classmates considered him normal, even if a bit odd and seclusive, and he was never bullied. Thus, Anders did not need any special help until after school, and it can be speculated that his self-esteem and emotional well-being might have been disturbed by earlier interventions. However, it seems unnecessary and unhelpful that Anders had to wait for 8 years of repeated failures in jobs until his problems were recognized and accordingly managed.

7. Mats — An adolescent with combined SLI and ASD

Mats was the second born child, with a sister 3 years older. The sister was diagnosed with high functioning autism with normal language acquisition at 5 years of age. The mother had Asperger's syndrome. Mats was evaluated at 4 years of age due to delayed language development. He also had severe communication problems especially with his peers but normal development regarding gross and fine motor function and nonverbal problem solving. The evaluation resulted in a diagnosis of ASD. He started at a normal school and never got any special education for the first 7 years in school. At that time he developed a severe depression with suicidal and homicidal ideation. A new evaluation by a speech and language therapist revealed major difficulties in both impressive and expressive language as well as in syntax and word mobilisation. His cognitive function was normal on performance tests but his verbal IQ was in the range of intellectual disability. This resulted in a transition to a special education class. His depression was somewhat improved but he refused to engage in any activity outside school and home. He loved watching violent Youtube scenes. He also refused to see a therapist and eventually decided to stop talking altogether. He communicated with gesture and by writing. He explained that he never could fully grasp what people were saying in a conversation and that he could not find words for what he himself would like to say, therefore he found it better to be mute.

8. Summary

The development of human society is totally dependent on our ability to interact, which requires language in order to communicate. Difficulties in communication underlie many human problems and, if severe, can jeopardize a person's adaptation to society. Communication problems are at the heart of many psychiatric disturbances, in particular ASD. Speech and language therapists have, from another perspective, studied language development and described many aspects of language such as phonology, semantics, grammar and pragmatics. A psychiatrist and clinical psychologist evaluated the case Anders, whereas a speech and language therapist evaluated the case Anna. Anders was judged to have ASD and Anna

pragmatic language disorder. Could Anna have got the diagnosis of ASD if evaluated by a psychiatrist? Would a more thorough assessment have revealed problems like circumscribed interests, obsessive symptoms and/or difficulties with change so that Anna would have met the full criteria for autism? Similarly, Anders might have got a diagnosis of pragmatic language disorder if evaluated by a speech and language therapist. The status of pragmatic language impairment as either a subtype of SLI or a form of ASD has been discussed for many years [4, 38]. Given the huge complexity as well as variability and instability of symptoms involving social interaction, language and communication, it is a big challenge to differentiate and discriminate between diagnoses such as LI, SLI and ASD [20]. Since these problem areas have been suggested to share a common genetic etiology and vulnerability it might be more fruitful to ask ourselves how we can help these individuals by supporting them and preventing secondary consequences emanating from their primary vulnerability. In order to see the whole picture we need to collaborate in multidisciplinary teams and to build bridges between specialists focusing on children, teenagers and adults. What was helpful to Anders was an understanding of his problems by his employer and work mates, whereas Anna benefitted from social training as a child, but as a teenager she had severe difficulties to cope with. Mats had a combination of autistic traits and SLI. He did not get any special help during his important first tears of schooling. It is difficult to assess how much of his communication problems, which were a basis for the diagnosis of autism in reality were due to his severe language impairment. As a conclusion we will underline the central role of language and communication in each of the three diagnoses LI, SLI and ASD, regardless if the language and communication problem is a specific or a more general problem, and regardless if it is a core problem or the consequence of another one. Working together in multidisciplinary teams over time adopting a longitudinal perspective from childhood to adulthood with the goal of promoting language and communication skills, can be a key to success in helping individuals develop academic and social skills.

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Chapter 6

Social Communication and Language Deficits in Parents and Siblings of Children with ASD — A Short Review

Ewa Pisula and Karolina Ziegart-Sadowska

Additional information is available at the end of the chapter

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1. Introduction

Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders associated with severe deficits in social communication, often accompanied by restricted patterns of behaviour, activity and interests [1]. ASD prevalence has been on the rise and is currently estimated to be 1:68 with higher rates for boys (1:42) than girls (1:189) [2].

Social, communication and cognitive deficits typical for ASD can affect individual sufferers with various severity and in many different combinations, which prompted the concept of autistic continuum, later replaced by autistic spectrum [3, 4] Already in the earliest publications on autism, Kanner [5] and Asperger [6] identified certain similarities in the untypical severity of certain traits and behaviours in children with autism and their parents, such as tendency to social withdrawal, limited interest in people, late speech development and pedantry. Further research demonstrated that autistic traits are more prevalent in the closest relatives of individuals with ASD than in other groups [7-11].

Subtle, subclinical traits or characteristics that parallel the defining features of autism, present in non-affected individuals, in particular the first-degree relatives of people with autism, are referred to as "Broader Autism Phenotype" (BAP) [10-13]. The presence of specific characteristics in terms of social and communication skills, cognitive processes and personality in parents and siblings of individuals with ASD may suggest genetic involvement in the aetiology of autism, what is strongly supported by evidence obtained from twin and family studies. Research in this area may expand our knowledge of the nature of autism and the mechanisms underlying the emergence of its characteristic symptoms [14].

It has been estimated that BAP characteristics may be presented in at least 10-20% of parents and siblings of children with these disorders [12, 15]. For instance, Bolton et al. [12] found out

that 12,4% of siblings of the autistic probants compared to only 1,6% of the siblings of Down's syndrome were described as performing autistic traits, but of a less severe degree. In spite of many studies considering difficulties demonstrated by relatives of children with ASD, specific determination of characteristics included in BAP requires further research.

A number of publications have described the specific personality traits of parents and siblings of children with ASD: shyness, preference to be alone, insistence on sameness, reluctance to change and obsessive-compulsive behaviours [16, 17]. There are also data on the mental health problems in members of these families [18], although the results of studies in this area are not consistent (see: [19] for review).

In addition, the relatives of children with ASD demonstrate a specific cognitive characteristics. They achieved lower scores in attribution mental states based on facial expressions tasks [20], showed weaker central coherence (e.g. [16, 20, 21]), and a lower level of efficiency in planning, attention shifting and other executive function [22-26].

Several comprehensive reviews of the few dozen years of research on BAP have been published (e.g. [7, 14, 27, 28]). In this article we will be focusing on social communication problems such as understanding body language and emotional expression, as well as specific language characteristics in parents and siblings of people with ASD. Impaired language and social communication problems are defining elements of autism and include a delay or lack of spoken language that cannot be compensated by other means of communication, difficulties in initiation and maintenance of conversation as well as repetitive and stereotypic language patterns and expressions [29]. The deficits in these domains are recognized as the key features of broader autism phenotype [13, 30, 31].

This review was conducted in the first half of 2014 using the following electronic databases of international literature: Web of Science, MEDLINE/PubMed, SCOPUS, EBSCO. The articles reviewed were published from 1992 to May 2014. Keywords related to phenotype, endophenotype, autism, parents, siblings and family were used. The next step was to select studies meeting the following criteria: a) published in English; b) the social communication and language characteristics of autism in parents and siblings of individuals with autism were objects of study; c) original studies. We have excluded articles that did not explore the themes of social communication and language, those that discussed research on BAP in general population or more distant relatives of individuals with ASD rather than in their parents and siblings, as well as studies that did not include a control group.

2. Research on social communication and language in parents and siblings of individuals with ASD

Tab. 1 presents a summary of information about research on social communication and language in parents and siblings of individuals with autism. Descriptions of individual studies are limited to themes associated with social communication and language, although the majority of reviewed articles covered other aspects of BAP as well.

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Study	Characteristics	Participants	Main results
Landa et al. (1992) [32]	Pragmatic language; verbal interactions	43 ASD parents (sex ratio not reported); 21 control adults (sex ratio not reported)	42% of ASD parents had some pragmatic language deficit, compared to 2% of controls
Szatmari et al. (1993) [33]	Cognitive impairments including language; developmental history	The unaffected siblings and parents of 52 PDD probands and 33 Down syndrome and low birth weight controls	No differences on the social and communication domains of the Vineland Adaptive Behavior Scales in ASD siblings compared to control siblings; No group differences in developmental history of language delays
Bolton et al. (1994) [12]	Social and communication impairments	ASD relatives (198 parents, 137 siblings); Control relatives (72 parents, 64 siblings)	20.4% of ASD siblings (and 3.1% of control siblings) showed communication atypicalities, social impairments, or restricted behaviors; The same pattern of results in parents, but to a lesser degree
Baron-Cohen and Hammer (1997) [34]	Reading emotions in the eyes	30 ASD parents (15 mothers and 15 fathers); 30 control adults (15 females and 15 males)	Parents of children with autism were slighly impaired in emotion recognition
Fombonne et al. (1997) [35]	Verbal intelligence, reading and spelling skills	99 first-degree ASD relatives; 36 relatives of individuals with Down syndrome	Slightly higher mean verbal IQ scores in relatives of ASD individuals; Siblings of ASD individuals, affected with the broad phenotype of autism, had significantly lower IQ scores, poorer reading and spelling abilities than unaffected siblings
Piven and Palmer (1997) [25]	Reading and spelling performance	25 mothers and 23 fathers from 25 multiple-incidence autism families; 30 mothers and 30 fathers from 30 Down syndrome families	ASD parents showed weaker reading performance (passage comprehension and rapid automatized naming) compared to parents of individuals with DS
Piven, Palmer, Landa, Santangelo, Jacobi, Childress (1997) [10]	Pragmatic language	39 multiple-incidence autism parents (having two children with autism); 58 parents of children with Down syndrome	Higher rates of speech and pragmatic language deficits in multiple-incidence autism parents
Piven, Palmer, Jacobi, Childress and Arndt (1997) [11]	Social and communication deficits	25 multiplex autism families; relatives of 30 Down syndrome probands	Higher rates of social and communication deficits in the families with multiple-incidence autism
Folstein et al. (1999) [36]	Pragmatic language; verbal IQ; reading and spelling performance	166 parents and 87 siblings of individuals with autism; 75 parents and 64 siblings of children with Down syndrome	No differences in verbal IQ scores, reading and spelling skills; More deficits in pragmatic language in parents of individuals with autism

Study	Characteristics	Participants	Main results
			as well as early language-related difficulties in that group
Hughes et al. (1999) [22]	Verbal fluency	31 siblings of children with autism; 32 siblings of children with developmental delay	Superior verbal span in siblings of children with autism; Bigger than expected part of that group of siblings achieved poor results in verbal fluency tasks
Pilowsky et al. (2003) [37]	Language abilities	27 siblings of children with autism, 23 siblings of children with mental retardation of unknown etiology, 22 siblings of children with developmental language disorders	Higher scores in siblings of children with autism on receptive, expressive, and total language scales of the Children's Evaluation of Language Fundamentals and on verbal IQ compared to siblings of children with developmental language disorders
Bishop (2004) [8]	Communication skills (self-report measure)	Children with ASD (59 with autism, 21 with PDD-NOS); ASD parents (65 mothers, 46 fathers); Control parents (48 mothers, 37 fathers)	Communication skills significantly lower in ASD parents (particularly fathers) compared to control parents
Bishop et al. (2004b) [38]	Phonological processing, communication	145 parents of children with ASD; 96 parents of typically developing children	No difference in phonological processing; In the group of parents classified as BAP there was a history of more language and literacy problems than in other ASD parents
Dorris et al. (2004) [39]	Mind-reading (Eyes Test)	27 siblings of children with Asperger syndrome (AS); 27 control children	Poorer performance of the AS siblings in the Eyes Test
Hill, Berthoz and Frith (2004) [40]	Emotion processing	27 high-functioning adults with autistic spectrum disorders, their biological relatives (n = 49), and normal adult controls (n = 35)	No significant differences between relatives of individuals with ASD and controls in identifying and describing feelings
Bishop (2006) [41]	Communication deficits (assessed by parents using Children's Communication Checklist-2, CCC-2)	43 ASD siblings; 46 control children	The only difference between groups in syntax; 23.8% of ASD siblings scored 2 SD below the control mean on CCC-2, compared to 2.2% of controls; Some differences in structural language skills
Palermo et al. (2006) [42]	Recognition of schematic displayed emotions	40 parents of children with autism, 40 control adults	Poorer performance in parents of children with autism; Fathers of children with autism had more difficulties than mothers
Chuthapisith et al. (2007) [43]	Language development	32 preschool siblings of children with autism (aged 2-6 years); 28 control children	Delayed language development in 8 of autism siblings; After excluded the siblings with ASD and DLD diagnosis, in the remaining 29 siblings

Study	Characteristics	Participants	Main results
			verbal IQs were not significantly different from the control group
Di Michele et al. (2007) [44]	Pragmatic language (evaluation of the taped conversations)	23 parents of children with autism; 12 parents of children with Down syndrome and 23 parents of healthy children	More pragmatic language difficulties in parents of people with autism; Problems in identifying relevant and redundant, non-essential information
Losh and Piven (2007) [45]	Ability to read complex psychological states from viewing only the eye region of faces	48 parents of individuals with autism; 22 control parents, including parents of individuals with Down syndrome and typically developing children	No differences between parents of individuals with autism and Controls; There was an „aloof" subgroup identified among parents of individuals with autism (n = 13); The results of that group were lower than the results obtained by Controls in the Eyes Test
Ruser et al. (2007) [46]	Communicative competence; pragmatic language, over-talkativeness	47 parents of individuals with autism; 47 parents of children with specific language impairment (SLI); 21 parents of children with Down syndrome	Parents of children with autism and SLI presented lower communication abilities than parents of children with DS; Severe pragmatic language deficits in about 15% of autism and SLI parents
Pilowsky et al. (2007) [47]	Neurocognitive functioning	30 siblings of children with autism; 28 siblings of children with mental retardation, 30 siblings of children with developmental language delay	No differences between siblings of children with autism and the other groups
Whitehouse et al. (2007) [48]	Communication (self report measure: Autism Quotient by Baron-Cohen et al., 2001)	30 parents of children with autism; 30 parents of children with specific language impairment; 30 parents of children typically developing	Communication difficulties in parents of children with autism
Adolphs et al. (2008) [49]	Face processing	15 socially 'aloof' parents of individuals with autism; 27 'nonaloof' parents of children with autism; 20 control parents of neurotypical children	Socially 'aloof' parents showed poorer performance compared to 'nonaloof' parents and control parents
Scheeren and Stauder (2008) [50]	Communication (measured by AQ)	25 parents of children with HFA; 25 parents of typically developing children	No differences between groups
Schmidt et al. (2008) [51]	Phonological processing	22 parents of children with autism; 22 controls	ASD parents achieved lower scores on the nonword repetition task; No differences between groups in figurative language, receptive language, expressive language, verbal fluency and in history of reading difficulties
Losh et al. (2008) [13]	Pragmatic language	48 parents of individuals with autism (multiple-incidence	More pragmatic and speech errors in MIAF parents than in SIAF parents; SIAF parents

Study	Characteristics	Participants	Main results
		autism families - MIAF); 78 parents of individuals with autism (single-incidence autism families - SIAF); 60 parents of individuals with Down syndrome	committed significantly more pragmatic violations and speech errors than Down syndrome parents
Gamliel et al. (2009) [52]	Language development	37 siblings of children with ASD (SIBS-A); 47 siblings of typically developing children (SIBS-TD) (longitudinal study: from 4 months to 7 years)	At 7 years, 40% of the SIBS-A (and 16% of SIBS-TD) showed cognitive, language and/or academic difficulties (this sub-group was named SIBS-A-BP); Early language scores (14–54 months) were significantly lower in SIBS-A-BP compared to the language scores of SIBS-TD. Language was a major area of difficulty for SIBS-A during the preschool years
Lindgren et al. (2009) [53]	Syntax memory for language, Lexical comprehension, Semantics, Morphology, Reading abilities	62 parents of children with autism and language impairment; 39 parents of children without autism and language impairment; 70 parents of children with specific language impairment	Parents of people with autism and language impairment had a better performance in language tests than parents of children with specific language impairment
Losh et al. (2009) [54]	Reading complex psychological states from the eye region of faces	36 high-functioning individuals with autism, 41 controls (neurotypical individuals with no family history of autism), 83 parents of individuals with autism, 32 control parents (with no family history of autism or developmental delays)	There were three groups of parents of individuals with autism extracted: group of parents with social BAP characteristics (n = 22); group with the rigid/perfectionistic BAP traits (n = 34), and group without BAP features BAP (−) (n = 40). In Reading the Mind in the Eyes Test parents of individuals with autism with social BAP performed poorer than control parents. No difference between Controls and BAP (-) parents
Ben-Yizhak et al. (2011) [55]	Pragmatic language, school related linguistic abilities	School-age siblings of children with autism (SIBS-A), n=35; Controls (n = 42)	Lower pragmatic abilities in a subgroup of SIBS-A identified with BAP related difficulties; No differences between groups in school achievements and reading processes
Losh et al. (2010) [23]	Rapid automatized naming	Three samples: I: 48 parents of multiple children with ASD; 62 parents with a single child with autism; 53 parents of children with Down syndrome;	Longer naming times in parents of individuals with autism and in people with HFA compared to controls

Study	Characteristics	Participants	Main results
		II: 167 parents from multiplex families; III: 83 parents of individuals with autism, 32 parent controls, 36 high-functioning individuals with autism, 38 controls	
Wheelwright et al. (2010) [56]	Communication (self-report using AQ)	2,000 parents of children with ASD (571 fathers and 1429 mothers); 1,007 parents of typically developing children (349 fathers and 658 mothers)	Parents of children with ASD showed more communication difficulties
Whitehouse et al. (2010) [57]	Language (speech, syntax and semantics), pragmatic skills, communication style	238 parents of children with autism; 187 parents of typical individuals	No differences between groups in the language subscale
Levy and Bar-Yuda (2011) [58]	Language performance	Siblings of nonverbal children with autism SIBS-ANV (n=28); Controls (n = 27); aged 4–9 years	SIBS-ANV achieved lower scores on the Receptive Scale, Expressive Scale and the Total Language Scale of the Clinical Evaluation of Language Fundamentals; Differences in the language scores were associated with IQ
Neves et al. (2011) [59]	Facial emotion recognition	40 parents of children with autism; 41 healthy controls	Parents of children with autism performed worse in the facial emotion recognition test than controls
Bernier et al. (2012) [60]	Conversational skills	39 parents of multiple-incidence autism families (M-parents); 22 parents of single-incidence autism families (S-parents); 20 parents of children with developmental delay without ASD (DD); 20 parents of typically-developing children	Greater impairment in social communication skills in M-parents compared with S-parents, DD parents, and parents of typically developing children
Berthoz et al. (2013) [61]	Emotional impairments	High functioning adults with ASD (n = 38), parents of individuals with ASD (n = 87), typical adults (n = 47)	Parents differed from controls on social anhedonia; Higher proportion of parents were classed as alexithymic, compared with controls
Sucksmith et al. (2013) [62]	Emotion recognition	314 adults with ASD; 297 parents with children with ASD; 184 controls	No difference between parents of a child with ASD and controls at recognising the basic emotions (after controlling for age and non-verbal IQ)
Gizzonio et al. (2014) [63]	Verbal IQ	32 children with ASD, 21 siblings of these children,	No significant difference between Verbal Intelligence Quotient and Performance Intelligent Quotient scores between groups;

Study	Characteristics	Participants	Main results
		43 children with typical development	Not significant, a predominance of performance over verbal abilities observed in siblings group
Kadak et al. (2014) [64]	Recognition of emotion (face expression)	36 mothers and 36 fathers of children with ASD; 19 mothers and 19 fathers of typically developing children	Poorer recognition of emotional expressions in ASD parents
Oerlemans et al. (2014) [65]	Recognition of facial emotion and affective prosody	90 children with ASD (43 with and 47 without ADHD), 79 ASD unaffected siblings, 139 controls aged 6-13 years	The worse performance of unaffected siblings than the controls and better than the ASD probands in recognition of facial emotion and affective prosody tasks

Table 1. Social communication and language characteristics in parents and siblings of individuals with ASD

As it is shown in Table 1, many authors have found social communication and language deficits in first-degree relatives of individuals with ASD. Both receptive and expressive language is affected [37]. Difficulties include, among others: pragmatic language deficits (e.g. [10, 12, 13, 32, 36, 44, 46, 55]), verbal fluency [22], reading abilities [25, 35], delay of language development and problems in language developmental history [11, 38, 43, 52], conversational skills [60] and syntax [41].

Some researchers, however, found no differences between first degree relatives of people with ASD and the comparison groups in the social communication and language (e.g. [33, 47, 51]). No such differences were found, among others, in the language development history [33], verbal fluency [51] and reading and spelling abilities [36, 55]. Similarly, there were no differences between parents or siblings of individuals with autism and control groups in terms of phonological processing [38, 51] and structural language [53, 57].

Findings on the development of verbal and non-verbal intellectual skills in first-degree relatives of people with autism are less consistent. Some comparisons have shown that first-degree relatives of individuals with ASD had lower verbal IQ compared to control groups (e.g. [37]), while other studies found no such differences [36, 63]. Fombonne with colleagues [35] even reported slightly higher verbal IQ in relatives of individuals with autism than in relatives of people with Down syndrome.

Studies using self-reported measures to assess difficulties in communication experienced by parents of individuals with ASD have also failed to provide a clear picture. In the majority of those studies parents reported more severe difficulties in that area compared with adult controls (e.g. [8, 48, 56]). Scheeren and Stauder [50], however, found no differences when comparing parents of high-functioning individuals with autism and parents of typically developing children.

In a similar way several studies have indicated also that parents or siblings of children with ASD showed lower scores in recognize emotions tasks [34, 39, 42, 59, 61, 64, 65] than Down syndrome or typically developing children relatives. However, Sucksmith with colleagues

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[62], after controlling for age and non-verbal IQ, did not detect differences in recognizing the basic emotions between parents of children with ASD and controls.

It should be noted that in some studies in which differences between first-degree relatives of individuals with autism and controls were not significant it was possible to identify subgroups of participants demonstrating traits similar to those seen in individuals with ASD. Subgroups with BAP characteristics are significantly more numerous in the groups of parents or siblings of individuals with ASD than subgroups with similar problems in control groups. For instance, Landa with colleagues [32] stated that 42% of parents of children with ASD had some pragmatic language deficits, compared to 2% of control parents. Findings from research where it has been shown that among parents or siblings of people with autism there were the subgroups that manifested some difficulties in social communication and language, but it does not apply to these groups as a whole (e.g. [43, 45, 49, 54, 60, 66]) may be particularly relevant to further research on genetic involvement in BAP. Schmidt with colleagues [51] showed impairments in phonological processing in parents of children with low functioning autism. In their study on emotion recognition, Adolphs with colleagues [49] found difficulties in parents identified as "socially aloof", while "nonaloof" parents were similar to controls. Folstein et al. [36] found that only those parents of individuals with autism who showed cognitive deficits associated with language in childhood performed worse than parents of individuals with Down syndrome in reading and writing tasks. By controlling for a variety of variables, including autism severity and developmental characteristics individuals with autism, as well as the number ASD cases in the extended family (e.g., taking into account the siblings of both parents of an individual with autism, as well as their children) we are likely to find out more about BAP.

Some empirical data suggest that families may differ in terms of genetic liability to autism. Losh et al. [13] compared three groups of individuals: 25 parents from multiple-incidence autism families, 40 parents from single-incidence autism families, and 30 parents from Down syndrome families. They found that autistic characteristics were most pronounced in parents from multiple-incidence autism families, less pronounced in single-incidence autism families, and weakest in parents of children with Down syndrome. In the majority of families with two children with autism, both parents demonstrated autistic characteristics; by contrast, in families with one child with autism the likelihood of both parents showing those characteristics was the same as for one parent or neither parent to have autistic traits. Gerdts and Bernier [66] showed that mothers, fathers, and siblings from multiplex ASD families were less expressive in their use of nonverbal communication compared to mothers, fathers and siblings from simplex families. Thus, it appears that research on multiple-incidence autism families can provide valuable information with respect to the hereditary mechanisms underlying autism. Schwichtenberg et al. [67] found that children from multiplex autism families had greater BAP traits than simplex siblings, and ASD multiplex infant siblings were more likely to develop ASD than ASD simplex and control. Findings from research on BAP in monozygotic and dizygotic twins are also interesting. It was shown [68] that concordance for BAP was much greater in MZ pairs than DZ pairs.

Recently there has been a surge in research on infants at high familial risk for ASD (see [69] for review). An estimated 10-20% of at high risk infant siblings may be affected by sub-clinical

ASD symptoms or other developmental impairments [70]. These studies are not included in Table 1 because participants included children with ASD. Nevertheless, their findings with respect to social communication and language are relevant to the understanding of BAP. A number of those research projects have shown that some siblings of individuals with ASD demonstrate observable communication deficits already in the first three years of life and that these impairments can change over time. They include, among others, lower receptive language scores, delayed receptive and expressive language [15, 71-74], requesting behavior [75, 76], understanding words and phrases, gesture use, and social-communicative interactions with parents [77]. The important question is how early are those problems manifested. It was shown that at 6 months of age there were no statistically significant group differences in language development between high risk (HR, children having sibling with autism) and low risk (LR) infants (no autism history in family) [15, 78]. No differences in gaze following were found in children of 7 and 13 months between HR and LR groups [79]. Georgiades et al. [80] concluded that pragmatic language deficits were not relevant traits of BAP at 12 months. Obviously, this does not mean that HR children experience no deficits in language development at that age. Ozonoff with colleagues [78] found atypical language development in high-risk infants of 12 months of age. Differences in language between HR and LR infants of 24 months of age are found much more often [15, 73, 74]. Longitudinal studies are the most desirable as they offer insight into the dynamics and changes in the development of these children. While problems are overcome in some, in others they persist at later stages. As demonstrated by Gamliel et al. [71], expressive and receptive language deficits were still present in HR children at 54 months of age despite the resolution of some other developmental problems. Another important issue is to find out how many of 24-months old HR siblings demonstrating language difficulties are eventually diagnosed with ASD. Hudry et al. [81] found that reduced receptive vocabulary advantage in high risk infants at 14 months, maintained to 24 months only in the subgroups of ASD or other atypicality outcome. This suggests a close to typical development of other children in the HR group. The results of these sample studies on HR infants expose gaps in the knowledge on the issue.

3. Conclusions

Currently, it is difficult to identify universal, clear regularities relating to social communication and language deficits in parents or siblings of children with autism, but they have been found in some subgroups. A more complete knowledge in that area can contribute to a better understanding of autism. It can also provide hints for future research, by focusing attention on selected subgroups of parents and siblings.

There are many reasons for the variation in empirical results discussed in this section. Specific ones include methodological considerations such as sample size, research methods, enrolment criteria, as well as specifics of control groups (Cf. [19]).

It would be difficult to identify the components of BAP in terms of social communication and language based on currently available data. The best documented aspect of BAP appear to be

pragmatic language deficits. Other characteristics analysed in the above studies as BAP components, such as delay of language development, difficulties in reading, spelling and writing, difficulties in structural language use or verbal fluency, remain controversial.

A number of studies on BAP focus on parents, and there are also many that analyse HR infants. In other studies on siblings, groups tend to be very heterogeneous, e.g. in terms of age. Longitudinal research on the development of social communication and language deficits in preschool and school age siblings are particularly necessary, especially that, as shown by Gamliel et al. [52], language may be a major area of difficulty for siblings of individuals with autism during the preschool years.

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Chapter 7

Implicit and Spontaneous Theory of Mind Reasoning in Autism Spectrum Disorders

Beate Sodian, Tobias Schuwerk and Susanne Kristen

Additional information is available at the end of the chapter

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1. Introduction

In a seminal study, conducted almost 30 years ago, Baron-Cohen, Leslie and Frith [1] provided first empirical support for the idea that individuals with autism spectrum disorders (ASD) have a Theory of Mind (ToM) deficit, i.e. they are impaired in the fundamental human ability to attribute mental states like beliefs, desires or intentions to themselves and others and therefore fail to explain and predict behavior in a commonsense way in everyday interactions (see [2]). Baron-Cohen et al. [1] used a task in which story character Sally does not witness story character Anne transferring a ball from a basket to a box and thus falsely believes it is still in its original location. Twelve-year-old participants with ASD systematically based their prediction of Sally's search behavior on their own knowledge about the situation and failed the test, answering she will look for the ball in its new location. Crucially, typically developed children and children with Down's Syndrome who were matched for mental age, passed the task. It was concluded that participants with ASD were specifically impaired in adopting Sally's perspective, that is, in attributing a false belief to her. Since then, a wealth of studies confirmed this ToM deficit in children and adults with ASD (e.g., [3]).

Despite its major contributions to explaining core symptoms of autism (social deficits, deficits in pragmatic language, imaginative play, and empathy), the ToM hypothesis has also been criticized for failing to provide a specific account for the social and cognitive impairments, especially in high functioning individuals with ASD [4]. First, verbal skills strongly predict performance on verbal ToM tasks [5]. In some studies, when verbal ability was entered as a covariate, ToM did not predict the degree of social impairments in children and adults with ASD [6]. Second, ToM deficits are not specific to ASD, but have also been observed in clinical groups with for example schizophrenia [7] and deafness [8]. Third, ToM skills assessed in standard experimental tasks may not be informative of real-world social competencies and

deficits, since experimental situations do not pose the kinds of stressful demands on individuals with ASD that real-life social situations do. This may be one reason for the failure of ToM-based interventions to enhance real-world social competencies [9].

In the last ten years, new methods, relying on spontaneous and implicit ToM processing have been productively used to further investigate the social and cognitive impairments in ASD. These methods were first used in infant research; infants and young children under the age of about 4 years, like patients with ASD, fail explicit ToM tasks, but nevertheless show a spontaneous sensitivity to others' mental states in looking-time, eye-tracking, and interactive tasks [10]. An implicit ToM appears to developmentally precede an explicit one (two-systems accounts; [11]).

Explicit ToM reasoning describes the ability to deliberately consider others' mental states and provide reasons in order to explain their behavior ("Sally will look for the ball in the basket because she falsely believes it is still in there"; see [12]). This form of ToM reasoning acts consciously, can be flexibly employed in various situations, and is cognitively demanding. Explicit ToM tasks, like the Sally-Anne task, test this ability by assessing verbal responses to the direct question for the protagonist's mental state and belief-based behavior.

Implicit ToM reasoning refers to the spontaneous sensitivity to others' mental states without the need to deliberately reflect on them. It is supposed to work fast, unconsciously, but rigidly. Implicit ToM tasks, clever nonverbal versions of the Sally-Anne task, assess the participant's gaze in anticipation of the protagonist's belief-based behavior as an indicator of implicit ToM reasoning (e.g., [13]). In the first section of the present chapter, we review the research on implicit ToM processing in ASD.

Not all spontaneous ToM processing is implicit. The spontaneous use of mental state terms in everyday conversations is one of the first signs for an explicit understanding of mental states in child development, with talk about volitional states and emotions, beginning in the second year of life and preceding cognitive language by over one year [14]. While some usages of mental state terms serve conversational functions without genuine reference to mental states [14], there is evidence for specific relations between cognition terms and perspective taking abilities [15] and for predictive relations between preverbal communicative abilities and mental state language [16] in child development. Since the study of mental state language in ASD poses fewer restrictive task demands than experimental ToM tasks, it may add to our understanding of mental state representation in ASD in important ways. The second part of the present chapter focuses on this line of research.

2. Implicit theory of mind reasoning in Autism Spectrum Disorders: Insights from the analysis of eye movements

In the last years, eye tracking gained massive popularity in ASD research [17]. This method aims at linking gaze patterns to cognitive processes [18]. Tracking eye movements while watching social stimuli on a computer screen is especially suited for ASD research because it

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is independent of verbal abilities of the participants and avoids possible aversively experienced social interactions with the experimenter during the test.

Senju, Southgate, White and Frith [19] were the first to combine eye tracking and an implicit ToM task in an experiment with individuals with ASD and found a striking dissociation between explicit and implicit ToM reasoning: Participants with Asperger syndrome did not differ from a neurotypical control group in their performance on explicit ToM tasks. However, their eye movements in the implicit false belief task revealed an intriguing group difference. In this task, just like in the explicit version, the participants watched an agent who did not witness the transfer of a ball from one box to another and thus has a false belief about its location. However, in the subsequent test phase, participants were not explicitly asked where the agent would search for the ball (in the now empty box), but eye movements in anticipation of the following reaching action of the agent were measured. This allowed for assessing whether participants kept track of the agent's belief about the object's location without explicitly asking for it. Whereas neurotypical adults correctly anticipated that the agent would search for the ball in the now empty box, individuals with ASD lacked this anticipation of the false-belief congruent behavior.

Senju et al.'s [19] groundbreaking findings corroborated two-systems accounts of ToM. Furthermore, the findings suggest that while the explicit ToM deficit can be alleviated by compensatory strategies [20], the implicit ToM reasoning deficit is sustained and not addressable with learning strategies [21].

The following section reviews recent empirical findings on implicit and explicit ToM in ASD to shed light on the cognitive characteristics of ToM reasoning in ASD. In the beginning we provide a short rationale of why and how eye movements can be utilized to draw conclusions on the cognitive nature of ToM reasoning. Subsequently, we review the fast growing body of evidence on implicit ToM reasoning in ASD in the light of two-systems accounts. We will particularly discuss the fit of recent empirical findings with the notion of a sustained implicit ToM deficit which cannot be compensated for.

2.1. What eye movements reveal about ToM reasoning

In the past years the analysis of gaze behavior became more and more popular in ToM research. The investigation of eye movements aims to relate gaze patterns to cognitive processes. In two-dimensional scenes two basic types of eye movements occur: First, fixations, the persistence of the center of sharp vision for a specific amount of time on an item in the scene; second, saccades, jump-like movements of the eyes from one fixation to the next. Since visual information is only obtained during fixations, fixation patterns can very precisely reveal what visual information is taken into account at a given point in time [18]. On the basis of such data, conclusions can be drawn on the cognitive processes that underlie visual search [22]. Eye tracking systems provide an abundance of precise information about the focus of visual attention in time and space. These systems record gaze data from one or both eyes, providing x-and y-coordinates of the fixated location of a screen. This happens on a millisecond level with a spatial resolution of around 0.1° of visual angle, depending on the system, sampling

rate, and accuracy of calibration. But how can this method tell us something about ToM reasoning?

In the 1990s eye movements started to be employed in ToM research. Clements and Perner [13] investigated whether eye movements in the false belief task reveal children's understanding of others' mental states. Video recordings of children's looking behavior were decoded and raters judged which of the two locations in a false belief task the child was looking at. Although the 3-year-olds provided a wrong answer, supporting the claim that children before 4 years of age are not able to understand false beliefs [23], their looking patterns suggested sensitivity to the character's false belief. This pioneering eye tracking work started a line of research and a heated debate on when and how children are able to attribute mental states [24]. Furthermore, this study showed that the analysis of eye movements might be an interesting approach to indicate ToM reasoning.

Psycholinguistic research employing the visual world paradigm [25] showed that eye movements are influenced by mental representations. An example of how this paradigm can be used comes from Altmann and Kamide [26]: In their experiment they presented a scene depicting a woman and table, for example. A bottle and a glass were on the floor. Subjects listened to the sentence "The woman will put the glass on the table. Then, she will pick up the bottle, and pour the wine carefully into the glass." This scene either remained unchanged (experiment 1) or it was completely removed before the sentence was spoken (experiment 2). Eye movements towards the table, or towards the location where the table had been, after hearing "pour" revealed an influence of the mental representation of the glass (according to the sentence it should now be on the table) on fixation patterns.

If one's own current and past mental representations of an object's locations in a scene influence eye movements, they might also be sensitive to the processing of another's mental representation. Adapting the visual world paradigm Ferguson and Breheny [27] reported evidence that eye movements indeed provide insight into the real-time processing of others' mental states. In an interactive video task, a participant and a confederate watched movie clips of an object that was put into one of two boxes and subsequently was pulled out of it again. After that the object was either put back into the same place or transferred to the other box. In half oft he trials the confederate did not witness whether there was a transfer or not. Thus, unlike the participant, the confederate was unsure about the final location of the object. At the end of the trial the confederate verbally described the situation as in the following scheme: "The [object] is in box [A/B]". The participants' fixations on the boxes were linked to the onsets of critical words in this verbal description. This analysis revealed a tendency to fixate the box in which the object actually ended up. Only when the confederate did not witness the object transfer, this gaze pattern changed towards an increased probability to anticipatorily fixate the alternative box, which was empty, but the confederate might have assumed that it could have been in there. This suggests that participants took into account what the other had or had not seen.

First, this finding demonstrates that neurotypical adults are rapidly and spontaneously sensitive to other's mental states during communication. Second, this study shows that eye movements are a sensitive indicator of spontaneous and "online" ToM reasoning without

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explicitly asking for mental states of others. Thus far, the fast growing field of eye tracking research on ToM has employed a number of paradigms and measures (Box 1 provides an overview of hitherto used eye movement measures).

Anticipatory eye movements. The analysis of predictive saccades and fixations is an appealing way to address ToM reasoning. If the location where someone will fruitlessly search for an item (because of a false belief about the objects' location) is anticipated by predictive saccades and fixations, these eye movements are indicative of cognitive processes that account for the other's false belief (Schneider, Bayliss, Becker & Dux, 2012; Schneider, Lam, Bayliss & Dux, 2012; Senju, Southgate, White & Frith, 2009; Southgate, Senju & Csibra, 2007).

Location of first fixation. The direction of the first saccade on a scene can reveal what item is prioritized (Fletcher-Watson, Findlay, Leekam & Benson, 2008). A tendency to direct the first saccade towards the location where subjects believe an object is, rather than towards the location where the story character falsely believes it is located, may reflect an interference from one's own perspective in a false belief task (Rubio-Férnandez & Glucksberg, 2012).

Fixation latency. How long does it take after trial onset until a certain part of a scene is fixated? The latency until the fixation of a false belief-congruent location is informative about the characteristics of false belief attribution (Rubio-Férnandez & Glucksberg, 2012).

Number of fixations and fixation duration. Analyzing how often and for how long an item is fixated when viewing a scene provides information on the importance this item had in processing the scene and also on the influence of anothers' belief about that item (Keysar, Lin & Barr, 2003). Klein, Zwickel, Prinz and Frith (2009) employed fixation durations on items that elicited mental state attribution as an indicator of processing depth and interpreted it in terms of a high cognitive load, required when we ascribe mental states.

Probability of fixating an object as a function of time. Ferguson and Breheny (2012) showed that when another person might falsely assume an object could be in a certain location, the probability of fixating this location rose when the person started to report his or her assumption about the object's location. This procedure can reveal sensitivity to other's mental states with a crucial advantage: it serves as online measure of ToM reasoning in a natural social interaction without overtly asking for other's mental states (cf., Tanenhaus & Spivey-Knowlton, 1996).

Pupillary dilation. It may also be worthwhile to consider pupillary dilation. Changes in the diameter of the pupil can be linked to attentional shifts and changes in mental states (Laeng, Sirois & Gredebäck, 2012). This might not only be useful to detect if subjects react to another's mental state, but also to see which information at what point in time has led to such a response.

Box 1. Extractable eye movement measures in Theory of Mind (ToM) research

When interpreting eye movements in terms of underlying cognitive functions, a few methodological limitations have to be considered. When an item is fixated during a task, it may be because crucial information of that item is processed, but this must not inevitably be the case. It might also be that during the recorded fixation no information at all or different information is processed, for example in the periphery of the visual field. Aslin [28] pointed to a limitation of global looking time measures that also affects the investigation of the microstructure of eye movements via eye tracking: looking times consist of active information processing as well as blank stares. It cannot be premised that for example in free visual exploration of a scene each

recorded fixation reflects active information processing of the fixated item. Furthermore it is possible that during a fixation, not the focused item is regarded, but rather different information is processed. Relevant information about objects can also be obtained in periphery [29]. Additionally, if a fixation reflects cognitive processing of the fixated information, conclusions to a specific cognitive process have to be drawn carefully. Depending on the employed paradigm, observed fixation patterns may reflect the detection, identification, discrimination, categorization or integration of visual stimuli. These factors have to be considered carefully when designing eye tracking paradigms to test ToM reasoning.

In sum, the rapidly increasing number of eye tracking studies on ToM reasoning suggests that the analysis of eye movements is a sensitive measure to address implicit ToM reasoning (cf., [30]). Furthermore, eye tracking appears to be especially well suited to test participants with ASD. First, it allows for inferences on social cognitive processes independent of the verbal abilities of the participants. Second, video presentation takes advantage of a strong preference of individuals with ASD for electronic screen media [31]. Third, unlike in classical false belief tasks (e.g. [32]), eye tracking versions of this task do not entail actual social interactions during stimulus presentation and assessment of measures of interest. In this way social cognition can be studied without possible aversively experienced interactions with the experimenter (cf., [33]). This promises to reduce the burden for participants with ASD to engage in the task and to enable tapping social cognitive process, otherwise masked by a disadvantageous test setting.

A recent study by Chevallier et al. [34] provides empirical support for this idea. In this study children with and without ASD completed a ToM task in a social (instructions by an experimenter) and a nonsocial setting (computer-based instructions). Intriguingly, the ToM performance gap between children with ASD and neurotypical children, consistent with previous literature, was only found in the social setting. Accordingly, recording eye movements while presenting stimuli on a computer screen seems to provide comparable test conditions for participants with and without ASD. To be clear, research on social cognition in ASD should entail the study of real reciprocal social interactions (see [35]). However, one must be aware that such studies might impose too much demand on social interaction and obtained results might lead to an underestimation of social cognitive competencies of individuals with ASD.

2.2. Implicit ToM reasoning and compensatory learning in ASD

To date, the implicit ToM deficit, assessed with an implicit version of the Sally-Anne task, has been documented in adults [19] and eight-year-old children with ASD [36]. Recently, Gliga et al. [37] expanded these findings by showing that this implicit ToM deficit can not only be found in participants with an ASD diagnosis, but also in three-year-old children with an older sibling with ASD. Those children being at risk of developing a disorder from the autism spectrum, differed from a control group in their anticipation of a false-belief congruent action. Morever, Gliga et al.'s results tentatively suggest a gradient in spontaneous sensitivity to others' mental states in the autism spectrum. Within the at-risk group, only children who received an ASD diagnosis themselves later on significantly differed in their anticipatory looking from the control group. Neither at-risk children who developed typically, nor at-risk children who showed subclinical abnormalities later on, differed in their gaze behaviors from the control

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group. This study suggests that an implicit ToM deficit may not merely originate from isolated intra-individual factors, but may be genetically and/or environmentally determined. Further research is needed to characterize the implicit ToM deficit in the broader autism spectrum.

Both ToM reasoning systems, the explicit and the implicit one, appear to be affected in ASD. However, there seems to be a dissociation with respect to the possibility to tackle an explicit and an implicit ToM deficit by compensatory strategies (see [2,21]): On the one hand, individuals with ASD are able to alleviate an explicit ToM deficit through compensatory learning. Experience with social situations may have led to the acquisition of non-mentalistic routes to deal with mental states of others. Evidence that high functioning individuals with ASD pass explicit ToM tasks supports this notion [20].

On the other hand, based on the finding that those participants with ASD who passed explicit ToM tasks, showed no spontaneous sensitivity to a character's false belief in an implicit ToM task [19], it was argued that this implicit ToM deficit is pervasive and cannot be modulated by compensatory learning. Moreover, if implicit ToM reasoning runs automatically, without top-down control [38], it should not be susceptible by alternative, non-mentalistic, strategies.

Callenmark, Kjellin, Rönnqist and Bölte (2013) [39] report a similar dissociation between explicit and implicit social cognitive processes. In an explicit version of a social cognition task (multiple-choice rating of other people's thoughts about violations of social norms) adolescents with ASD did not differ in their performance from neurotypical controls. However, in a more implicit version of this task (free interview instead of multiple-choice format) the ASD group performed more poorly as compared to the neurotypical control group. In a similar vein to Senju et al [19], the authors concluded that in explicit but not in implicit tasks, compensatory strategies which were acquired through learning and experience with social situations, can be employed.

A limitation of the above described implicit false belief tasks is that they only employed one critical test trial to assess gaze behavior that indicates a lack of spontaneous sensitivity to mental states in ASD. However, claiming that individuals with ASD have a persisting implicit ToM deficit requires testing whether atypical gaze behavior is sustained over time. Such an implicit ToM deficit, impenetrable by learning from experience, should be observable in the consecutive presentation of multiple test trials and should not be alleviated by the repetition of those trials.

Using a methodologically refined version of the implicit false belief task, Schneider, Slaughter, Bayliss and Dux [40] tested this hypothesis in adults with ASD. First, they replicated the previously observed group difference between participants with and without ASD in false-belief congruent anticipatory looking. Second, for both groups gaze behavior remained stable over the repetition of test trials: Whereas the neurotypical control group showed sustained false belief-congruent anticipatory looking, individuals with ASD revealed a persisting lack of this false belief tracking. Additionally, just like in Senju et al.'s [19] study, the same participants passed explicit ToM tasks. This empirically underpins the proposal that individuals with ASD can employ explicitly learned strategies to face an explicit ToM deficit and that those strategies are useless to tackle an implicit ToM deficit. Furthermore, these findings critically

extend previous suggestions by adding the notion that experience with the implicit false belief task (through repeating the test trials) does not trigger spontaneous compensatory learning.

In contrast to the finding by Schneider et al. [41], Schuwerk, Vuori and Sodian [42] reported apparently contradictory results. They also adapted Senju et al.'s [19] paradigm to test learning effects on false belief-congruent anticipatory looking in adults with ASD. In order to assess the impact of experience on gaze behavior, the critical false belief test trial was repeated once. Eye movement patterns in the first presentation of the false belief test trial revealed the well-documented group difference between the participants with ASD and the neurotypical controls. However, in the subsequent repetition of the test trial, anticipatory looking of the ASD group no longer differed from the neurotypical control group.

Why did Schneider et al. find no effect of experience in a total of ten subsequently presented false belief trials whereas in Schuwerk et al.'s study the single repetition of the false belief trial was sufficient to make the group difference disappear? One task property, which was changed by Schuwerk et al., but not by Schneider et al., can serve as explanation of those discrepant findings. In contrast to previous versions of this implicit false belief task, Schuwerk et al. presented the belief-corresponding action (the agent is searching for the object in the now empty box), and its outcome (the actor does not find the car). Therefore it is possible that presenting a perception-action contingency (agent does not witness the transfer – agent searches for the object in the wrong box) provided a basis for individuals with ASD to learn about the association between the agent's gaze direction and the subsequent action. Notably, this learning from experience can result in the observed alternation of gaze behavior without the need to actually consider the actor's mental state. Thus, this finding suggests that individuals with ASD are sensitive to behavioral cues to learn about perception-action contingencies. Furthermore, this knowledge can be employed as compensatory strategy to rapidly adapt action predictions in an implicit ToM task.

2.3. Summary

In sum, evidence is accumulating that implicit ToM reasoning is impaired in individuals with ASD and also their younger siblings. Moreover, compensatory non-mentalistic strategies, which are useful in explicit ToM tasks, fail to alleviate the deficit to spontaneously appreciate another's mental state. However, recent findings show that the strict distinction that explicit, but not implicit ToM reasoning can be addressed by compensatory learning, may not be tenable. It rather seems that also the implicit ToM deficit can be modulated by compensatory strategies: if individuals with ASD are provided perception-action contingencies, they may also be able to rapidly use this information to anticipate another's false belief-based action. We propose that the implicit ToM deficit in ASD is not as persistent and impenetrable as it seems. Future research has to evaluate possibilities to tackle the lack of spontaneous belief appreciation with learning from experience. More evidence for compensatory learning in implicit social cognition would support the previously tentatively stated idea that compensatory strategies can be taught to face impaired implicit social cognitive processes in ASD [43].

To conclude, the analysis of eye movements has substantially advanced our understanding of ToM reasoning in ASD. The advantage of eye tracking to tap into more implicit social cognitive

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processing makes this method an integral part of future research on two-systems accounts of functional and dysfunctional ToM.

3. Explicit theory of mind reasoning in Autism Spectrum Disorders

3.1. Early explicit ToM in spontaneous mental state language

In the second year of life, typically developing children begin to refer to invisible and abstract entities, like their own and others' psychological states. Such states can be volitional states (e.g., "want"), ability terms (e.g., "hard to do"), perceptions (e.g., "see"), physiological states (e.g., "hungry"), emotional states (e.g., "sad"), moral terms (e.g., "good"), or cognitive states (e.g., "know") (cf. also [44]). All of these states have in common that they describe intangible processes within a person. One key aspect of children's mental state references is that they indicate the development of children's explicit, verbally expressible ToM, which begins to emerge in the second year of life. Mental state vocabulary may serve a variety of conversational functions in discourse (e.g., "you know?" is often used in a colloquial way rather than to inquire after someone's knowledge state) and thus might not always indicate psychological comprehension. However, there is evidence for genuine references to mental states (desires, knowledge, beliefs, emotions) early in development [14].The definition of what a ToM is has different shades of meaning across different areas of research. According to Premack and Woodruff [45] ToM is the ability to attribute mental states to one self and others. This ability can be understood as a "theory" because mental states cannot be observed but have to be inferred. Thus, just like a scientific theory helps researchers explain their data, a ToM helps humans explain the underlying causes of the observable behaviour of others. Since autistic children are impaired in their mental state representation, as assessed in ToM tasks, it seems likely that their spontaneous mental state language production should also be impaired.

The evidence on the development of mental state language in ASD is scarce and partly contradictory. While some studies indicate impairments across a broad range of internal state term categories, others provide evidence for specific impairments or, dependent on the context, even no impairments. For instance, when playing with their preferred toys, children with ASD were specifically impaired in their use of cognitive terms (e.g., "think") and were less other-oriented than neurotypical controls by using fewer mental state terms to call for attention [46]. To detect specific impairments in autistic children, Tager-Flusberg [46] compared 6 boys with Down syndrome (DS) to 6 boys with autism matched for age (range 3 to 6 years) and mean length of utterance (MLU). The children with autism exceeded controls in their use of desire terms (e.g., "want") and references to causes and antecedents of desires. However, they were impaired in their use of cognitive terms and used fewer mental state terms to call for attention. With increasing MLU, autistic children were shown to increase their use of desire, emotion, and perception terms, but not their use of cognitive terms. In contrast, another study [see 9] reported in a sample of 30 autistic children from age 4 to 13 years that in interactions around a wordless picture-book they produced fewer internal state words in any category (emotion, volition, cognition, or perception). Tager-Flusberg [46] reports that in their study the mothers

were asked to select activity toys or games that would best suit the individual interests of the children. Thus, parent-child object play with a familiar toy, due to its interactive nature, might have elicited more desire, perception, and emotion talk in autistic children than would normally be the case. This is corroborated by the fact that in the Tager-Flusberg [46] study autistic children's conversational use of desire terms by far exceeded the genuine use of desire terms. Studies using storybook narratives and memory narratives rather than toys showed that children with ASD were less likely to include terms that referred to cognitive, emotional or perceptual states [46]. Even when using as many internal state terms as controls, children with ASD made less effort to explicate the causes of mental states in their narratives and they were also limited in their ability to monitor and sustain listeners' attention when compared to the narratives of matched controls [47]. This indicates that internal state language might not always be indicative of autistic children's awareness of their own and other's psychological states. This could explain why training autistic children's mental state understanding is not related to their mere use of mental state terms when narrating a wordless picture-book [9], while training their communication of internal state terms in a truly intentional way might be. However, some studies indicate interrelations between autistic children's cognition talk and their overall comprehension of the mind, including more complex emotion understanding. For instance, two studies found significant positive associations between autistic children's use of cognitive terms (while narrating stories to others) and their ToM abilities [48], as well as more specifically, their false belief abilities [49]. In contrast, Losh and Capps [47] found that autistic children's use of mental state terms in personal and storybook narratives (cognitive or affective) were significantly associated with their ability to define emotions, but not to ToM abilities. Recent work [50] showed that autistic children's general ToM scores were related to their use of emotion terms during a wordless picture book interaction, but not to their use of cognition terms. Differences across studies might have to do with context effects on internal state talk. In some contexts autistic children might communicate psychological meaning, in some contexts they might not. Note that internal state talk was assessed differently in each study. Further, as tasks tap into different facets of ToM, including children's comprehension of hidden emotion, moral and irony, developmental links between talk about psychological states and children's conceptual comprehension might also become increasingly complex. In regard to ToM development, consistent with the development of mental state talk in English-speaking (Bartsch & Wellman, 1995) [14], as well as in children speaking other languages [51], typically-developing children [52] usually first come to understand own desire and own beliefs, before they come to understand perceptions and others' false beliefs, as well as hidden emotions and finally, children grasp that other people can misconstrue others' minds (second-order theory of mind) [53]. In contrast, autistic children show the same developmental sequence up to a point, but in the later steps of progression, they show a significantly different sequence of understandings [54]. While they lag behind several years, like in typically-developing children, autistic children's understanding of desires precedes an understanding of belief. In addition, they comprehend knowledge and ignorance before they develop a grasp that someone can hold a belief that differs from reality and is false. In contrast to typical development, autistic children were shown to understand hidden (or false) emotions slightly earlier than false beliefs.

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In order to provide a fuller picture, future research needs to explore context effects on autistic children's internal state language. For instance, situations that prove motivating for autistic children are likely to be nonsocial in nature and might involve mechanical systems (e.g., mechanical toys) [55]. These situations might provide autistic children with opportunities to talk about their own volitional and eventually, also emotional states. Consistently, autistic toddlers were found to exceed boys with Down syndrome in their use of desire terms (e.g., "want") and references to causes and antecedents of desires when playing with their own toys [46]. Further, children with autism were found to use less mental state language when describing picture-sequences involving human intentions than controls, while they did not differ from controls when describing pictures depicting behavioral interactions or mechanical actions [56]. Finally, when describing mechanical or intentional launching effects of animated stimuli, 6-to 15 year old autistic individuals [57] were found to use as many mental state terms as controls. What remains unclear is if this kind of mental state talk is related to child ToM. Further, studies need to explore if and how autistic individuals' impaired social attention (e.g., [58]) is related to both children's talk about and comprehension of the mind. According to socio-constructivists, triadic interactions, which emerge at about the end of the first year of life and involve the infant, another person and an object, event, or mental states, are thought to be the basis of children's ToM development (cf. [59]). Note that consistent with the socio-constructivist view of language development, longitudinal work in typically-developing children showed that joint attention skills are developmentally related to children's internal state language vocabulary [16]. A rather general main proposal of the socio-constructivist view is that children actively construe [60] a ToM by interacting and communicating with other individuals, as opposed to "passively" acquiring a theory of mind. According to socio-constructivists, triadic interactions, which emerge at about the end of the first year of life and involve the infant, another person and an object, event, or mental states, are thought to be the basis of children's theory of mind development. For instance, talk about cognitive states within the family is thought to be causally related to inter-individual differences in ToM development. The developmental process itself is gradual and cumulative. This view corresponds to the contextual view of semantic development [61]. In summary, the contextual view emphasizes the relevance of early communicative exchanges in establishing the meaning of mental verbs. It is the functional use of mental state terms in familiar and recurrent contexts, in which children communicate pre-linguistically and verbally with others, which according to this view plays a central role for the development of mental state language. This view suggests that the pre-verbal obtainment of objects (such as the use of proto-imperatives [62] is at the centre of joint attentional communicative exchanges from which desire verbs emerge and that the subsequent linguistic development involves expanding the number of ways of talking about desires within communicative acts. For instance, children have to learn that "like" is used to describe a general preference which is distinct from seeking to obtain something for the moment being, as would be indicated by "want". In sum, the contextual view considers semantic development to be the product of the social practices, framing the purpose of words, the pragmatic purposes of the words, the peculiar syntactic properties of the verbs, and the relevant cognitive development. Turnbull & Carpendale [63] found numerous examples of

criteria displays (pointing to a person's puzzled look and describing the person to be "thinking") in typically-developing mother-child dyads.

One direct implication of the contextual view is that if the criteria that are normally displayed in parent-child dyads are impaired, as is the case in autism, this might be related to children's delayed ToM performance. Further, mothers might also be influenced by children's skill level. Recent research by Slaughter, Peterson, & Carpenter [64] suggests that mothers' mental state talk is connected to both infants' joint visual attention and their emerging pointing skills. For instance, mothers seem to switch their conversational focus from their infants' visual behaviour and experiences to the object of their mutual attention and children's imperative pointing gestures are directly followed by mothers' talk about volitions and intention, while later, declarative gestures are followed by both, epistemic and cognitive state talk. If children point less, this might lead parents to talk less. For instance, in a case study [65], all parental talk directed to a young child with autism at home over a day-period was analysed for internal state language focusing explicitly on the thoughts, feelings, and perceptions of animate beings. Compared to what has been found in parents of typically developing children, the parents rarely elaborated on the causes and consequences of these internal states and they primarily referred to sensory and desire terms (the mother did so in 24% of her utterances, while the father did so in 33% of his utterances).

3.2. Later explicit, spontaneous ToM: Mind-Mindedness

There is ample evidence for a deficit in ToM for others in adults with ASD (see [66] for a review). More specifically, autistic adults are severely impaired in their ability to decode affective (e.g., reading emotions from the eye region) and cognitive states. There is, however, a growing dissatisfaction with the tasks used to assess ToM abilities in adults with ASD.

One prominent task to measure autistic individual's emotion understanding (affective ToM) is the Reading-the-Mind-in-the-Eyes task (RME task; [3]). The task contains 36 black/white photographs of the eye region expressing complex mental states in terms of emotions, such as 'jealous', 'bored', or 'admiring'. Participants have to distinguish the correct mental state from three distractors (i.e., mental state terms with the same emotional valence as the target) on each trial. Previous research has shown that the performance on the RME task is inversely correlated with the degree of autistic impairments and is significantly lower in autistic adults when compared to controls (e.g., [67,68]). Autistic individual's comprehension of cognitive states is usually measured with the Strange Stories-test [69]. This test is also called the short stories task and comprises five mental short stories referring to five different advanced ToM abilities: double bluff, white lie, deception, misunderstanding, emotion understanding. The short stories require participants to provide mental state justifications for story characters' nonliteral statements and thus measure ToM for others. Research has shown a general deficit on advanced ToM tasks in adults with ASD which appears on the social-perceptual level, as well as on the conceptual level, with reference to self and others (e.g., [70]), In regard to ToM for other, the worse performance of the ASD group on the RME task compared to controls provides further evidence for an impairment of social–perceptual processes, which enable mental state decoding from nonverbal cues (i.e., eye gaze), in ASD (e.g., [3]). The results from the mental

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short stories clearly indicate that adults with ASD have difficulties in providing mental state justifications for story characters' nonliteral statements (i.e., double bluff, white lie, deception, misunderstanding), as well as in emotion understanding. In most studies, the deficit in mental state reasoning observed in ASD appears largely independent of verbal and non-verbal intelligence. Few studies have explored ToM for self, with results indicating severe and specific deficits in self-knowledge in ASD (see [71]). In sum, the assessments of ToM abilities and deficits in adults with ASD are highly specific, posing considerable verbal demands, and neglecting a wide range of competencies underlying spontaneous mentalizing.

In developmental research, the concept of Mind-Mindedness (MM) has been productively used by Meins and her colleagues to capture individual differences in the spontaneous tendency to conceive of a person in mentalistic (as oposed to behavioural) terms. Meins, Fernyhough, Russell & Clark-Carter, 1998 [72] first studied the concept in mothers by letting them describe their children. They found that mothers differ in the degree to which they reflect upon their children in mentalistic terms rather than based on their outward appearance or behaviour. Thereby, a greater number of mental terms (e.g., "*he is reflective*") instead of behavioural terms (e.g., "*he likes to ride his bike*"), physical (e.g., "*he has brown hair*") or general terms (e.g., "*he is my neighbour*") indicate a higher degree of mindedness in regard to others' mind (mind-mindedness) (cf. [73]). Meins and colleagues [73] have since extended the concept to friends, romantic partners and works of art.

If individuals with ASD are impaired in their everyday, spontaneous ability to conceive of themselves and others as mental agents, then this deficit should be reflected in their person descriptions. To date, the concept has only been employed in one study [74] with respect to self-descriptions. Few studies have investigated self-concepts of individuals with ASD at all (e.g., [75]). In an early study, Lee and Hobson [76] employed a self-understanding interview [77] in a sample of children and adolescents with and without ASD and found that participants with ASD produced significantly fewer self-descriptors scored as "social" compared to controls. Further, an elaborated analysis of the content of psychological statements highlighted qualitative differences: More than half of the psychological self-descriptors in the ASD group referred to preferred activities (e.g., 'I like swimming.'). The study by Kristen, Rossmann, Sodian, [74], used the MM-task adapted from Meins & Fernyhough (cf. [73,78]). Since MM was assessed in adults, a representational measure of MM was used. Participants were given a simple, open-ended instruction: "Can you describe yourself for me? What kind of a person are you? Tell me everything you consider as important to describe yourself!" Participants were not given any hints on how to answer the question. The results suggest that when compared to typically-developing controls, individuals with ASD use fewer mental self-descriptors, which appears to point to their inability to reflect on their own mental states in a mind-minded way. This result remained stable when controlling for verbal and non-verbal IQ.

The following paragraph is an example (translated from German) of an autistic male's self-description referring mainly to general information and physical aspects.

"First, my age and I have siblings and so on. I am 37 years of age and will turn 38 on the 29th of november. My hobbies are varied: I hike, I ride my bike, I watch TV, I go to the theatre and to the ballet, the opera. I perform on stage and I write poems. I have brown-blond hair and blue eyes. I always smile. I have had

surgery, but I don't want people to know. I'm autistic and this is important for people to know. I also repeat myself sometimes. But I will manage this problem. I work 8 hours a week. I'm very interested in the weather, that is my work and in maps, as a hobby. Sometimes I read books".

The following paragraph constitutes a more mind-minded description from a participant from the control group. Note that even a less talkative person's self-reflection can contain a high percentage of mind-minded comments. This demonstrates that mind-mindedness is independent of verbosity. The paragraph also shows the relatively low levels of general and behavioral information in a typically-developing person's self-description.

"I am a very considerate person. I reflect a lot upon myself and others. I am also very sensitive and interested in artistic aspects of human existence. I am also a bit arrogant, or at least, others might think I am arrogant. But I am also honest and trustworthy. "

ToM for self does not take into account the accuracy or appropriateness of mental state ascriptions (cf. [73]). Thus, it remains an open question how appropriately autistic adults reflect on themselves. Consequently, studies need to address not only if, but how appropriately ASD patients ascribe mental states to themselves.

Since impaired ToM for self is connected to an impaired episodical, autobiographical memory it might also be seen as a valid indicator of an impaired identity development in autism. In contrast to semantic traces, episodic traces cannot be formed (i.e., events cannot be encoded as experienced) without a ToM. According to Tulving [79,80] and colleagues [81], the involvement of self (autonoetic) consciousness is assumed to be critical for episodic autobiographical memory in adulthood. Thus, episodic memory deficits in adults with autism might be due to a diminished level of self-consciousness at encoding. The work by Kristen et al. [74] showed a specific correlation between MM for self and personal episodic memory that was independent of verbal and non-verbal IQ and that can be interpreted in terms of introspection. Introspection is essential for ascribing mental states to oneself as well as for re-experiencing personal episodic memories. A study by Perner et al. [82] showed that a modality-specificity test of ToM, which required introspection, yielded the highest predictive value of episodic memory performance compared to other ToM tasks. This was seen as evidence that introspection is functionally related to children's understanding of the sources of their experience. More specifically, when children re-experience (i.e., remember actively) a past event, they have to understand that the origin of this experience lies in the past (understanding source of experience) and that this experience is a representation of the original experience (meta-representational understanding). Further, the correlation might reflect autobiographical meaning making skills. It has been proposed that the construction of autobiographical memories constitutes a complex, narrative process [83,84]. Thereby, the use of mental state terms is a good indicator that one has formed organized explanatory accounts of past events that are integrated with a subjective perspective on one's own thoughts and emotional reactions to autobiographical events [85]. Further, if autobiographical memories are less coherently constructed this, in turn, might lead to the need for more prompts to retrieve personal episodic memories. In support of this view, a study of young school-children [86] suggests that controlled retrieval processes are required to tell about one's past. Like younger children, individuals with ASD might have a less coherently constructed cognitive memory network (i.e., they might not have linked

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causes to consequences of events) and thus, they might also encounter difficulties in triggering specific nodes within that semantic network (cf. [87]).

3.3. Summary

In sum, studies in autistic children as well as in adults demonstrate a clear deficit in referring to internal states. Further, autistic individuals also lack the ability to comprehend mental states. Thereby, early in development children might lack implicit understanding needed for interactions involving joint attentional cues [88], which in turn, might lead to delayed and impaired mental state language development. Further, work from our own laboratory (Kristen, Vuori, Sodian,[89] submitted) suggests that even if autistic children refer to internal states, it is only the internal state language they utter in a joint attention context in combination with their sustained attention that is related to children's more complex ToM-skills. One possible reason is input poverty, since parents might use less complex internal state language towards children who provide them with fewer joint attention cues and are less attentive. As a result, as adults autistic individuals are not only impaired in their spontaneous explicit ToM, involving implicit decoding skills (as measured by the REM task), but also show deficits in explicit mental verb usage (as measured by the Mind-Mindedness task) that might be based on joint attention deficits.

To conclude, studies on spontaneous explicit ToM support the idea of a ToM deficit in autism. Impairments occur independently of verbal and non-verbal IQ. Thus, the deficit seems to be specific.

4. General conclusions

The empirical investigation of implicit and spontaneous ToM reasoning in ASD is still in an early stage. Yet, the available evidence supports the ToM hypothesis by indicating specific impairments in ASD. With regard to implicit ToM processing, available eye tracking evidence consistently indicates that implicit ToM reasoning is impaired in ASD even in high-functioning adults with ASD, who pass experimental explicit ToM tasks. Individuals with ASD seem to lack a spontaneous sensitivity to other's mental states. This specific deficit might be one origin of social-cognitive deficits and difficulties in social interactions. Further research is needed to evaluate how persistent this implicit ToM deficit is and if learning through experience, or even explicit instructions, can compensate for it. To this end more within-subject studies that systematically assess implicit and explicit ToM task performance, as well as the influence of different forms of training, are desirable.

Moreover, for a better understanding of social-cognitive deficits in ASD we need to gain more knowledge about how individuals with ASD process social signals in general, not only how they process false beliefs. According to a recent account, sensitivity to ostensive signals, such as direct gaze or addressee-directed speech, is essential for learning through social interaction [90]. An impaired processing of ostensive signals in ASD could result in insufficient learning from others, another burden in the life of individuals with ASD.

Another important issue in research on implicit and explicit ToM in autism concerns task analysis: To what extent do certain tasks require automatic, on-line tracking skills (e.g., non-verbal decoding skills) versus conscious and learned reflection on mental states (e.g., the use of mental state vocabulary when describing oneself). The REM task, for instance, requires both types of processing, since one has to decode emotions but also to ascribe the correct verbal label to the emotion. Therefore, it is difficult to pinpoint the nature of autistic individuals' impairments in the task. Similarly, self-descriptions pose complex demands on different levels of processing. Impairments of individuals with ASD may arise from deficits in the fast and automatic retrieval of self-related information as well as from an inability to express their ideas about themselves with a mentalistic vocabulary they have not fully acquired, thus leading to a less detailed and mentalistic account of themselves as individuals. Future research needs to further analyze the relative contribution of implicit and explicit skills in solving a wide array of ToM tasks.

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Interventions

Chapter 8

Speech-Language Pathology in the Assessment and Diagnosis within the Autism Spectrum

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Additional information is available at the end of the chapter

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1. Introduction

The main purpose of this chapter is to discuss assessment tools that can be used with children and adolescents of the autism spectrum and verify their effectiveness. It will be based on two studies that present the application and comparison of 4 different diagnostic tools. These four instruments are not language-specific and therefore can be used with different groups of children that speak different languages. Certainly cultural variations must be considered but the possibility of using tools that are internationally recognized may contribute to the efforts in improving the amount of information about diagnosis and treatment as proposed by the World Health Organization (WHO) in the World Report on Disabilities (2012).

The first study associates two different methods for identifying the functional communicative profile of children with autism, specifically regarding the initiative and interactivity of communication of individuals with autism.

The FCP-R is a protocol designed to the individual communication assessment developed by Kleiman (1994). It provides a simple and organized evaluation procedure based on age and acquired and/or developmental deficits. It can be used in four different ways: based on an interview with the therapists or the parents; direct assessment of the child/adolescent of observation of filmed samples.

This tool assesses the individual communication abilities in the following areas: Sensory/ Motor; Attentiveness; Behavior; Receptive Language; Expressive Language; Pragmatic/Social;

Speech; Voice; Oral; Fluency and Non-Oral Communication. To this study the areas of Behavior; Attentiveness; Receptive Language; Expressive Language and Pragmatic/Social were selected.

The analysis of the functional communicative profile (FCP) adopts the criteria proposed by Fernandes (2004). It uses 15-minute filmed samples of patient-therapist interaction. In these situations the dyads play with toys regularly used in language-therapy sessions and that usually produced good communicative situations. Data are recorded, transcribed and analyzed with a specific protocol.

The analysis of the FCP uses the Pragmatic Recording Protocol [8]. This study used the data about the communicative functions. After the record of the data in the specific protocols the incidence of each communicative function expressed by the participant is determined as well as the proportion of the communicative space occupied, the number of communicative acts expressed per minute and the proportion of more interactive communicative acts expressed.

The occupation of the communicative space is determined by the ratio of communicative acts produced by the participant and by the therapist in each sample. The number of communicative acts expressed per minute was obtained by the ratio of communicative acts expressed and the size of the sample (in minutes). The proportion of interactive communicative acts is defined by the ratio of all communicative acts expressed by the participant and those that expressed one of the more interactive communicative functions.

2. Methods

This chapter will describe two different studies and discuss their results.

2.1. Study 1. Comparison of the *Functional Communicative Profile and the Functional Communicative Profile-Revised* of children and adolescents with autism spectrum disorders

2.1.1. Methods

Participants were 50 children and adolescents with ages between 3 years 9 months and 14 years 8 months (average 7 years 11 months) of both genders with Autism Spectrum Disorders (ASD) attending a specialized Speech-Language Pathology (SLP) service for periods of six months to two years.

All participants were assessed according to the criteria of the *Functional Communicative Profile* (FCP) and of the *Functional Communication Profile – Revised* (FCP-R). The results were recorded, scored and classified.

Since the FCP-R is a tool with technical data, extensive and detailed; therefore it was applied by means of interviews with the speech-language therapist of each participant. All the SLPs have been assigned to each participant for at least six months prior to the interview. This time was considered enough to the therapists to have all the information demanded by the FCP-R.

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The analysis of the FCP considered the five minutes with more symmetric interaction of each sample.

2.1.2. Data analysis

The data obtained by the FCP-R and FCP assessments were individually analyzed, identifying the global performance based on individual comparison.

This comparison used the following areas of the FCP-R:

- Behavior;
- Atention/Concentration;
- Receptive Language;
- Expressive Language;
- Social/Pragmatic.

Data obtained with the use of both tools were compared by the t-Student test and the adopted significance level was 0.05 (5%).

With the purpose of verifying if there were linear correlations between the analyzed areas of both tools the Correlation test was also used. The correlation test identifies the correlation coefficient, that can be positive or negative. In the first case, the positive correlation, the variables present a similar behavior, i.e., if one of them increases the other increases also, and vice-versa. In the negative correlation the variables present the opposite behavior, i.e., if one of them increases the other decreases, and vice-versa.

Data about communication interactivity, number of communicative acts expressed per minute (CAM) and the proportion of communicative space occupied (CSO) were analyzed by means of their averages.

2.1.3. Results and comments

The comparison between the FCP and the FCP-R used the proportion of communicative interaction (CI), the CAM and the CSO obtained by each participant's FCP. CI was obtained by the ratio of the more interpersonal communicative acts expressed and the total of communicative acts expressed. It is considered a very significant data about the overall interactivity of the communication. CAM and CSO were obtained as described above.

The descriptive statistics is presented in the following tables.

The median of the results regarding CI was determined in order to classify the participants as more interactive or less interactive. The individual results presented large variation and the objective of this classification was to associate theses results with the selected areas of the FCP-R. The areas of *Behavior, Attentiveness, Receptive Language, Expressive Language* and *Social/Pragmatic* of the FCP-R were considered the most relevant to this comparison. The median of CI in the FCP was 53.75. Therefore, individuals with interactivity above this level were

considered the more interactive group and those bellow this level were considered less interactive participants.

The association of values of CI obtained in the area of *Behavior of the FCP-R* is presented in Figure 1.

Average	54.35
Standard error	3.05
Median	53.75
Standard Deviation	21.61
Variance	466

Table 1. Descriptive statistics – Communication Interactivity-FCP

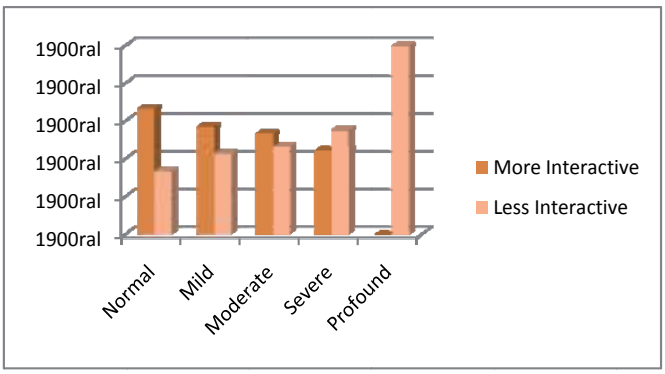

Figure 1. Proportion of communication interactivity de interactivity in the area of *Behavior*

Table 2 shows the comparison of the results in the area of *Behavior in the FCP-R* and its correlation with the proportion of interactivity of communication verified by the FCP.

Severity	**Normal**		**Mild**		**Moderate**		**Severe**		**Profound**	
Behavior(%)	6		14		60		18		2	
Interactivity	More	Less	More	Less	More	Less	More	Less	More	Less
	2	1	4	3	16	14	4	5	0	1
p-value	0.5		0.39		0.16		0.37		0.72	
Correlation coefficient	-0.33445									

Table 2. Association between the area of *Behavior* in the FCP-R and the proportion of communicative interaction in the FCP.

Data suggest that the group defined according to behavioral disorders do not present significant differences regarding the proportion of communication interactivity. However, when the

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linear correlation is considered it can be observed that as the severity increases in this domain the communication interactive proportion decreases. It characterizes a negative correlation, suggesting that participants with more sever behavioral disorders show less interactive communication.

Considering behavioral issues, [21] suggests that intervention focus on communication and interpersonal relationship tends to decrease the behavioral disorders of persons with ASD such as aggression and disruptive behaviors.

The values obtained to communication interaction in the FCP in the area of Attentiveness in the FCP-R are presented in Figure 2.

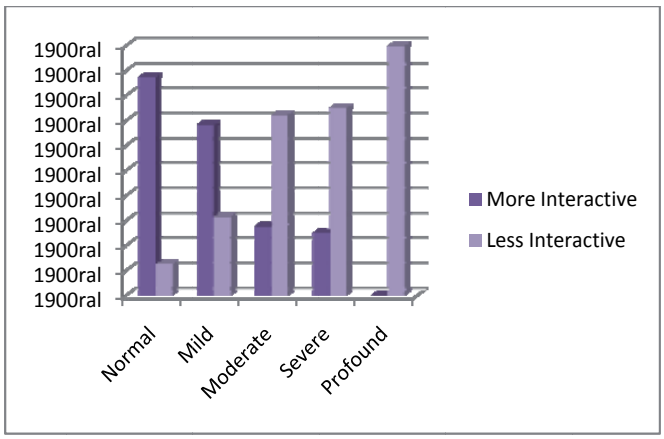

Figure 2. Proportion of communicative interaction in the area of Attentiveness.

Table 3 shows the association of the results in the area of *Attentiveness* of the FCP-R and the proportion of communicative interaction of the FCP.

Severity	Normal		Mild		Moderate		Severe		Profound	
Attention/ Concentration (%)	16		38		36		8		2	
Interactivity	More	Less	More	Less	More	Less	More	Less	More	Less
	7	1	13	6	5	13	1	3	0	1
p-value	0.0009*		0.002*		0.0008*		0.18		0.72	
Correlation coefficient	-0.44623									

*Significant value in the t-Student test at 95%

Table 3. Association of the area *Attentiveness* of the FCP-R and the proportion of communicative interaction of the FCP.

Observing the data we may conclude that the groups defined by deficits in *attention/concentration* present significant differences regarding the proportion of communicative interaction

in the first 3 levels of severity: normal, mild and moderate. In the normal and mild levels the significant results are associated to individuals with high proportions of communicative interaction whereas in the moderate level they are associated with the individuals with low communicative interaction. Analyzing the linear correlation it can be observed that the proportion of communicative interaction decreases as the severity of the *Attentiveness* deficits increases. These data indicate that attentiveness interferes directly in the IC since individuals with better attentiveness results also have higher proportions of IC. In this aspect, [14] have already stated that an attention deficit may be responsible for both the functional language disorders and the social impairment of individuals with ASD.

Figure 3 shows the values regarding the area of *Receptive Language* of the FCP-R and *communicative interaction* according to the FCP.

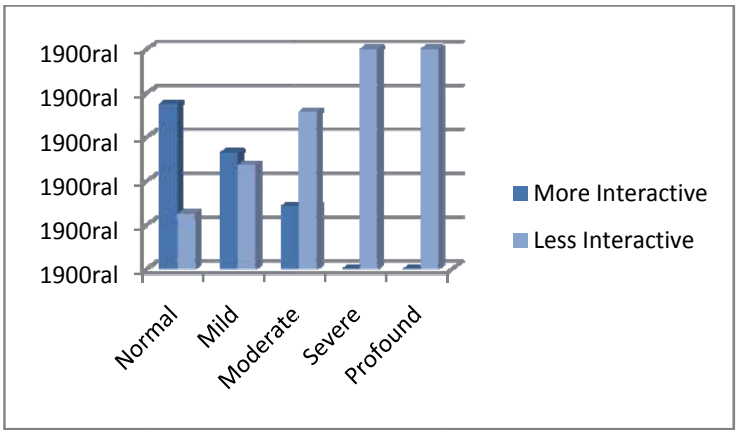

Figure 3. Communicative interaction and Receptive Language.

Table 4 shows the association of the results in FCP-R's area of *Receptive Language* and FCP's communicative interaction.

Severity	Normal		Mild		Moderate		Severe		Profound	
Receptive Language (%)	40		34		14		10		2	
Interactivity	More	Less	More	Less	More	Less	More	Less	More	Less
	15	5	9	8	2	5	0	5	0	1
p-value	<0.001*		0.34		0.07		0.03*		0.72	
correlation coefficient	-0.74981									

*Significant value in the t-Student test at 95%

Table 4. Association of the Receptive language area of the FCP-R and the proportion of communicative interaction of the FCP.

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It is possible to consider that there is a negative correlation between the area of Receptive Language of the FCP-R and the communicative interaction of the FCP. As the severity of receptive language disorders increase, the communicative interaction decreases.

Figure 4 presents the results of the *Expressive Language* area of the FCP-R according to the communication interactivity of the FCP.

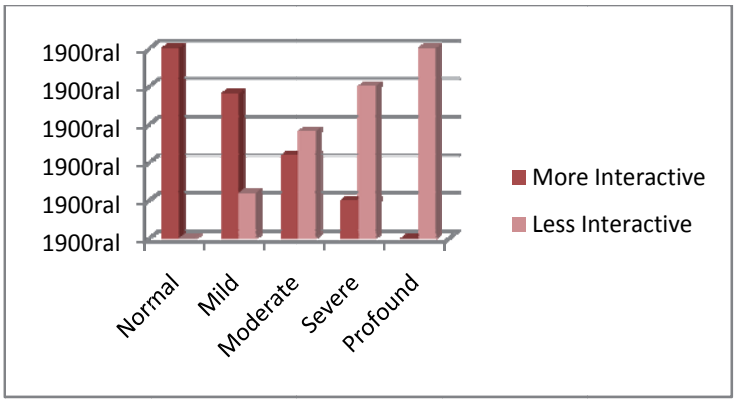

Figure 4. Communicative interaction and Expressive Language

Table 5 presents the association of the results in FCP-R's area of *Expressive Language* and FCP's communicative interaction.

Severity	Normal		Mild		Moderate		Severe		Profound	
Expressive Language (%)	2		42		32		20		4	
Interactivity	More	Less	More	Less	More	Less	More	Less	More	Less
	1	0	16	5	7	9	2	8	0	2
p-value	0.72		<0.001*		0.16		<0.001*		0.46	
Correlation Coefficient	-0.10007									

*Significant value in the t-Student test at 95%

Table 5. Association of the Receptive language area of the FCP-R and the proportion of communicative interaction of the FCP.

These data suggest that there is a negative correlation between the area of Expressive Language of the FCP-R and the communicative interaction of the FCP. As the severity of the expressive language disorders increase, the communicative interaction decreases.

The negative correlations in both receptive and expressive language areas of the FCP-R indicate that IC decreases as the language disorders severity increases. A study conducted by [19], analyzing the functional aspects of the answers of children with severe Specific Language Impairment (SLI) observed that this children are less efficient than their peers of the same age. The authors suggest that this indicates that the formal aspects of language interfere directly in its functional efficiency.

Data about the association between communicative interaction as assessed by the FCP and the area of Social/Pragmatic of the FCP-R are displayed on Figure 5

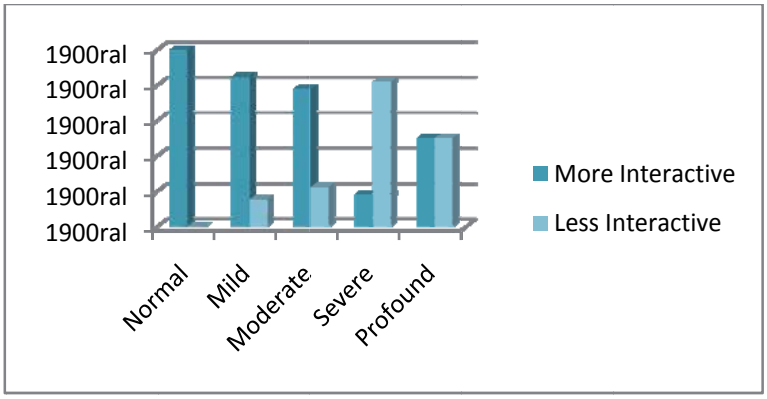

Figure 5. Communicative interaction and Social/Pragmatics

Table 6 presents the association of the results in FCP-R's area of *Social/Pragmatics* and FCP's communicative interaction.

Severity	Normal		Mild		Moderate		Severe		Profound	
Social/ Pragmatic (%)	4		26		18		44		8	
Interactivity	More	Less	More	Less	More	Less	More	Less	More	Less
	2	0	11	2	7	2	4	18	2	2
p-value	0.46		<0.001*		0.008*		<0.001*		1	
Correlation coefficient	0.683702									

*Significant value in the t-Student test at 95%

Table 6. Association of the Social/pragmatics area of the FCP-R and the proportion of communicative interaction of the FCP.

These results suggest that as the disorders in the social/pragmatic area increases, the communicative interaction decreases.However, there is no linear relation between these variables. The

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questions of the FCP-R regarding this area focus on some important social situations and pragmatic abilities but the answer takes into account just the occurrence of the situation, regardless of its frequency or of the consistency with which happens and not considering the focus of the subject's intention.

These findings suggest that objective protocols to the characterization of the pragmatic abilities may not be sufficient to determine the functional communicative profile of a person with ASD. The specific functional assessment of communication seems to be necessary, with the FCP-R providing complementary but not exclusive information. Other studies also suggest the use of complementary assessment tools in order to characterize, identify and assess individuals with ASD due to the variability of the symptoms presented [2, 20].

Still considering the social/pragmatic area of the FCP-R it could be observed that the group with severe disorders has shown significant difference in the IC proportion. This result indicates that both protocols agree that individuals with low social/pragmatic abilities also have less communicative interaction.

These results also agree with several prior studies regarding this issue. [22] observed that children with ASD present less answers to interactive attempts by others and less spontaneous communication. [13] reported that children with ASD have great impairments in the functional use of communication. [1] observed that, even when interacting with a familiar interlocutor, children with ASD have great difficulties with the interactive use of communication. These authors point out that the FCP usually confirm these difficulties.

Data regarding the average of IC and the severity degree in the FCP-R show large deficits in IC as the severity increases. Figure 6 shows the association of the mean proportion of communicative interaction and the areas of the FCP-R that were considered in this study. It indicates that the overall severity of the FP-R is determinant to the proportion of IC.

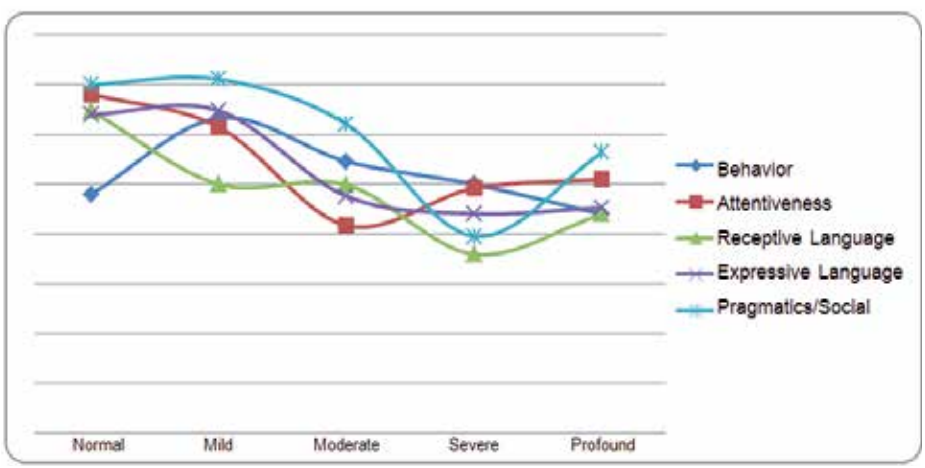

Figure 6. Mean proportion of communicative interaction associated with the FCP-R

The distribution of the average proportion of communicative interaction in this group of participants shows that there is an important decrease in interactivity associated to the increase in severity of the disorders in the areas of the CFP-R that were analyzed.

The following data refer to the association between other aspects of the FCP – communicative acts expressed per minute (CAM) and proportion of the communicatuve space occupied (CSO) and the same areas of the FCP-R.

	Behavior				
	Normal	**Mild**	**Moderate**	**Severe**	**Profound**
CAM	11.3	7.4	7.9	8.1	15.4
CSO(%)	38	42.6	44.1	39.7	39

Table 7. Average of CAM and CSO associated to the *Behavior* area of the FCP-R

The number of communicative acts expressed per minute was similar in the participants with mild to moderate behavior disorders; but it varied in those with *normal* behavior and even more to the ones with profound behavior disorders. However, considering the proportion of the communicative space that was occupied by the participants, all groups had an average bellow 50% (that would indicate an even distribution of CEO among the dyad). It suggests that the large number of communicative acts expressed per minute doesn't leads to communicative efficiency.

The association of behavior disorders identified by the FCP-R and the indicators of communicative intent (CAM and CSO) of the FCP has similar results for the various severity scores. It may suggest that the isolated communicative intent (no adequately addressed) doesn't result in functional efficiency. This brings to attention the issue of the need to take the communicative context into consideration when analyzing pragmatic abilities of individuals with ASD [5, 12].

The averages of CAM and CSO associated to the Attentiveness area of the FCP-R are presented in Table 8.

	Attentiveness				
	Normal	**Mild**	**Moderate**	**Severe**	**Profound**
CAM	8.3	9.1	7.2	9	7
CSO(%)	41.4	45.7	40	39	52

Table 8. Average of CAM and CSO associated to *Attentiveness*

Although the CAM average didn't present a linear distribution, it has a slight decrease between the *severe* and *profound* groups. It suggests that the participants with large attention deficits may even occupy the communicative space symmetrically but their communicative intent is

reduced. Children with severe attention deficits may show more difficulties to start communication when compared to children with mild no none attention deficits.

The averages of CAM and CSO associated to the *Receptive Language* area of the FCP-R are presented in Table 9.

	Receptive Language				
	Normal	**Mild**	**Moderate**	**Severe**	**Profound**
CAM	8.5	8.2	8.7	6.2	7.8
CSO(%)	43.7	40.9	45.1	40.4	42

Table 9. Average of CAM and CSO associated to *Receptive Language*

CAM's average shows a decrease tendency as the deficits in receptive language increases, although this is not a linear association. These data seem to suggest that language comprehension is closely associated to the performance regarding the initiative to communicate that is reflected in the number of communicative acts expressed per minute. The association of the severity of the deficits in receptive language and IC has shown that the difficulties in understanding the language expressed may be associated with the few IC. The same occurs with the expressive language: individuals with more impairments tend to show less CAM.

The averages of CAM and CSO associated to the *Expressive Language* area of the FCP-R are presented in Table 10.

	Expressive Language				
	Normal	**Mild**	**Moderate**	**Severe**	**Profound**
CAM	13	8.4	8.3	7.8	5.6
CSO(%)	24	43.7	44.6	38.7	44.5

Table 10. Average of CAM and CSO associated to *Expressive Language*

These data point out to the interdependency between the severity of the deficits in *expressive language* and the CAM. There is a clear decrease in the number of communicative acts expressed per minute as the severity of the deficits increases. Therefore, it seems clear that the expressive language abilities are directly associated to the CAM in the FCP.

A longitudinal study of the pragmatic abilities of children with SLI [3] indicated that the CAM is the clearer parameter of disorder for these children.

The association of the social/pragmatic area and CAM and CSO has shown that even small impairments in this area of the FCP-R have are related to proportional deficits in the FCP. These data confirm prior studies [6, 7] that assessed pragmatic therapeutic intervention processes in 6-month to 1-year periods and observed association of results regarding CAM, CSO and IC.

The averages of CAM and CSO associated to the *Social/ Pragmatic* area of the FCP-R are presented in Table 11.

	Social/Pragmatic				
	Normal	**Mild**	**Moderate**	**Severe**	**Profound**
CAM	9.8	8.8	8.8	7.5	8.1
CSO(%)	33.5	45.2	40.1	42.5	44.8

Table 11. Average of CAM and CSO associated to *Social/ Pragmatic*

The CAM average for the *normal* group is higher than all the other groups. It may suggest that any social/pragmatic deficit interferes with the communicative initiative of individuals with ASD.

The analysis of the CAM and CSO averages regarding the selected areas of the FCP-R are presented in figures 7 and 8.

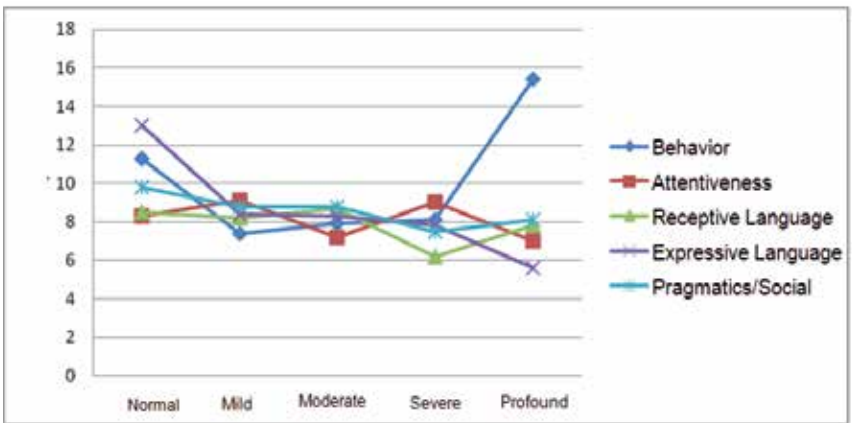

Figure 7. Average of CAM and the selected areas of the FCP-R.

Several studies have been conducted regarding the development, adaptation and validation of diagnostic and severity scales for ASD in Brazil [15, 17]. There is still no single tool that can provide all the information regarding characterization and severity scores. Therefore the use of complementary protocols seems to be the better alternative for comprehensive and detailed diagnostic and description that will allow efficient planning of intervention procedures. It is true to other countries where other languages are used. Linguistic and cultural adaptations are at least as important as the translation from one language to the other when the use of a foreign assessment toll is proposed.

The second study aimed to identify useful tools to the assessment of the diagnostic hipothesis of ASD and their specific characteristics

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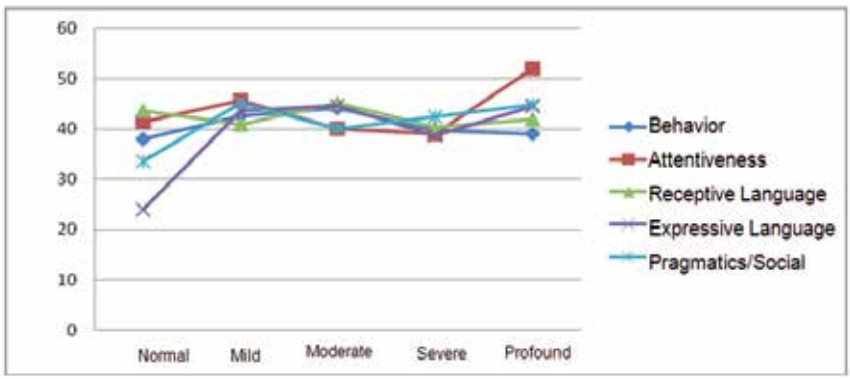

Figure 8. Average of CSO and the selected areas of the FCP-R.

2.2. Study 2. Comparing the results of DAADD and ABC of children included in Autism Spectrum Disorders

2.2.1. Methods

Participants were 45 individuals with ASD and their language therapists. All the individuals were assessed and received language therapy at the Speech-Language Research Laboratory in Autism Spectrum Disorders (LIF-DEA) of the School of Medicine – University of São Paulo (FMUSP), Brazil. They all had been diagnosed with ASD by neurologists and/or psychiatrists according to the DSM-IVtr (2002) or the IDC-10 (2003) criteria.

The *Differential Assessment of Autism and Other Developmental Disorders* (DAADD) [10] was proposed to differentiate, by means of the identification of the child's behavior, specific developmental disorders such as autism, Rett syndrome (RS), Asperger syndrome (AS), pervasive developmental disorders not otherwise specified (PDD-NOS), apraxia, mental deficits (MD) and other syndromes (OS). These three last categories were not focused in this study because they are not included in the ASD according to the DSM-tr or the IDC-10.

According to the DAADD guidelines the participants were divided groups according to their ages (2-to-4years; 4-to-6 years and 6-to-8 years) and age-specific protocols were used to the assessment. Each group comprised 15 participants. Familiar income and school level were not considered inclusion criteria. The DAADD uses technical data, is extensive and demands detailed information; therefore it was applied during an interview with the speech-language therapists of the 45 participants. All the therapists are speech-language pathologists and audiologists (fonoaudiólogas) and were working with the participants for at least 1 year [10].

Figure 9 shows the distribution of the participants according to their ages.

The medical diagnosis of the participants was determined by psychiatrists or neurologists working in public and private services of the state of São Paulo (Brazil). And the distribution of the diagnosis was: 29 children with ASD; seven with PDD; five with PDD-NOS; two with AS; one with High Functioning Autism (HFA) and one with Atypical Autism.

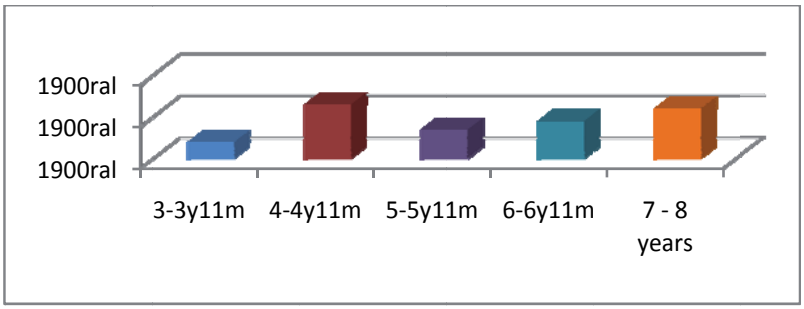

Figure 9. Age of the participants.

Data regarding the Autism Behavior Checklist (ABC) were retrieved from the individuals protocols registered at the LIF-DEA of FMUSP where it is regularly used during the annual assessment process. The ABC (Krug, Arick & Almond, 1993) identifies the non-adaptative behaviors and indicates the probability of the diagnosis of autism. The questionnaire focus on 57 items of atypical behavior within 5 areas: language, sensorial, relational, use of body and object and social abilities. The scores are totaled by area and generate the final general score.

Figure 10 shows the distribution of the participants according to the results of the ABC.

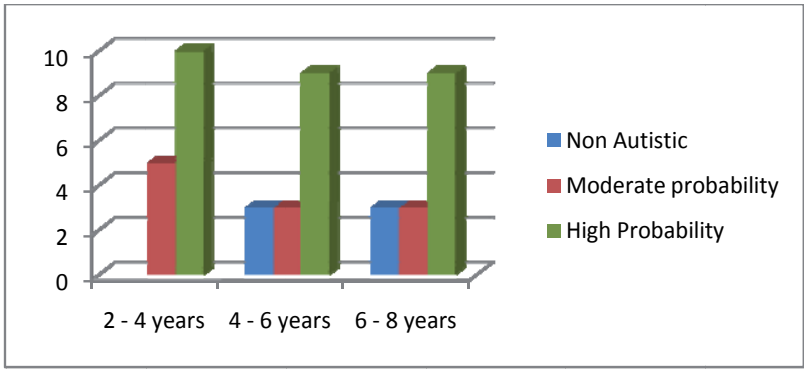

Figure 10. Autism probability according to the *Autism Behavior Checklist*.

2.2.2. Data analysis

Data obtained in the two assessments were analyzed for each subject and the global performance was based on the overall results. Data resulting from the ABC and the DAADD wee associated according to their categories, as shown in Table 12.

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Data of both protocols were compared and the adopted significance level was 0.05 (5%). The significant areas were analyzed by the t-Student test and the Wilcoxon test was used to verify linear correlations between them.

Autism Behavior Checklist (ABC)	Differential Assessment of Autism and Other Developmental Disorders (DAADD)
Language	Language
Relational	Pragmatic
Sensorial	Sensorial
Use of body and object	Motor
Social abilities	Behavior

Table 12. ABC and DAADD areas

2.2.3. Results

It was observed that 20% of the older children were considered "without risk for autism" by the ABC.

Table 13 presents the more frequent answers to the DAADD regarding the developmental disorders considered. It was verified that either in G2 and G3 the most frequent diagnosis was "autism".

Age Groups	Diagnosis	Number of participants
G1	Autism	4
	Rett	9
	Asperger	2
G2	Autism	13
	Rett	2
G3	Autism	10
	Asperger	5

Table 13. Developmental disorders according to the DAADD in all age groups

Comparing the DAADD and the ABC it can be noted that although there is no significant difference, there is a great occurrence of RS according to the DAADD. In G1 these children were rated as with high risk for autism, maybe due to the several motor disorders observed.

With the increasing age these proportion decreases and the high risk for autism is the most frequent score of the ABC in groups G2 and G3. In G3 the DAADD attributes the diagnosis of AS to 75% of the participants of G3.

The Wilcoxon test was applied in the comparison of the ABC and DAADD areas. They were compared within each age group in tables 14, 15 and 16.

The answers to the DAADD and to the ABC are similar in each area. These data indicates that with increasing age the diagnosis identified by the DAADD is closer to the medical diagnosis.

Variables	n	Means (%)	Standart deviation (%)	Minimun (%)	Maximum (%)	Percentile 25 (%)	Percentile 50 (Median) (%)	Percentile 75 (%)	p-value
ABC LG	15	28.39	20.41	6.45	80.65	9.68	25.81	41.94	0.003
DA LGG AUT	15	48.44	13.21	33.33	80.00	40.00	46.67	53.33	
ABC LG	15	28.39	20.41	6.45	80.65	9.68	25.81	41.94	0.003
DA LGG RETT	15	54.44	11.73	41.67	83.33	41.67	50.00	58.33	
ABC LG	15	28.39	20.41	6.45	80.65	9.68	25.81	41.94	0.012
DA LGG DN	15	43.14	12.31	29.41	70.59	3.29	41.18	47.06	
ABC RE	15	48.25	17.37	19.05	78.57	35.71	47.62	61.90	0.001
DA PRAG AUT	15	74.67	11.60	60.00	100.00	66.67	73.33	80.00	
ABC RE	15	48.25	17.37	19.05	78.57	35.71	47.62	61.90	0.001
DA PRAG RETT	15	79.56	11.67	66.67	100.00	66.67	80.00	86.67	
ABC RE	15	48.25	17.37	19.05	78.57	35.71	47.62	61.90	0.002
DA PRAG AS	15	75.83	9.99	62.50	93.75	68.75	75.00	81.25	
ABC RE	15	48.25	17.37	19.05	78.57	35.71	47.62	61.90	0.002
DA PRAG DN	15	75.42	10.15	62.50	93.75	68.75	75.00	81.25	
ABC BO	15	62.67	15.76	36.00	84.00	48.00	68.00	76.00	0.017
DA BEH AS	15	43.33	26.01	8.33	91.67	16.67	50.00	66.67	
ABC BO	15	62.67	15.76	36.00	84.00	48.00	68.00	76.00	0.041
DA BEH DN	15	43.03	29.05	0.00	90.91	18.18	54.55	72.73	

Legend:ABC=Autism Behavior Checklist; LG=language, DA=Differential Assessment of Autism and Other Developmental Disorders, LGG=language, AUT=autism, RETT=Rett Syndrome, DN=pervasive developmental disorder not otherwise specified, RE=relating, PRAG=pragmatics, AS=Asperger Syndrome, BEH=behavior, BO=body-object use.

Table 14. Comparison of the different areas of the DAADD and the ABC to G1

Variables	n	Means (%)	Standart deviation (%)	Minimun (%)	Maximum (%)	Percentile 25 (%)	Percentile 50 (Median) (%)	Percentile 75 (%)	p-value
ABC LG	15	60.00	25.51	22.58	93.55	35.48	61.29	83.87	0.001
DA LGG AS	15	25.56	19.02	8.33	75.00	8.33	25.00	33.33	
ABC LG	15	60.00	25.51	22.58	93.55	35.48	61.29	83.87	0.001
DA LGG DN	15	14.44	15.26	0.00	50.00	0.00	16.67	16.67	
ABC RE	15	61.11	17.33	19.05	95.24	57.14	61.90	69.05	0.018
DA PRAG DN	15	46.67	17.99	20.00	80.00	40.00	40.00	60.00	
ABC SE	15	59.09	19.59	22.73	100.00	45.45	63.64	72.73	0.005
DA SE AUT	15	34.81	20.52	11.11	88.89	22.22	33.33	44.44	
ABC SE	15	59.09	19.59	22.73	100.00	45.45	63.64	72.73	0.005
DA SE RETT	15	34.81	20.52	11.11	88.89	22.22	33.33	44.44	
ABC SE	15	59.09	19.59	22.73	100.00	45.45	63.64	72.73	0.001
DA SE AS	15	23.33	22.54	0.00	83.33	16.67	16.67	33.33	
ABC SE	15	59.09	19.59	22.73	100.00	45.45	63.64	72.73	0.001
DA SE DN	15	24.00	20.28	0.00	80.00	20.00	20.00	40.00	
ABC BEH	15	49.12	23.91	13.16	81.58	26.32	52.63	73.68	0.008
DA MOT AUT	15	28.00	23.66	0.00	70.00	10.00	20.00	50.00	
ABC BEH	15	49.12	23.91	13.16	81.58	26.32	52.63	73.68	0.009
DA MOT RETT	15	26.67	22.91	0.00	72.73	9.09	18.18	45.45	
ABC BEH	15	49.12	23.91	13.16	81.58	26.32	52.63	73.68	0.016
DA MOT AS	15	27.50	25.09	0.00	75.00	12.50	25.00	37.50	
ABC BEH	15	49.12	23.91	13.16	81.58	26.32	52.63	73.68	0.001
DA MOT DN	15	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
ABC BO	15	64.00	17.63	32.00	88.00	52.00	68.00	80.00	0.005
DA BEH AUT	15	30.91	26.35	0.00	90.91	9.09	27.27	36.36	
ABC BO	15	64.00	17.63	32.00	88.00	52.00	68.00	80.00	0.009
DA BEH RETT	15	36.19	27.46	0.00	85.71	14.29	42.86	57.14	
ABC BO	15	64.00	17.63	32.00	88.00	52.00	68.00	80.00	0.003
DA BEH AS	15	30.30	23.47	0.00	81.82	9.09	27.27	36.36	
ABC BO	15	64.00	17.63	32.00	88.00	52.00	68.00	80.00	0.003
DA BEH DN	15	32.12	25.22	0.00	81.82	9.09	27.27	45.45	

Legend:ABC=Autism Behavior Checklist; LG=language, DA=Differential Assessment of Autism and Other Developmental Disorders, LGG=language, AUT=autism, RETT=Rett Syndrome, DN=pervasive developmental disorder not otherwise specified, RE=relating, PRAG=pragmatics, AS=Asperger Syndrome, BEH=behavior, BO=body-object use, SE=sensory, MOT=motor

Table 15. Comparison of the different areas of the DAADD and the ABC to G2.

Variables	n	Means (%)	Standart deviation (%)	Minimun (%)	Maximum (%)	Percentile 25 (%)	Percentile 50 (Median) (%)	Percentile 75 (%)	p-value
ABC SE	15	43.94%	21.37%	0.00%	77.27%	31.82%	45.45%	59.09%	0.030
DA SE AS	15	28.33%	28.14%	0.00%	75.00%	0.00%	25.00%	50.00%	
ABC SE	15	43.94%	21.37%	0.00%	77.27%	31.82%	45.45%	59.09%	0.020
DA SE DN	15	13.33%	35.19%	0.00%	100.00%	0.00%	0.00%	0.00%	
ABC BEH	15	40.00%	24.33%	0.00%	73.68%	13.16%	47.37%	57.89%	0.001
DA MOT DN	15	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	

Legend: ABC=Autism Behavior Checklist, DA=Differential Assessment of Autism and Other Developmental Disorders, DN=pervasive developmental disorder not otherwise specified, AS=Asperger Syndrome, BEH=behavior, BO=body-object use, SE=sensory, MOT=motor

Table 16. Comparison of the different areas of the DAADD and the ABC to G3.

3. Discussion

The results of the two protocols tend to be more similar with the increasing age. The DAADD has shown to be more sensible in the different age-groups, while the ABC seems to be more specific only in the older group. It must be noted that the ABC aims just to identify the risk for autism while the DAADD differentiates the children that already have the diagnosis within the autism spectrum.

The need for diagnostic protocols that consider the association of communication and behavior disorders of children with ASD is clear. These protocols must provide means for the careful observation and record of communicative behaviors [16, 18].

The comparison of the different areas of the DAADD and the ABC has shown that the DAADD is more efficient to the identification of language disorders. It must be considered, however, that this is not the purpose of the ABC. The use of both protocols may be complementary, applied as needed along the diagnosis process. In several countries and in different regions of many countries providing services of medical diagnosis for children with ASD takes precious time. The time spent waiting for the conclusion of the diagnostic process would be extremely important to the child's development. The sooner the child receives appropriate therapy and education, the better the prognosis (Volkmar, Chawarska & Klin, 2005) Therefore, the use of screening tools that helps to identify children at risk for ASD or with some probability of receiving this diagnosis may represent the better use of resources that are frequently limited.

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The comparison of different protocols, especially considering the needs of non-English-speaking groups, allow a more comprehensive perspective about tools that can be used in the assessment process of children with developmental disorders.

4. Conclusions

During the last decades important changes have taken place regarding the concept and prevalence of ASD. This resulted in a greater need for screening tools that can be used in public health programs designed to provide services to an increasing number of children as soon as possible in their development.

The diagnosis of ASD often produces, besides the emotional stress in the affected families, large social and emotional impact. It implies in the urgent need for efficient models of screening and diagnosis that can support intervention plans that are individually planned and implemented. Early diagnosis and intervention are essential to the better prognosis; therefore clinicians and researchers have been dedicated to the development of efficient strategies to the identification of disorders and intervening factors.

Several diagnostic and assessment tools have been proposed, aiming the early identification of ASD. However, the efforts to improve the early identification of children with ASD will only be effective if the diagnosed children have access to appropriate intervention services. Considering that the assessment process may be long and expensive and that the diagnosis frequently depends on clinical impressions, the use of specific and sensitive tools is essential.

In this context an important aspect to be considered in the use of specific tools to the assessment and diagnosis of children with ASD is that it should be possible to use them despite the diversity of symptoms that are characteristic of these children. Besides, these tools should also be able to identify the central features of ASD. Cultural aspects and the possibility of use in different contexts should also be considered.

Finally, although there are several tools for the screening, assessment, diagnosis and follow-up of children with ASD, there is not just one protocol that can be universally used. In the clinical practice the assessment, diagnosis and follow-up of intervention processes still depends on the clinician's abilities that chooses specific and complementary tools.

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Chapter 9

Occupational Therapy in Autism

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Additional information is available at the end of the chapter

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1. Introduction

Autism, a developmental disability, is defined by behavioural characteristics. Primary features of autism are described as problems in language skills, plays and social interaction [1]. It is considered a spectrum disorder, as the abilities of children with autism may very greatly from one child to another [2]. Symptoms begin during early childhood and distinctive incompetence and limited, repetitive behaviours are seen in socio-communicative field. In addition to these primary features, individuals with autism generally have sensory processing and sensory integration dysfunction, which affect adaptive behaviour and participating daily activities. Many children with autism are unable to register many of the sensations from their environment. They cannot integrate those sensations to form a clear perception of space. Atypical sensory registration and orientation can interfere with the processes of inhibition and facilitation in sensory systems. Some self-stimulatory behaviour is the expression of a sensory need in children with autism. Assessing sensory integrative functioning in children with autism is critical for planning and implementing effective intervention in occupational therapy [3-5]. As far as motor functions are concerned, motor impairments have been reported in children with autism. The studies shown that problems are observed in coordination, posture and balance control, locomotion and motor preparation in individuals with autism [6-10].

Due to sensory integration dysfunction, individuals with autism have difficulty fulfilling the roles they are expected to accomplish in their life and they can display behaviours that can hinder their participation in daily life. The primary aim of occupational therapy practices is to ensure that the individuals with autism participate in communal life through minimizing the difficulties in the daily activities they experience at home, school or in communal life and maximizing their independency. Occupational therapists believe that the individual with autism's community participation can be increased through their participation in

meaningful and purposeful activities they have in their daily roles and aims to achieve. They also make use of client-centred and holistic therapeutic interventions both in analysing and evaluating the problems which individuals with autism face and in their treatment and support system.

Occupational therapy interventions, which are designed according to standardized assessment tests, questionnaires, skilled observations, provide considerable advantage in dealing with the problems individuals with autism and their families face in daily life.

This chapter will give information on standardized assessment tests and practices applied in occupational therapy interventions such as sensory integration therapy, auditory integration training, activities of daily living training, play therapy, social skills training, cognitive behavioural therapy, school based intervention, recreational activities and sports and vocational rehabilitation.

2. Sensory integration therapy

Current estimates indicate that accompanying sensory processing problems are reported in more than 80% children with autism. Hyper or hypo reactivity to sensory inputs is now a diagnostic criterion for Autism Spectrum Disorders in the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition [11, 12]. A. Jean Ayres, an occupational therapist, developed the sensory Integration theory [13]. Theory is based on neuroscience, developmental psychology, occupational therapy and education sciences. Sensory integration therapy is a common method used in paediatric occupational therapy. Results of a survey made on occupational therapists working with children with autism report that 99% of therapists stated that they were referring to sensory integration therapy [14]. According to this theory; 1.sensorymotor development is important for learning 2. Individual's interaction with environments shapes brain development 3. Neurological system has plasticity capability. 4. Meaningful sensorymotor activity is a strong mediator of plasticity [15]. Sensory integration is a process of organizing sensory information in brain in order to create an adaptive response. The aim of sensory integration therapy is to provide controlled and meaningful sensory experiences so that the child can spontaneously and appropriately form responses that require integration of those sensations [16].

2.1. The importance of sensation

According to the theoretical basis of sensory integration vestibular, proprioceptive, tactile, auditory and visual systems as well as olfaction (sense of smell) and gestation (sense of taste) have a significant importance. The tactile/proprioceptive and vestibular/proprioceptive systems interact routinely with the auditory and visual systems to supply the multimodal sensory information needed to make a meaningful motor response. It's reported that sensory integration is a dynamic process that sustains during development and sensory information can be organized as a result of interaction with environment [17].

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2.1.1. Tactile system

Skin has numerous receptors that perceive touching, pressure, texture, heat, pain and movement. A signal is transmitted to the related parts of the brain when tactile receptors are stimulated with touch, heat or vibration. Tactile system is a sensory system that affects behaviour both physically and mentally. Sense of touch is quite important for neural organization and praxis development [16, 18].

2.1.2. Vestibular system

Vestibular receptors related with balance and gravity, and located in inner ear consist of semicircular canals, utricle and saccule. Semi-circular canals are responsible for detection of angular, fast, short bursts of motion, and result in phasic limb movements and momentary head righting. Vestibular system is a system that affects balance, eye movements, posture, muscle tonus and attention [16, 19].

2.1.3. Proprioseptive system

This system is related with position and movement. Pushing and pulling activities related with muscles and joints are activities that provide maximum stimulation for this system. Proprioceptive system provides information on postural and oculomotor control, position in space and balance together with vestibular and visual system. In terms of the problems reported in vestibular and proprioceptive system, difficulties in good body scheme and laterality development, poor balance, poor postural control and difficulties in coordinated movements are observed in children with autism [2, 16-18].

Children who are hypo responsive against proprioceptive stimulation have weak proprioceptive discrimination and awareness and fail to use proprioceptive input correctly. Therefore they tend to break their toys easily and have low postural tonus. Bites, pushes, hits, scratches, bumps, hurls, hangs and aggressive behaviours as well as self stimulatory and hyperactive behaviours such as banging head, biting hands are observed in children seeking for proprioceptive inputs [20].

2.1.4. Auditory system

The sound information from each ear goes to auditory cortex of opposite hemisphere. The relation between the auditory system and valgus nerve is important in sensory modulation [16].

2.1.5. Visual system

The light received stimulates retina in order to send sensory input to the processing centre in the brain. Integration of visual inputs with different senses provides our awareness about our environments. Visual and vestibular systems work together for perceptual motor integration and visual perception [16, 18].

2.1.6. Gustatory sense

Different senses of tastes ensure that we like the food we eat and distinguish those that may be harmful [16].

2.1.7. Olfactory sense

Smell is directly processed via limbic system and creates memories and associations that influence some of our choices and preferences [16].

It's reported that sensory processing problems observed in individuals with autism are associated with behavioural and/or functional performance problems and specifically stereotypical or repetitive are associated with self-calm or sensory seeking [21]. The studies show that repetitive behaviours, behaviours such as climbing, turning and twirling may indicate existence of sensory processing behaviours [12].

Sensory registration, modulation, discrimination and praxis defined as motor behaviour planning capability are performance components, which are important for sensory integration. Sensory registration is receiving different stimulus from body or environment [17]. Sensory registration process is important for the individual to perform effective function by paying attention. Children with autism who have sensory registration problems fail in creating appropriate adaptive responses against pain, touch, movement, taste, smell, light and sound [22]. Sensory modulation is defined as "capacity to regulate and organize the degree, intensity, and the nature of responses to sensory input in a graded and adaptive manner" [17]. Sensory discrimination is important for development of motor functions, postural tonus and postural adjustment. Different sensory modulation problems such as hyporesponsivity, hyperresponsivity, sensory avoiding or sensory seeking are reported in children with autism. Hypersensitivity is the most common auditory and tactile defensiveness. High pain tolerance is the most significant indicator of hypo responsiveness in children with autism [2].

Difficulty in starting and sustaining a social interaction and relation, delays in speaking or communication disorders such as echolalia, repetitive stereotypical plays, visually focusing on any object, cognitive deficits and confusions in impacts and results of behaviours are common sensory integrative – related behaviours in children with autism spectrum disorder. Poor sensory processing affects the child with autism in successful involvement in daily life activities such as playing and participating in social activities with peers, tooth brushing, eating, self care etc. [23].

2.2. Sensory integration assessment and intervention

"The Occupational Therapy Practice Framework: Domain and Process (AOTA, 2002)" which is a comprehensive guideline of assessment and intervention is used in the assessment of individuals with autism and in occupational therapy interventions. Accordingly, occupational profile should be initially defined, occupational performance should be assessed, intervention plan should be designed, objectives and goals should be identified and documented, intervention should be implemented and results of intervention should be assessed and documented [24].

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2.2.1. Assessment

It is important to identify sensory responsiveness (over, under or labile) and sensory preferences (likes and dislikes) praxis and sensory processing problems that affect involvement in daily life activities in the assessment of sensory integration in children with autism [25].

Numerous tests like given below are used for assessment of sensory integration in occupational therapy.

Sensory Integration and Praxis Test (SIPT): It is developed to identify sensory integration problems. Test is standardized for use in children 4 –8 : 11 years of age. SIPT assesses sensory and neurological process, which leads to behavioural, learning, language and praxis problems. It consists of 17 subtests, which assess tactile, vestibular proprioceptive processing; form and space perception, visual-motor coordination, praxis, bilateral integration and sequencing, and it takes nearly 90 minutes to complete the test [26].

Southern California Sensory Integration Test (SCSIT): It is developed by Ayres for use in physically and mentally normal children with specific learning disorder. It is standardized for children 4-8:11 years of age. It takes nearly 75-90 minutes to complete the test [27].

Southern California Postrotary Nystagmus Test (SCPNT): This test developed by Ayres to evaluate of nystagmus to field of occupational therapy. This test measures the amplitude of the eye's side to side excursion and the total duration in seconds of ocular movements following rotations [28].

Sensory Profile: The Sensory Profile is a caregiver questionnaire, which measures children's responses to sensory events in everyday life for children 3-10 years of age. 5-point likert scale (nearly never, seldom, occasionally, frequently, almost always) is used for assessment [29].

Evaluation of sensory processing: This questionnaire is intended to identify behaviors thought to be indicative of sensory processing problems [30].

Tests such as *Developmental Test of Visual Motor Integration* [31], *Motor Free Visual Perception Test* [32], *Test of Visual Perceptual Skills* (Non motor) [33] are used for the assessment of visual perceptual skills.

Besides standardized assessments, many occupational therapists refer to clinical observations for assessment of sensory and praxis functions. Clinical observation of postural control, behaviour organization and vestibular functions offer significant information in addition to sensory tests. It's important to observe playing skills, social interaction and other relevant behaviours of the child in child's natural settings [23]. *Clinical Observations of Motor and Postural Skills* is a screen tool for motor deficits and assessment of cerebellar function, postural control and motor coordination [34]. It's reported that Goal Attainment Scale (GAS) can used in measurement of results in sensory integration studies [35].

2.2.2. Intervention

It's reported that sensory integration therapy should be individually implemented with the consideration of the "inner drive" of the child, based on the sensory experience, challenge and

interest and in a structured environments with active participation of the child [16, 22]. More effective feed-forward mechanism required for optimum adaptive response are created with child-directed actions. In responding children with autism, it is important to use controlled and meaningful sensory stimulus to create organized behaviour and to make environmental adaptations when needed. Due to the problems in body awareness, a child with autism fails in receiving sufficient tactile, proprioceptive and vestibular inputs from his/her body. Therefore, environmental arrangements should be adjusted according to motor planning and body awareness required for praxis. It's important to refer to sensory experiences that motivate and please the child with complex motor planning, social interaction and language skills. Therapist should integrate activities that contain sensory experiences required by the child into daily routine in cooperation with the family, caregivers and teachers [23]. Validity of the results in sensory integration studies are reported to be influenced by different practices in the intervention process and it's further reported that "Ayres Sensory Integration Fidelity Measure" which is a reliable and applicable verification measure for studies on sensory integration disorders should be used [36, 37].

Fidelity measure consists of 10 essential elements is used in clinic based sensory integration treatment. These essential elements are as follows: a) ensuring safety b) presenting a range of sensory opportunities (specifically tactile, proprioceptive, and vestibular) c) Using activity and arranging the environment to help the child maintain self regulation and alertness d) challenging postural, ocular, oral, or bilateral motor control e) is challenging praxis and organisation of behaviour f) collaborating with the child on activity choices g) tailoring activities to present the " just –right challenge", h) ensuring that activities are successful, i) supporting the child's intrinsic motivation to play, and j) establishing a therapeutic alliance with the child [37].

Activities for proprioceptive system

Proprioception is defined as a cornerstone in sensory integration therapy. Muscle movements against resistance or gravity, traction, compression, movements related with muscles and joints provide proprioceptive stimulus and are used to improve motor coordination, to increase body awareness and to help arousal level modulation [2, 20].Practices like jumping on trampoline, climbing a mountain of bolster and crash onto mats, jumping games, roller skating, bicycle riding, throwing and catching a heavy ball, wheelbarrow walking, pulling and pushing activities, carrying or moving heavy objects, imitating animal walks that require heavy work (crab, bear), swinging from trapeze bar, wearing a weighted west, weighted blanket, wearing ankle or wrist weights in activities stimulates proprioceptive system [23, 38]. (Figure 1)

Activities for tactile system

Activities like playing with dough or clay type materials, drawing on mirror with shaving cream, finger painting, drawing shapes with fingers in sand, foam etc, massage, vibrating toys, using different textures for playing and bathing, playing hide and seek games in dried beans or rice, asking the child to define shapes drawn on this/her back with fingers, finding objects from a bag full of rice or beans etc. can be used to improve tactile awareness [23, 38].

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Figure 1. Activity examples for proprioseptive and vestibular system stimulation

Activities for auditory system

The child may be asked to listen his/her favourite soft music on headphones in order to reduce auditory sensitivity [23].

Activities for vestibular system

Activities such as linear swinging on a swing or ball on facedown position, throwing and catching objects while swinging, sliding down a slide, climbing, using scooter board or skateboard, jumping games, rolling activities, toys like rocking horse can be used to reduce sensitivity against vestibular senses. The child tolerates linear vestibular stimulus more than rotational stimulus [23, 38].

Activities for ocular-motor control

Toys and pens with lights, throwing balls at a target while swinging, games of ball throwing and catching, bubble blowing can be used to improve ocular-motor control [23, 38].

Activities for postural control and motor skills

Ball catching games can be played on the floor or on a ball or while sitting in different positions on a swing [23, 38].

Activities for bilateral motor coordination and praxis

Activities such as creating shapes by tearing papers with both hands, making shapes with play dough, cutting papers etc. with scissors, making necklace by placing beads through a string, closing/opening clothe fasteners, ball catching and throwing and clapping type hand games[23, 38].

Activities for praxis and behaviour organization

Therapeutic activities, which are for sensory processing and facilitate skills such as initiation, sequencing, bilateral coordination, timing and imitation can be used [5]. Activities of clapping

and rhythm patterns hand games, building obstacle courses, activities that require whole body movements and timing such as kicking a rolled ball, hitting a ball with a bat, imitation of animal postures etc. can be used to improve motor planning [23, 38].

2.3. Researches about sensory integration therapy

Sensory integration therapy is a clinical based intervention that uses play activities and sensory integration principles to increase adaptive responses of children [12]. In a systematic review research by Benson and Koomar, 27 studies on the impact of sensory integration approach on children were reviewed. It's reported that sensory integration approaches are effective in terms of sensory-motor skills, motor planning, socialization, attention and behavioural regulation, skills related with reading, active participation in plays and personal goal attainment, however, the findings are limited due to small sample size, different practice dosages, therapy duration and result measurements not being appropriate [39].

Schaaf *et al* implemented sensory integration protocol for 10 weeks on a case with autism and consequently an increase was reported in sensory processing and home, school and family activities measured with Goal Attainment Scale [40]. Another study by Schaaf *et al* reviewed the safety, validity and applicability of sensory integration and occupational therapy in children with autism. 10 children with autism at 4-8 years of age were under therapy for 3 days a week for 6 weeks and an assessment was made with Ayres Sensory Integration Fidelity Measure. Sensory integration approaches in children with autism were reported to be a safe and applicable intervention [41]. Sensory integration therapy of 10 weeks for pre-schooler children with autism resulted with a decrease in non-engagement behaviours and an improvement in purposeful behaviours [42].

Pfeiffer *et al* reviewed the impact of fine motor activity with sensory integration therapy in 37 children between the ages of 6 and 12 with autism spectrum disorders in randomized controlled studies. Consequent to practice of 18 sessions, each for 45 minutes for six weeks, a significant improvement was reported in the sensory integration group. In sensory integration group, positive changes in sensory processing, motor skills and social functions and decrease in stereotypical and self-stimulating behaviours were reported [43]. A study by Smith *et al* reports that self-stimulating and self-injurious behaviours remain stable in children with pervasive developmental disorders as a result of sensory integration therapy [44]. Sensory integration and sensory based treatments resulted in increase in engagement in plays and social interaction, proper adaptive response, decrease in stereotypical and self-stimulating behaviours, decrease in sensitivity against touching and movement in hyper responsive children and decrease in sensory vulnerability. Sensory integration therapy improves skills of engagement in social interaction and modulating behaviours [45, 46].

Some studies report that sensory integration therapy does not have a positive impact due to small sample size, short therapy duration, no fidelity measure, study design and due to the fact that assessments are not blinded [47-51].

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The last systematic review study by Smith et al. on sensory integration notes that evidence based studies where blinded evaluation, larger samples and randomised trial are used should be conducted [12].

3. Auditory integration therapy

Auditory processing problems are one of the sensory processing disorders commonly reported in children with autism. These disorders are classified either as auditory hypersensitivity or auditory underresponsivity [3, 52, 53] and Rimland and Edelson reported that nearly 40% of 17.000 children with autism have sound sensitivity [54].

Auditory Integration Therapy is a technique developed by Dr Guy Berard, an otorhinolaryngologist in order to reduce abnormal sound sensitivity in autism spectrum disorders. In this method, electronically modulated music is listened by headphones for half an hour twice a day for 10 days. Audio metrical assessment is made before the therapy. Auditory integration training devices filters peak frequencies against which the individual has hypersensitivity. It aims to regulate behaviour by reducing hypersensitivity. The filtered music is modulated by a brief dampening of high and low frequencies for periods ranging from 250 milliseconds to 2 seconds [54-56].

445 individuals with autism who received auditory integration therapy were reported to have a decrease in problem behaviours and increased hearing acuity and the observed changes remained stable for nine months [57].

Changes in brain functions were measured before and after auditory integration therapy with positron emission tomography and an increase in occipital lobe activity and a decrease in hyper metabolism in frontal lobe were reported [58]. Auditory therapy according to Tomatis method is reported to create an increase in daily life skills, motor skills, socialization and communication skills in 6 cases. Furthermore, decrease in hyperactivity, atypical behaviours and increase in attention was reported in cases [59]. Brockett *et al* assessed impacts of auditory integration training on behavioural changes related with sensory modulation in children with autism. Following a 10-days training for two times a day, a decrease was reported in sensory behaviour problems of children [60]. In 72 cases with autism spectrum disorders, auditory integration therapy was reported to have a therapeutic impact on social awareness, social cognition and social communication as well as speech and communication [61]. Some studies report that there is not difference between auditory integration therapy and control group and that evidence based studies are required [62-64].

4. Activities of daily living

Activities of daily living (ADLs) are oriented toward taking care of one's own body and include bathing, dressing, eating, feeding, bowel and bladder management, functional mobility,

personal device care, personal hygiene and grooming, sexual activity and toilet hygiene. These activities are "fundamental to living in a social world; they enable basic survival and well-being". Instrumental activities of daily living (IADLs) may require more complex interactions with one's environment; these activities support daily life within the client's home and community. IADLs include: communication management, home establishment and management, meal preparation and clean up, financial and health management and maintenance, community mobility, shopping, safety and emergency maintenance, care of others and pets, child rearing and religious observance. Children and young people learn to perform ADL and IADL activities with socially appropriate ways in order to engage in education in family and society, game playing, leisure, social participation and work occupations [65].

Individuals with autism generally have the risk of limited engagement in activities. Studies show that such individuals engage in less activities less frequently and have weaker daily life skills when compared with individuals with other developmental disorders or with typical development [66-70]. Most common areas reported by families are limited independence in dressing, rigid eating routines, interruption of eating time because of difficult behaviour, limited independence and discomfort in many hygiene tasks, obvious difficulty in toilet training, limited engagement in chores and continuous and intense supervision to provide safety [71]. Engagement of individuals with autism in daily living activities may be effected by core characteristics specific to autism as well as sensory processes. Studies show that 42-88 % of individuals with autism experience sensory integration disorders [72-76]. Koenig and Rudney demonstrate in a review that children and adolescents who have sensory processing deficits have difficulties in completing their daily occupations, including ADLs and IADLs [77]. While the literature underlines the need to increase evidence-based studies, sensory integration deficits of individuals and sensory features of environment should not be ignored in assessments and interventions for activity engagements of individuals with autism.

4.1. Assessment

ADL and IADL assessments start with analysis of occupational performance. For this purpose, interviews, inventories, observation and various standardized tests can be used as an assessment method. In the initial stage, interview with family, child, teacher and other care givers is important in learning child's skills, habits, routines and roles, environmental features, goals and dreams [78]. If the family reports difficulties about some ADL or IADLs of child, therapist should observe the child in clinic or ideally at home if possible and in child's environment during the activity. Assessment should contain information on social, cultural and physical environment, which affect activity performance as much as motor, process and communication/ interaction skills of the child. Environmental factors such as division of labour division of family members for child's care, safety issues in physical environment and cultural habits and social routines of family may be registered. Task analysis is made to define activity demand, activity is divided into steps and reviewed, steps are listed and requirements are defined. The Functional Independence Measure for Children (WEFIM), Waisman Activities of Daily Living (W-ADL) Scale, The Paediatric Evaluation of Disability Inventory (PEDI), The Vineland Adaptive Behaviour Scales, The Assessment of Motor and Process Skills (AMPS),

The Canadian Occupational Performance Measure (COPM) and Sensory Profile (SP) for sensory integration are some of the examples of standardized methods that can be used in the assessment of performance in daily living activities [29, 79-85].

4.2. Intervention

Occupational therapists may refer to different approaches to improve ADL and IADL performances in children, including 1) establishing and maintaining performance, 2) activity adaptations or compensatory methods [78].

4.2.1. Establishing and maintaining performance

At the initial stage of intervention, therapist uses an activity analysis to define which steps of activity process are problematic and defines behavioural and educative methods to be used [78].

Behavioural approaches has been used, often in combination with other approaches, to obtain a baseline of the child's behaviours and as a way of establishing clear goals. Behavioural methods like reinforcement and token systems are useful in attainment and sustainment of skills in individuals with autism. Furthermore, besides guiding learning, they may facilitate visual (showing), verbal (speaking or written information), tactile (guidance or using a part of body) or environmental (colour coded materials) cues. Cues are important to improve the quality of performance and to brief individual on what to do in the next step. As individuals with autism may experience difficulties in understanding natural cues and verbal communication, context or activity demands such as use of prompting can be modified [86].

One of the important training methods used in ADL training is chaining. Training of complex skills generally requires chaining steps of the task. Three chaining options are available for functional task training: a) Backward chaining in which the last step of the task is trained first, followed by the second to last step and the last step, and so on, progressing backward through the chain, b) Forward chaining in which the first step of the chain is trained first, followed by the first and second step, and so on, progressing forward through the chain c)Whole task method in which each step of the chain is trained on each presentation [87]. Another method is time-delay procedures. The time-delay cueing system typically involves two training stages: 1) A cue designed to elicit the next step in the chain is delivered so as to coincide with the stimulus (i.e., the completion of the previous step in the chain). 2) A defined interval is inserted between the occurrence of the stimulus and the response-eliciting cue [88]. These educational methods include strategies that occupational therapists can use in skill training. Repetition and development of habits and routines are required to sustain the skill after it is learned and to reduce environmental supports. Furthermore, generalization of skill in different environments should be emphasized [78].

4.2.2. Activity adaptations or compensatory methods

Compensatory strategies may include modification of task or task method, use of assistive technology or modification of environment. Therapists may also refer to the combination of these methods [78]:

- **Adaptation of task methods**

"Grading" is a method commonly used by therapists. Grading is adaptation of task or parts of a task according to the capability of child. Activity is divided into subtasks with task analysis and task is modified depending on the difficulty or easiness level for the child [78].

- **Visual Strategies**

Individuals with autism can process visual information easier than auditory information [89]. Visually based interventions include visual (e.g., picture, written) schedules, visually organized tasks, written or pictorial scripts, rule reminder cards, and visual task analyses [90]. Such interventions are reported to be effective in individuals with autism [90, 91]. These activities may be used for individuals with autism to learn activities of daily living skills, to foresee daily routine and to become independent from various environments [92].

- **Assistive Technology**

In literature, technologies like video modeling, video prompting, handheld devices, structured computer games and virtual reality environments are used for training purposes. Research incorporating technology has consistently demonstrated good effects to daily living skills for children with autism. Additionally, assistive technology requirement of occupational therapist, which technological tool is applicable and proper assessment of factors related with accessing technology such as economical status of family are important [92-95].

- **Sensory Strategies**

Creating sensory-friendly environments and implementing adaptive sensory strategies are important for effective ADL and IADL performance in children with sensory modulation problem. For instance, environment should be structured to be silent when an activity is performed with a child who has auditory-hyperresponsiveness responses. Use of earphone is recommended in environments that cannot be controlled. Another example is that preparation of a child with deep pressure and organized, rhythmical touches might be facilitating before starting a dressing activity with a tactile defensive child [23].

5. Play in occupational therapy

Besides being an activity that exists in every stage of life, play is the most proper way for a child to learn the world he/she lives in and to express emotions such as happiness, anxiety, and joy particularly during the first years of life. Bundy describes it as ''play is a transaction between an individual and the environmental that is intrinsically motivated, internally controlled, and free of many of constraints of objective reality'' [96].

Play is primer occupation of the child. Through play, children can gain developmental milestones, learn about occupational role, behaviours, and how to interact safely and appropriately within their environment. Children with autism display atypical and insufficient play skills at different levels. This atypical and insufficient play skill is generally reported as playing

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with a toy stereotypically (rotating, shaking, sequencing, putting one on top each other) which is not suitable for its function, lack of social skill, flexibility and creativity skill to continue the play. Developments in symbolic activity, play and social relation areas observed in children younger than three years of age are not generally reported in children with autism [97]. Rare interaction of children with autism with their peers limits their attainment of playing in solitary and group plays with their peers [98]. Since game playing requires developed motor planning and praxis skill, this may result in child's showing motor planning and praxis during play [96].

Occupational therapists are concerned with the occupation of play and the child developing as a lifelong player [99, 100]. Providing engagement with play in children with autism is one of the most important parameters of occupational therapy interventions [101]. The primary goal of occupational therapy interventions in children with autism is to ensure attainment of motor planning and praxis skills, which will improve child's concrete thinking and play setting skills [99-101].

Play is multidimensional phenomenon that includes entertainment, spontaneous problem solving skill and creativity and requires collaboration of different disciplines [101-103]. Engagement in play and sustainability of play continue as long as the self-motivation and creativity of the player continue. Active engagement of children with autism in play and sustainment of play with adaptive response is one of the most important objectives in occupational therapy interventions [96, 99-101].

Our senses (tactile, visual, auditory, olfactory, gustatory, proprioceptive and vestibular) help us to collect information from the environment we live in and provide that we give adaptive responses suitable for the environment and we generalize what we learn. Sensory information is effective in the establishment of body scheme, which is one of the most components of motor planning skill [13, 104-106]. Studies reported that integration of tactile, visual, proprioceptive and vestibular sensory inputs offer improvement of body-spatial awareness [106-108]. When children with autism fail to produce adaptive response suitable for their environment and have insufficient body scheme, such may lead to negative experiences in their occupational performances and may result in anxiety, frustration, anger and avoidance [109]. Therapeutic play used in occupational therapy intervention can lead the child into a motivating activity with inner drive that encourages active movement, self direction, interaction, sensory building blocks and help addressing occupational performance and occupational profile of the child with autism [106, 109]. A study assessing the effectiveness of play therapy in literature reports that DIR-Floor Time and similar developmental approaches have a positive impact on emotional functioning, communication, and daily living skills and moreover creates positive changes in parent-child interactions [110]. It's noted that play based occupational therapy improves motor and social skills in children with developmental delay [111]. Hebert reports in his study that therapeutic plays practiced for children with developmental delay in line with their occupational frameworks improve their non-verbal and verbal communication skills [112]. As noted by such evidence-based studies, well structured play which is commonly used in occupational therapy interventions has a positive impact on motor skill and planning, communication-interaction and social skills of children with autism.

5.1. Assessment

Play is what children to do and they expend considerable social, cognitive and motor resources while playing, therefore play assessment may provide very meaningful insights about a child's interests, functional abilities and behaviours [113-115]. The selection of a play assessment will vary depending upon the developmental status of the child, the purpose of the assessment and the intervention plan. Test of Playfulness [114], Knox Preschool Play Scale [115], Play History [116-118] and Trans-disciplinary Play-based Assessment [119], My Child's Play [120, 121] tests are among the common standardized tests used to plan occupational therapy interventions for the improvement of play skills [117]. Furthermore, occupational therapists frequently refer to Observations of Factors Influencing Playfulness Form [121, 122] to plan their interventions.

5.2. Intervention

Occupational therapists frequently use sensory integration framework where sensory differences of individuals are taken into account in improving play skills of children with autism. Developmental approaches like Dr. Stanley Greenspan's "Floor Time" method which aims to turn the relation between children and their families into a play with mutual interaction that contains trust and pleasure and philosophy of "Follow the child's lead" [123-126]. Additionally, virtual reality studies are also included under play interventions [127]. During occupational therapy interventions, in addition to therapeutic use of play, occupational therapists play an effective role in the organization of play environment and parent education with the consideration of developmental level, challenges and strengths of child [128].

It's important for the occupational therapists to implement therapy programs designed according to sensory integration framework, under the leadership of child in structured environments for the improvement of motor skill, social-emotional well-being, cognitive process, praxis, attention, intimacy, interaction expression, use of feelings/ideas and logical thinking development of child with autism in play based occupational therapy interventions [129].

6. Social skills training

Social skills have a significant place in diagnosis of autism. Children with autism experience difficulties in using non-verbal behavioural social skills such as eye-to-eye gaze, facial expression, body postures and gestures to regulate social interaction; failure interaction with peers, problems on sharing enjoyment, interests or achievements with other people and problems in social–emotional reciprocity and may require support as of early ages. Individuals with autism have difficulty in understanding nuances and informal rules, which are spontaneously used during communication. Such social interaction problems may lead to indifference, teasing or bullying. Social interaction efforts of many individuals with autism result in negative experiences as the individual is over stimulated or confused and negatively effects the social engagement of individual. Studies report that negative reactions against individuals

with autism from their environment are more challenging that their communication problems [130]. Difficulties in social skill behaviours observed in individuals with autism are defined with neuropsychological models such as the theory of mind [131, 132], executive functions [133, 134] and weak central coherence [135, 136].

Theory of mind is defined as the capacity of interpreting, deducing and explaining the underlying mental situations in other's behaviours. Preschool children are expected to have developed their theory of mind skills. Insufficient development of theory of mind are reported to lead to difficulties in interpreting emotional status from voice tone and facial expression and in social skills and negatively affects empathy skill of individual [131, 132]. Theory of mind is used to describe the major deficits in social functionality and communication in autism [132].

Dynamic and complicated nature of information process in brain reveals definition of high-level cognitive functions and concept of executive functions. This theory covers skills such as self-regulation of behaviour sequence, flexibility, response inhibition, planning and organization of behaviour. Executive functions where prefrontal cortex play a central role provides that an individual thinks about himself/ herself and defines what can happen in future and how they can be affected [133]. Executive functioning in autism is an approach studied fort he last 20 years. Studies on executive functioning and frontal lobe functions report that performances of children with autism in executive functions are lower than expected [133, 134]. Social skill deficits, namely executive function disorders or stereotypical behaviours, which are considered to be caused by their deficits, are observed in individuals on the spectrum and in their relatives [132-134].

According to weak central coherence model, information received from different sources cannot be integrated in autism [135]. Meaningful and consistent meronymy relation cannot be established from stimulus perceived due to information processing deficit. Weak central coherence can be associated with disadvantages experienced by individuals with autism in areas such as learning, social, language and cognitive skills etc. and it's reported to be the reason for behavioural deviations in these areas [136].

Different disciplines commonly agree that autism is centrally a social skill deficit and therefore this area should be the first area to be targeted in training [137]. In social skill studies for children with autism, attainment of basic skills such as eye contact, using expressions like hello, thank you which are the basics for social communication, answering questions like how are you, playing with peers and getting in line in plays etc. are targeted with priority [137, 138].

There are many advanced social skills that should be attained by a child with autism after the attainment of basic social skills. These social skills can be classified under four main groups; communication skills: self introduction, asking proper questions to meet someone new, starting a conversation, involving in a conversation, not deviating from topic of the conversation, listening in a proper position, not keeping the talk too long, changing the topic properly, using voice tone, facial expression and body posture according to the topic of the conversation [139-141].

Social interaction skills (friendship): These are the skills like touching properly, ringing, answering a call, helping a friend properly, asking for help, spending time together, acting at

a proper distance depending on the type of relation, respecting ideas of others, not feeling uncomfortable with changes in rules etc. [140].

Social interaction skills (playing): These are the skills like engagement in play, sharing toys, playing games with rules, getting into a line during play, coping with winning and defeat [140, 141].

Emotion recognition and management skills: They include skills like awareness on emotions, consoling a sad person, anger control and expressing anger properly, accepting criticisms, coping with mocking, sharing happiness, coping with making mistakes, not feeling uncomfortable when trying new things. [140, 142].

Social skill training is not a routine part of occupational therapy interventions for individuals with autism. Occupational therapy interventions play an important role in designing intervention programs for the assessment and improvement of insufficient social initiations and responses against any occupational performance of the individual with autism at home, school or in society, and in enhancing social participation of individual [130].

In social skill studies with children with autism, skills are tried to be taught face to face or in groups or some skills are taught during playtime with parents or peers [140, 141]. It's reported that a shift can be made from individual works to group works for the development of empathy skill [139]. These working principles are also taken into consideration in occupational therapy interventions [16].

Among the studies on improvement of social skills in children with autism, there are researchers who think that "theory of mind" is the problem [133, 142, 143], and studies, which refer to, structured training programs [140, 144] or developmental approaches [145]. More than one technique is used in some studies. For instance various techniques like scenarios, social skill groups, self-control, class interventions, video modelling, social plays, peer training, peer mediation and circle of friends are used together [146-148]. There are also studies where a single technique is used like social stories [149], peer mediation etc. [150]. It's reported that social skill training of children with autism is more effective in communication with other children in a natural group setting [151].

In a study where 79 studies on children with autism under the age of 12 were reviewed, it was noted that modeling and reinforcement, approach, peer training, scenarios and social stories were used [138]. It's further noted that programs designed with techniques of approaches to learn social skills in groups or socially are more effective in children with autism [138, 152].

6.1. Assessment

In occupational therapy, social skills of individuals with autism are assessed with observational standardized tests and checklists [153]. Standardized tests helps assessment of social skills and daily living skills of an individual with autism. Vineland Adaptive Behaviour Scale [83] and Social Skills Rating System [154] can be given as an example of such tests.

Occupational therapists may make structured interviews with parents and caregivers in addition to the standardized tests, and make observations in the natural settings and structured

play settings of the child. During the assessment, informal rating scales can be used in the observation of social skills of the child such as spontaneously engaging in communication, imitation, socially responding, eye contact, game playing, asking for help/ helping, adjusting voice tone, using body language, expressing emotions verbally and non-verbally, giving proper responses, distance with others during communication and interaction [16, 128, 155].

6.2. Intervention

Occupational therapy interventions for improvement of social skills in individuals with autism should be client-centred, with concrete narrations, supporting active engagement in cooperation with family and teachers in the natural settings of the individual and should consider emotional differences. Individuals with autism may experience significant difficulties in implementing the social rules despite having memory skills that facilitate repeating and memorizing these rules. Occupational therapists can give social skills training with creatively referring to the routine daily activities of the individual with autism during the sessions. A therapy program which starts with individual works of 30-90 minutes where necessary considerations and modifications are made over an activity related with the occupations of the individual with autism in his/her life and progresses with group works is considered as an ideal occupational therapy intervention. Adult-mediated or peer-mediated activities can be used in intervention. Teaching that the same response would not be proper in every social situation with the consideration of social hierarchy and group work principles during the intervention is an important detail of the intervention [16, 128, 155].

Social Stories and Social Autopsies, Social Skills Lessons and Activities, Jump Starters, Social Skills Activities for Special Needs, and Walker Social Skills Curriculum: The Accepts Programme, Do-Watch-Listen-Say" Framework, Video Modeling methods are frequently used in occupational therapy interventions [156-158].

Occupational therapy interventions designed to improve occupational performance in line with the basic principles given above may help in the development of social skills in individuals with autism and can increase their social engagement levels.

7. Cognitive behavioral therapy

The cognitive behavioural approach assumes that a person's cognitive function and beliefs influence their behaviour, and that by helping a person dispute their irrational thoughts, they will be empowered to change their behaviour [159].

Each person's beliefs are developed through his or her own life experiences. These experiences can be lived as well as watched (observational learning, vicarious reinforcement etc.). Individuals with autism can have problems on learning from society, and vicarious reinforcement is key aspects of Bandura's social learning theory [160]. Cognitive behavioural therapy is used primarily to help individuals with autism to regulate their emotions, develop impulse control, and improve their behaviour as a result. In addition, some individuals with autism struggle

with fears and anxiety, or may become depressed. Cognitive behavioural therapy has been shown to be helpful for reducing anxious and depressed feelings and behaviour by making changes in thoughts and perceptions of situations through a change in cognition. The key ingredient of cognitive behaviour therapy based occupational therapy, which distinguishes it from regular behaviour therapy, is working on change in cognition or how thinking is processed [160, 161]. Occupational therapists seek to reduce challenging behaviours, such as interruptions, obsessions, meltdowns or angry outbursts, while also teaching individuals how to become familiar with and manage certain feelings that may arise during activities of daily living. Cognitive behavioural therapy can be individualized which matches client-centred approach of occupational therapy, and as a result, is very effective at improving very specific behaviours and challenges in each individual with autism. Stabilizing emotions and improving behaviour allows individuals with autism to prepare for and respond more appropriately in specific situations [159-161].

Occupational therapists working with individuals with autism refer to at least one behavioural approach, generally the frameworks of model of human occupation and biopsychosocial model in their therapy interventions [159, 162, 163]. Occupational therapists support the cognitive behavioural therapies implemented in line with these models with making changes in individual-environment-activity areas [159, 162-164]. Following cognitive behavioural therapy, occupational therapist assists an individual with autism to identify and change their irrational thoughts, then take this learning and use it in real life opportunities [159, 162, 163].

Although studies on mental health are frequently observed when cognitive behavioural therapy based occupational therapy interventions are reviewed, visually based interventions such as video modeling where behavioural changes are targeted with various activities have been demonstrated to be effective with children with autism. This approach has wide utility, is appropriate for a range of ages and abilities of children with autism. There are video modeling studies such as Video Self (modeling Tape the child and play back to give feedback), Video Instruction (tape another student doing the behaviour) and Video Feed-Forward Tape. These studies show the child the complete behaviour and promotes independent functioning, and can be used to address numerous learner objectives of occupational therapy, including behavioural, self-help, communication, and social objectives [164-166].

7.1. Assessment

Occupational therapists generally work in line with model of human occupation and biopsychosocial model in the interventions of cognitive behavioural-based therapies in individuals with autism [159, 162, 163]. Besides the assessments of occupational therapy frame of reference, assessments such as 5 Point Scale, Power Cards, Bibliotherapy, Video Modeling, Situations-Options-Consequences-Choices-Strategies-Simulation, Social Autopsies, Comic Strip Conversation, Social Stories and Hidden Curriculum are used [156, 167-173]. Furthermore, a review also found that ILAUGH Model had already been researched and demonstrated to be a relevant learning hurdle for individual with autism [174].

7.2. Intervention

There are some programs designed for children and adolescents to teach awareness of energy levels and self-regulation. Alert Programme "How Does Your Engine Run? " is one of them and it teaches awareness of energy levels and how to bring the energy level back to the centre and it focuses on self-regulation skills according to sensory integration theory [175].

Occupational therapists also aim to improve the skills of exploring feelings in their activities with children with autism. For this purpose, programs of *Thinking about You Thinking about Me* [176], *Think Social* like ILAUGH [174, 177] are frequently used to improve communication skills and problem solving skills of individuals with autism. Additionally, books used to improve social thinking skills of children with autism are also frequently used in activities of occupational therapists. Again, ''Superfleks Series'' [178] by Winner is commonly used in occupational therapies planned specifically for behavioural changes in children with high functioning autism.

Anxiety can be debilitating for a child with autism. Learning about emotions helps children recognize connections between thinking and feeling, and helps them identify the physiological effects of anxiety on the body (sweating, increased heart rate, crying, etc.). Learning and teaching to explore feelings can help the child with autism to identify situations that make them anxious and learn how to perceive the situation differently [179]. Therefore, occupational therapists frequently refer to self-management training in coping with anxiety and stress in their studies with children with autism. Effectiveness of intervention in individuals with autism who receive cognitive behavioural therapy based occupational therapy is assessed with Goal Attainment Scale (GAS) [35].

8. School based occupational therapy

Occupational therapy in school is quite different from clinic based occupational therapy. School-based occupational therapists focus on learning, developing skills which increase the student's independence in the school environment, and also educating the school personnel about the different considerations required for students to eliminate the barriers from participation [180-183].

Everything the occupational therapist does with student in school must be related to develop educational skills of the student with autism. The occupational therapist evaluates, assesses and accommodates functional abilities of the student with autism in school classrooms, hallways and other related education areas. The occupational therapist works with teachers to help student's acquire functional abilities necessary to access and use educational materials and be independent in the school [183]. Occupational therapists work with the students with autism on adapting or modifying school equipment/materials to help them function better in classrooms, the lunchroom, or restrooms. Other assistance includes helping students with autism to be sensory stable and participate in activities outside of the school through mobility on field trips, sports events, on playgrounds and within the community. Students with autism

face a demanding environment at school [183-185]. Presentation methods for educational materials must be modified to meet the challenges of students with autism, such as their ability to communicate, view and manipulate educational materials, and move about the school. Occupational therapists work closely with teachers to promote the highest level of function possible for a child with autism pursuing educational goals like fine and gross motor skills and attention skills [185-188].

8.1. Assessment

Occupational therapists use screening, assessment, and clinical observation tools and strategies to analyse why child with autism is having functional and sensory difficulties in educational settings not to establish interventions in school settings. During their interventions occupational therapists use some of the standardized tests like Sensory Profile [189, 190], Bayley Scales of Infant Development-II [191], Peabody Developmental Motor Scale [192], Bruininks-Oseretsky Test of Motor Proficiency [193], and Pediatric Evaluation of Disability Inventory Test [82] in school setting [194].

If the standardized tests are not appropriate, occupational therapist can give descriptive reports without using standardized scales. It is important to compare the child's performance with the previous scores than the normative sample. Occupational therapists can use play based performance profiles like Hawaii Early Learning Profile or Transdisciplinary Play-Based Assessment [194]. Additionally ecological/environment inventories should be used to evaluate child with autism within a variety of educational environments (classroom, garden, sports area etc.), curricular expectations; tools/instruments to help gather relevant information; whether the team needs expansion to obtain needed information [195, 196]. And also to determine and work with the educational team to determine functional strengths and challenges and providing information to design instructional programs of the student with autism. Occupational therapist should try to become familiar with the individual education plan [194-196].

8.2. Intervention

Occupational therapists use direct or indirect services for students with autism in school settings. Occupational therapy interventions purposes are to help students with autism to gain independence in daily living activities, feeding and oral functions, play skills, task organization and completion, written communication skills, hand function, sensory integration (processing), visual perception, campus/school mobility, participating on a regular and timely basis, using tools and supplies, participating in activities throughout school settings. Also when skill and strength cannot be developed or improved, occupational therapy offers creative modifications and adaptations for carrying out development-appropriate activities [195, 196].

In school practice, occupational therapists work with students, teachers, families, classes, schools, and school districts. Occupational therapists are experts at identifying ways to engage students with autism in educational activities and supporting them to develop competence in their roles as students.

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9. Recreation and sports

Recreation, a participation domain of the International Classification of Functioning Disability and Health (ICF), includes involvement in formal and informal activities such as play, sports, going to the theatre, crafts and tourism [197]. Leisure in occupational therapy is described as one of the occupational areas that cover recreational activities. *Leisure* is defined as "'A non-obligatory activity that is intrinsically motivating and engaged in during discretionary time, that is, time not committed to obligatory obligations such as work, self-care, or sleep'" [99]. Engagement in challenging and intrinsically motivating recreation and leisure activities is considered as an important part of development of children and young people [198]. These activities are reported to have positive impacts on physical and mental health, reduce behavioural and emotional disorders, facilitate becoming friends, widen interest areas of child and increase life satisfaction of family [199-202].

Besides being pleasant, recreational activities improve the life quality of individuals with autism, develop their social communication and acceptance, reduce inappropriate behaviours, improve fine and gross motor skills and helps in attainment of social skills [203]. Findings of studies on participation of children with autistic disorders in physical activities and sports activities show that sports and physical activities may create opportunities for social interaction, reduce repetitive movements and contribute in development of motor performance and physical suitability as well as self management skills [204-207].

Studies show that children with autism have more limited participation in recreational activities when compared with their peers with typical development or those in other disability groups [208-211]. Core impairments of autism spectrum disorders (i.e., communication impairments, social deficits, and abnormal restrictive, repetitive and stereotyped behaviours) and other features related with disorder (e.g. motor skills differences and maladaptive behaviour) affect recreational participation [212]. Another significant factor is sensory integration problems experiences by individuals with autism. It's reported that children with autism and sensory difficulties participate in recreational activities less and prefer more informal (not structured) and home activities [213]. Besides all these individual features, the impact of family and environmental factors are also described. The interplay is noted among the child's impairments, the family's style, preferences, and demands, as well as environmental or community-based limitations in restricting a given child's ability to participate in an array of recreational activities [199]. Studies show that participation of families in recreational activities positively affect child's participation [214]. Furthermore, it's observed that number of accessible services in society is parallel to participation in these activities [199]. Another factor is acceptance perceived from family, friends and neighbours. Families of children with developmental delay and behavioural problems may discontinues activities outside home as a response to negative reactions of people against the noise and temper tantrums of child [215]. As a conclusion, holistic perspective is important.

Individuals with autism are in need of programs structured and organized with proper support to reveal their recreational interests and to improve their leisure skills [203]. Therefore interdisciplinary teamwork is an important issue. Considering multifaceted factors that affect

participation in recreational activities, strong cooperation of families and professionals are required in the planning and implementation of intervention [208]. Occupational therapists are important both with their expertise in occupational participation and their knowledge on sensory integration interventions for participation of individuals with autism in recreational activities. Occupational therapists point out exploration and participation in leisure activities, which are one of the occupational areas. Leisure exploration refers to identifying interests, skills, opportunities, and appropriate leisure activities. Leisure participation is planning and participating in appropriate leisure activities; maintaining a balance of leisure activities with other areas of occupation; and obtaining, using, and maintaining equipment and supplies as appropriate [65].

9.1. Assessment

Occupational therapy assessment with an occupation-based, family-centred and top-down approach starts with an interview with the family and self-report. Family's perspective on interests and skills of child, life style, economical status, their access to social and community resources should be recorded. Ideally, leisure assessments should be made in the natural settings of the child whenever possible. Interview and observation made in this setting are important to assess physical, social, cultural, attitudinal or organizational environment factors which affect leisure participation of the child and to evaluate child's performance skills. It is important for the therapist to observe motor, process and social interaction skills and attitudes of the child against others during activities with peers [185].

Paediatric Activity Cart Shorting (PACS), Children's Assessment of Participation and Enjoyment (CAPE), Canadian Occupational Performance Measure (COPM) are some of the examples of standardized methods that can be used in the assessment of recreational interests and skills of the child [85, 216, 217]. It is important to assess the sensory integration skills of the child and impact of these skills on activities, to define strategies to meet the needs of the child and to create sensory friendly settings. Therefore Sensory Profile (SP) is a standardized scale used in defining sensory difficulties of child [29].

9.2. Intervention

Occupational therapists give trainings to families, friends and teachers on how to facilitate participation of individual besides teaching the most needed skills for participation of children in selected leisure activity. Additionally they give training on use of adaptive equipment required for activities and make environmental modifications.Participation of children with deficits in activities together with their peers without deficits is important for both groups. Some of the study results show that peer support programs are useful for both groups. Structuring recreational activities where children with autism can be together with children with typical development can be an effective for proper modeling and social integration of children with autism and for the positive attitude changes in others [218, 219].

One of the most important highlight of recreation and leisure activities is that they are "intrinsically motivated". Neurobiological studies show that limbic system which orchestrates

motivation and drive in brain is not adequately developed in individuals with autism. According to sensory integration theory by Ayres, purposeful sensory-based activities may increase natural inner drive. Therefore, carefully selected sensory-based activities may help finding activity meaningful and purposeful and sustaining participation [220, 221].

Virtual Reality (VR) technology is an important tool to widen leisure activity spectrum of intellectual and developmental disability population. Easy changeability of virtual environments, adaptation and scaling of difficulty of task according to the skills of the individual can be considered as advantages of VR [222]. Furthermore, it increases motivation and leads to positive impacts on the participation of individuals. In the intervention, its integration to home routine as a recreational activity is considered to be useful.

10. Vocational rehabilitation

Many people diagnosed with autism experience difficulties in finding and sustaining jobs. 50-75% of this population is estimated to be unemployed [223]. One of the basic problems of individuals with autism in finding jobs is the deficit in social and communication areas, which require advanced support in the workplace [224]. In addition to these personal features, availability and accessibility of services that support employment and existence of social supports are considered as significant environmental factors that affect employment rates [81]. Studies show that individuals with autism may be successful in business life and are considered as important by their employers together with proper vocational interventions [225-227].

Employment opportunities for individuals with autism may be based on two main categories; a) integrated, competition-based employment with supportive employment opportunities and b) separate, non-competitive opportunities including daily therapy, work activity centres and protected businesses. Supportive employment is a system where individuals are supported in the workplace, long term support is given with work coaching system and the support is reduced as the individual becomes more independent. This approach is based on the assumption that all people can work and argues that we should create long-term support mechanism nationally to support this assumption. So the actual question is not whether or not an individual with autism will work but whether or not there is support services required for the individual's success in work performance [228].

Studies show that supportive employment opportunities is the effective way for the participation of individuals with autism in work life [229, 230]. Supportive employment programs have a team consisting of different professions and who work together for common goals in the evaluation of work process, its referral, work analysis, work skills training and follow up of the working individual. This team includes occupational rehabilitation consultant, work coach, occupational therapist, physiotherapist, speech therapist, special trainer, psychologist, individual himself/herself, individual's family and other profession members who may contribute in employment process. Occupational therapists have different roles in assessment, recruitment and training, work development and supportive employment process stages of employment process of individuals with autism. During assessment stage occupational

therapists assess sensory and motor skills, professional interests, communication and transportation, daily living activities, cognitive, social and community skills, emergency response and safety in workplace and self-assessment skills. During recruitment and training stage occupational therapist work on training and adaptations about work task and settings, identification and training on auxiliary equipment and technology, training on or compensation of basic cognitive skills like attention, visual perception etc., training of work coaches and supporters on use of auxiliary technologies. During work development stage occupational therapist work for increasing environmental support and reducing barriers, doing work analysis, adjusting improvement of conformity between skills of the individual and expectations of the employer and work development in line with interests and skills of individual. In the supportive employment process stage occupational therapist interested in training of work coaches, training on complex cognitive skills such as problem solving, time management, advocating rights of the individual against the employer and other colleagues and cooperation with interdisciplinary team [231].

10.1. Assessment

Vocational assessment starts with interview, self-report and behavioural observation. Occupational profile is defined for the occupation and occupational performance analysis is made. It's important to assess strengths, interests and needs of the individual as well as environmental supports and barriers during the interviews [233]. Observation of the individual during occupational performance would provide important information for occupational performance analysis. Other assessments specific to occupational therapy may include sensory-motor skills, socialization skills, cognitive skills and participation in activities of daily living. The Vocational Index, The Autism Work Skills Questionnaire (AWSQ), Vineland Adaptive Behavioural Scale, Adult/Adolescent Sensory Profile, Waisman Activities of Daily Living Scale are examples for standardized assessments that can be used [80, 83, 234-236].

10.2. Intervention

Occupational therapists can train the person about skills required for occupation and train his/her natural supports, such as co-workers, supervisors, or family members in the use of adaptive equipment or techniques, environmental adaptations, sensory needs of the person, and compensatory strategies to help the person perform job tasks. Also teaching and compensating for complex cognitive skills such as problem solving, time management, and sequencing to higher functioning persons with autism is within the scope of occupational therapy [232].

Wilczynski, Trammell and Clarke describes forms of technology that can help individuals with autism acquire and maintain employment. According study assistive technology like computer-based systems, personal computers, video recorders, tablets, iPods, iPads, and other devices; video based instruction like video self-modeling, and video games to teach social interaction, covert audio coaching like video modeling instruction initially and follows with audio prompting and alternative support includes personal digital assistants, smartphones,

and other mobile devices that can be used for auditory and visual reminders, time management, organizational skills, and daily living tasks can enhance the natural support available for individuals with autism in the workplace [237]. Occupational therapists can compensate sensory needs through sensory stimulation or inhibition using techniques such as fidget toys, chewing gum, music, weighted clothing, lighting changes, and increases or decreases in environmental stimuli in workplaces.These changes in the sensory environment may lead to improvement in motor processes, which enable the person to be more productive on the job site [232].

11. Conclusion

This chapter provides a brief overview of the wide variety of occupational therapy intervention approaches for individuals with autism. Individuals with autism demonstrate complex behaviours that reguire the integration of different approaches and methods. Occupational therapy interventions varies according to the needs of the individuals with autism. The overall goal of occupational therapy is to help the individual with autism improve quality of life and to enable individuals to participate in everyday occupations. Sensory integration therapy are often used in conjunction with holistic and client centered occupational therapy treatment plan. This practice area is of great importance to the field of occupational therapy in children with autism. Different approaches can assist an individual with autism in a variety of life roles and tasks if it is incorporated into that individual's life in appropriate way. Using effective strategies and technics in occupational therapy intervention program provide opportunities to develop wide range of skills in individuals with autism.

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Chapter 10

Autism and Functional Language Development – An Experiment with AAC Intervention

Rubina Lal and Disha Sanghvi

Additional information is available at the end of the chapter

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1. Introduction

Communication is the base of human interaction. It is a process of sharing ideas, feeling, needs and desires through spoken and written word, signal, sounds, gestures, signs, pictures, symbols, music and body language Communication lends to the social and cognitive development of human beings. It helps in building relationships, acquiring knowledge, and taking decisions. Communication is a powerful tool, an eloquent weapon, a manipulative agent, a distinctive attribute and as recognisable as appearance of an individual.. From the most primitive to the most modern human being, communication as seen as the means to gain control over one's environment and to take one's personal and social needs forward. The ability to communicate and the selection of mode of communication varies from person to person. The most advanced the ability, the greater the learning capacity, and vice versa. Deficits in communication skills can prevent people from realizing their potentials. A communication deficit or disorder is reflected in the inability to receive and process or interpret and use concepts of linguistic symbol systems.

Autism is a developmental disability that affects the way a child's perceives the world and learns from his or her life experiences. Even among the most complex disabilities, autism remains an enigma [1]. It is the frequently occurring form of a group of disorders known as Autism Spectrum Disorders (ASD). The Autism Society of America [2] has defined it as a complex developmental disability that typically appears during the first three years of life and is the result of a neurological disorder that affects the normal functioning of the brain, impacting development in the areas of social interaction and communication skills. Persons with autism have deficits in verbal and nonverbal communication, social interactions, and leisure or play activities. However, as autism is a spectrum disorder, its effects may vary from person to person. Some may be severely affected and others less so. Occurrence of autism in

a child may affect such core human behaviours as social interaction, ability to communicate ideas and feelings, imagination, and establishment of relationships with others [3]. Children with autism often are self-absorbed and appear lost in their own world. They are unable to successfully communicate and interact with others. They may have difficulty developing both receptive and expressive language skills. They also may have difficulty in using and understanding nonverbal communication as body posture, hand gestures, eye contact, and facial expressions [4]

2. Autism and the language pattern

In typically growing children, communication and language emerge as an outcome of a neural integrity that helps them function in early social exchanges with parents or caregivers. These interactive behaviours are essential for the cognitive, affective and social growth that lead to development of communication and language skills. In case of children with autism there may be a relationship between atypical central nervous system functioning and impairments in communication and language [5]. The functional differences between typical children and those with autism may contribute to learning styles and strategies that interfere with acquisition of communication and language skills. Language pattern in autism may be understood well in the context of how nonverbal and verbal communication emerge in children with autism

- Nonverbal communication: Typically growing children use non-symbolic strategies for communicating in early infancy. A child may try to get a toy while looking at it and the parent who can help the child get the toy. This intentional communication is the result of infant and parent social exchange and the parent's ability to understand the infant's signals. These signals are manifest in infant's gestures (e.g. pointing and waving) and vocalizations. Children with autism use gestures and vocalization less frequently and with less sophistication than typically growing children. Their gestures often involve contact with people or objects such as leading people by hand or touching the object. Joint attention and pointing are rarely seen. While preverbal children with autism compare favourably to children with developmental delays with respect to production of syllables with consonants, they tend to produce more atypical vocal behaviours such as squeals and yells [6]. Additionally, aberrant or self-injurious behaviours are often used for communication by nonverbal children with autism. These excess behaviours serve a range of functions such as seeking attention, requesting, escaping and showing displeasure and protest. With respect to rate and reciprocity of communication, it is reported that children with autism compare well with typical children in terms of the rate of communication, although their communication is more primitive. However, respondent acts of communication are significantly lesser than initiated communications. This may be due to a limited ability for turn taking in communicative interactions [7].

- Productive speech and language: In verbal children with autism the articulatory and phonological abilities are better in comparison to the overall communication and language

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skills. However, many may suffer with dysprosody, and voice impairments as pitch and volume. These result in monotonous and staid speech patterns. With respect to language, the morphological and syntactical abilities develop slowly but in typical manner. The major difficulties faced by children are in encoding meaning relevant to conversation, meaningful interpretation of verbal messages, semantic confusion specific to temporal sequencing, and poor sensing of semantic relationships.

With the variety of language and communication issues discussed above, children with autism require appropriate and systematic intervention in this area. An intervention is deemed appropriate if it provides improvement in the child's functional communicative abilities. Over the years, development of language and communication skills has become the core of autism intervention efforts. Several methods and strategies have been used. Among such methods is Augmentative and Alternative Communication (AAC) system.

3. Augmentative and Alternative Communication (AAC)

AAC has Alternative and augmentative communication (AAC) includes a variety of methods which support or replace oral language. AAC refers to any attempt to improve communication success through unaided methods such as natural gestures, sign language, and vocalization or through use of such aids as pictures, communication boards, and speech generating devices. According to the American Speech-Language-Hearing Association [8] AAC is as an area of clinical practice that attempts to compensate (either temporarily or permanently) for the impairment and disability patterns of individuals with severe expressive communication disorders (i.e., the severely speech-language and writing impaired). It incorporates the individual's full communication abilities. AAC includes the use of visual language modes such as signs, pictures and visual icons representing specific linguistic units. These capitalize on strong visual processing of children with autism. Visual supports are reported to be useful in educational program for children with autism who experience difficulties in acquisition of functional speech or in processing and understanding spoken language & social interaction [9]. Since information provided through visual modes is predictable, static or less transient than words, it improves the autistic child's ability to recognise language input and generate language output [10]. Inability to communicate is often a major factor for emergence of challenging behaviours in children with autism. Training in AAC provides a simple way to communicate basic needs and may lead to a significant reduction in inappropriate behaviour events that hinder learning of social interaction skills [11].

Children diagnosed with autism are unable to verbally express feelings, thoughts and needs. Their struggle to communicate even the most basic needs through nonverbal or verbal modes can be frustrating to them and their caregivers. The lack of adequate communicative behaviour often hampers learning and literacy and creates significant obstacles to social and emotional development and independence. Use of an AAC system can serve as a bridge from a life where thoughts, feelings and needs are held in silence, to a life where interaction, expression and learning are possible. Additionally, use of AAC for children with autism may stimulate brain

development; facilitate access to social information and literacy experiences; reduce the need to communicate through aberrant behaviours, and enhance self-concept [12].

3.1. Types of AAC

While AAC has been categorized as aided and unaided [13], most AAC users and practitioners classify the system as given below.

- Natural communication methods: These include hand pointing, gestures, facial expressions and body language that people commonly use while communicating in spoken language. These natural methods augment what is being spoken.
- Sign language: Traditionally used by people with hearing impairments, sign language consists of manual symbols for linguistic units. Signing is useful for helping children with autism understand language. Signs provide information in visual form. They are also less dynamic than spoken words which helps processing of information. Signing can be used as a means of expression with other people who know the signs.
- Object symbols: Miniatures, models and parts of objects are used as symbols for real objects. Toy cars, doll's clothes, models of fruits etc. may be employed for comprehension and expression of language. At times an object may be used to denote an activity for example car keys may denote going for a drive.
- Photos and pictures: Photos, pictures and line drawings of real objects are commonly used as AAC system for children with autism. They are preferred for children with autism as they provide information in visual mode, are easy to handle and are low cost aids.
- Communication boards: They are introduced to children once they are familiar with a number of words, and are able to group them in categories, and use them with some syntactical structure. Communication boards consist of photos, pictures and/or words denoting people, objects and activities.
- Speech generating devices: These mechanical aids similar to communication boards. When the user presses a button, the machine speaks out the word or the sentence.

3.2. Guidelines for AAC use

Before introducing AAC to a child, his or her communication goals should be determined and discussed by professionals and parents. Assessments may be conducted to decide on the suitability of a specific method of AAC. The following general guidelines [14] may provide some direction for planning strategies for a child who uses an AAC system.

- **Restructure physical environment**: One must ensure that an appropriate technical or non-technical AAC system is easily available for the child. Additionally, a child should be seated or positioned so that he or she can access the AAC system independently.
- **Provide communication opportunities**: Communication is important for learning and development. All children need opportunities to communicate their ideas in order to learn from the environment. Unlike typically developing children, those who use AAC systems

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may not be able to start a conversation, get attention, or interrupt others, even if they wish to say something. Communication situations should be structured with a shared focus of attention, to enable children who use AAC systems have many opportunities to communicate and interact. By including communication opportunities in daily routines, the child who uses AAC will have frequent chances to interact.

- **Train communication partners**: Children with cerebral palsy and other physical disabilities often need extra support in order to get access to communication partners and to get involved in motivating activities. Their communication partners must be made aware of this. The communication partners should be taught how to talk to, understand, and respond to the child using an AAC system. They would then be able to find creative and rewarding ways for the child using AAC to participate in activities.

- **Positive expectation from an AAC user**: Communication is a two-way process. While having a conversation with someone, we expect interaction and responses. There should be same expectations for the children who use AAC systems. Expectation is a critical component of a successful communication partnership. If communicating partner expects an AAC using child to respond, the chances are that the child would. Expectation of participation, increases the possibility of its occurrence.

- **Provide sufficient time for communication**: People with verbal communication abilities can communicate at a faster pace. They can often carry on conversations, interrupt and interject with ease and great speed. Children who use AAC systems may process language inputs slowly, and thus communicate at a much slower rate. They must be allowed time for communication messages to be sent and received.

- **Respond to communication attempts**: It is essential that communication partners respond to the child's communicative attempts, confirm the intended message and/or clarify meaning. If required a communication partner may use the child's AAC system to participate in conversations, showing the child how to say specific messages and use appropriate interaction strategies, such as turn taking or asking questions. In case a child's communication is unclear, the partner should try different problem solving strategies to comprehend what the child is trying to communicate. A partner may look for gestures, eye pointing, or other body movements that might indicate a person or object related to the message.

- **Provide training for AAC usage**: Children need to be formally taught to use the AAC system and need frequent opportunities to practice using it in day to day situations. Instructors must set aside time to teach vocabulary, strategies for communication and interaction, and the skills for operating a technical AAC system. Instructions should be broken into small steps with well stated objectives built on previous learning. Systematic recording and monitoring of the child's progress and skill development helps in long-term planning for further learning.

- **Using of Speech generating devices**: If a speech generating device is being used the messages in the AAC system should be updated regularly to ensure that they meet the child's communication needs and are appropriate for the current environment. Review the

AAC system regularly to ensure that it continues to be the most effective communication tool for the child.

- **Include AAC in educational plan**: Every school going child with special needs has an Individual Education Plan (IEP). If a child is need of using an AAC system, it is important that training in AAC usage be included in the IEP. However, the AAC inclusion should not be as a separate area. Rather, it should be listed as a strategy or technique that a student will use to complete educational goals.
- **Develop community care plan**: The child requires a community care plan when it is time to leave the school. The plan should include needed revisions to the AAC system as the AAC user prepares for a major life transition. The AAC inclusion in the community care plan should be of similar nature as that in the IEP.

4. Picture exchange communication system

For children with autism who have severe speech and language delay, the goal of intervention should focus on developing their functional communication. Teachers and caregivers may enable a child to communicate functionally by selecting to teach those words/forms concepts that are meaningful and relevant to the child's environment; teaching the child to use the words/forms in functional manner, and preparing communication partners in the environment to respond to words/forms used by the child in functional manner. Given the importance communication has as a predictor of future social and educational development and later quality of life, it is imperative that intervention program for children with autism stress on alternative means of communication. These alternatives means consisting of visual icons, symbols and manual signs, capitalize on strong visual processing ability in many children with autism [1]. Picture Exchange Communication System or PECS, as it is commonly known, is an AAC system that primarily uses pictures to teach functional communication skills. Developed at the Delaware Autism Program by Bondy and Frost [15], PECS provides children with communication deficits a method to communicate in social settings. According to the designers of PECS, the rationale for PECS emerged from the failure of traditional techniques such as speech imitations, signing, and picture point systems. These techniques relied only on the teacher to initiate communication and did not enhance children's capacity to initiate social interaction. According to Bondy and Frost, PECS has several advantages over other communicative interventions for young children with autism. Speech training is very slow and leaves children no way to communicate in the interval until they can speak some words, if they acquire the ability at all. AACs using speech or sign also require children to have the ability to share a point of focus with an adult and to imitate actions that they see the adult do, both behaviours that children with autism have difficulty with. Finally, according to Bondy and Frost, typically developing children learn language in part because of the associated social rewards for doing so. Their social deficits mean that children with autism are generally not sensitive to such social rewards. Thus, they have little incentive to learn language. The protocol used in PECS provides material rewards for communication in the context of the communi-

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cative exchange, giving children with autism better reason to learn to communicate without artificial reinforcement. PECS allows children with autism who have little or no communication abilities, a means of communicating non-verbally. Children using PECS are taught to approach another person and give them a picture of a desired item in exchange for that item. By doing so, the child is able to initiate communication. The child with autism can use PECS to communicate a request, a thought, or anything that can reasonably be displayed or symbolized on a picture card. PECS works well in the home or in the classroom [16]. PECS is a low-tech AAC system. It does not require any electronic devices. It uses laminated line drawings and a phase-wise implementation protocol.

4.1. PECS phases

PECS is introduced by teaching a child to give a picture of a desired item to a "communicative partner", who immediately responds to the request by giving the desired item. With time the child learns discrimination of pictures and how to put them together in sentences. In the more advanced phases, the children are taught to answer questions and to comment. The PECS program has six phases of teaching.

- *The Physical Exchange*. In this phase, the child is taught to pick up a picture, put it into the hand of an adult, and release the picture upon seeing that the adult has an item that the child wants. Only one picture at a time with a corresponding item is introduced so that the task is simple and the child can learn the exchange of picture with desired item. For some children who require physical prompts it may be necessary to have two adults in the teaching session. While the first adult responds to the child's request for exchange, the second adult prompts the child to go through the motion of picking up the picture card and exchanging it for the item desired. The second adult may slowly reduce the support as the child learns to perform the exchange independently. The sessions occur while the child is seated at a desk with the adult.

- *Expanding Spontaneity*: This phase requires the child to be more actively involved in getting the desired item. The child is no longer working from the desk, instead he/she is expected to fetch the picture from the communication board and bring it to the adult for an exchange with the desired item. The communication board may be placed somewhere in the room.

- *Picture Discrimination*: Now the child is expected to understand that different pictures denote different objects in the real world. The training in this phase begins with just two pictures, one of a desired item and one of a non-preferred item. If the child is unable to discriminate between the pictures, he/she may pick up the picture of the non-preferred object for exchange, and result gets that corresponding object. This is done with the purpose of making the child focus on the selected picture. Prompts are provided to help a child discriminate between the pictures and select the right one. In this case a blank card serves as a distractor. On the other hand if the child can discriminate between pictures easily, number of distractor pictures are increased. As the child progresses, the adult may introduce abstract pictures or symbols denoting the desired items.

- *Sentence Structure*: Now the child is taught to use two pictures/symbols in combination. One symbol for the phrase 'I want' and the second for the desired item. At this stage, the child is given about 20-25 pictures on a communication board and a Velcro sentence strip on which to fix the appropriate cards. Initially the symbol for 'Í want' is fixed on the strip before it is given to the child, and the child is expected to select the desired item's symbol from the collection of symbols, fix it the adult for getting the item. Mastery of this phase occurs when the student can successfully add the symbols for both "I want" and the desired item to the sentence strip and exchange the sentence strip with a communicative partner without any prompts on 80% of trials.
- *Responding to 'What do you want?'*: In this phase, skill to responding to a question is taught. A desired item and 'Í want' symbol are available. The adult points to the 'Í want' symbol and asks 'What do you want?'. The child is expected to put the "I want" and the desired object's picture/symbol on a sentence strip and give it to the adult for exchange. As the child learns the skill, the adult slowly increases the time gap between asking the question and pointing to the "I want" symbol in order to help the child understand that the exchange can take place only when the "I want" symbol is placed before the symbol of the desired object. The child now picks up the skills of forming phrases to express his/her needs.
- *Responsive and Spontaneous Commenting*: In the sixth and the last phase the child learns to answer/comment to questions similar to 'what do you want?' The communication board now may contain a symbol for "I see" below the 'Í want" symbol along with several symbols that do not represent highly desired items. The adult shows one of the less desirable objects, the symbols for which is one the board, and asks the child 'What do you see?". The child is slowly led to place "I see" symbol on the sentence strip before the corresponding symbol for the object shown. The training follows the same process of prompting and rewarding correct response as in the previous phases. When the child gives the correct response, the adult reinforces it by saying "yes, you see a ___", and provides a reward of child's choice. The child is taught to answer several questions of similar nature such as "what do you have? What do you hear?, and what is this?" following the same procedure. In order to ensure that responses are generalized, the questions are asked by at least two different adults after the child demonstrates skill acquisition.

5. Research support for AAC and PECS

A variety of AAC methods have been used with people with autism who are either nonverbal or cannot speak intelligibly. Many of them have been investigated through single subject research protocols. In a meta-analytical research study [17] twenty-four single-case studies were analyzed via an effect size measure, the Improvement Rate Difference (IRD). Three research questions were investigated concerning the overall impact of AAC interventions on targeted behavioural outcomes, effects of AAC interventions on individual targeted behavioural outcomes, and effects of three types of AAC interventions. Results indicated that, overall, aided AAC interventions had large effects on targeted behavioural outcomes in

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individuals with ASD. AAC interventions had positive effects on all of the targeted behavioural outcome; however, effects were greater for communication skills than other categories of skills. Effects of the Picture Exchange Communication System and speech-generating devices were larger than those for other picture-based systems, though picture-based systems did have small effects. AAC is a multisensory intervention. SGDs provide a child with auditory feedback, images and symbols on communication boards and touch screens provide visual and tactile cues and reinforcement to give substance to words that are often abstract (e.g. "the") and difficult for children with autism to understand. AAC can help individuals with autism manage the challenges of social communication. When eye contact, facial expressions and sensory stimulation are over whelming individuals with autism may disengage from social interactions. A speech generating device can be their "voice" to clearly communicate messages and thereby encourage appropriate socialization. Evidence suggests that early augmented language intervention that emphasizes opportunities for communication and capitalizes on family involvement using AAC gets results. For this reason, and unlike conventional speech therapy, AAC therapy involves training both the user and his or her communication partners at home and in the community [18]. A study investigated the effect of AAC intervention on language and social behaviour of children with autism. The children were given training to use Makaton Vocabulary Language Program, a system of AAC. Results indicated that use of AAC had a positive effect on children's receptive and expressive language, and also enhanced social behaviour [1]. Researchers compared PECS and MTS (match the sample) methods on mastery of picture discrimination tasks. During MTS intervention, the children were asked to match a given picture to one of a set of objects. Correct matches were rewarded with w preferred item. In the PECS condition, child-preferred and non-preferred items were displayed, and the child was given two corresponding pictures. When the child gave one of the pictures, he/she received the matching item. Four out of five children required fewer trials to master the picture discrimination tasks under PECS condition than MTS condition [19]. Children with autism with poor communication abilities were taught spontaneous demand skill through PECS and cognitive interventions. Results showed that children learned spontaneous communication during PECs training. They were able to generalize the skills to non-structured setting too. Cognitive interventions served as necessary scaffold for acquisition of task [20].

According to the guidelines on nonmedical interventions that address cognitive function and core deficits in children with autism spectrum disorders (ASDs) and sets priorities for future research, there is scientific evidence (from controlled trials and observational studies) of the effectiveness of the Picture Exchange Communication System (PECS) in increasing child-to-adult initiated communication, primarily requesting communication acts. Therefore, Individuals with ASDs who have limited verbal language, or those who do not respond to multiple interventions aimed at improving communication, should be offered the opportunity to use the PECS [21]. A randomized clinical trial compared Pivotal Response Training (PRT), a verbally-based intervention to PECS on acquisition of spoken language by 39 young (2-4 years), nonverbal or minimally verbal children with autism. The children were randomly assigned to either PRT or PECS condition. All children received 23 weeks of intervention. The measured dependent variables included overall communication, expressive vocabulary, pictorial

communication and parental satisfaction. Children in both intervention groups demonstrated increases in spoken language skills, with no significant difference between the two conditions. Majority of the children exited the program with more than 10 functional words. Parents were very satisfied with both programs but indicated that PRT was easier to implement [22]. PECS has been found to be an effective intervention for reducing maladaptive behaviours in children with autism. In a study, 3 young boys with autism were given PECS training and its effect on requesting, use of intelligible words and maladaptive behaviour was measured. Results indicated that all participants quickly learned to make requests using pictures and that two used intelligible speech following PECS instruction. Maladaptive behaviours were variable throughout baseline and intervention phases [23]. Effectiveness of PECS protocol for the first three phases was evaluated with 3 adults with autism. A multiple baseline across participants design was used to assess the effect of the training package consisting of a video, written and verbal instructions, modelling, rehearsal, and feedback. Results showed significant improvements relative to baseline in a short amount of training time, and that skills generalized to a learner with a severe developmental disability [24].

6. Method

This experimental study used a pre-test post-test control group design. The study sought to determine the effect of PECS intervention on development of functional language of children with autism, and to compare the acquisition of functional language abilities by children who received the PECS intervention to those who did not.

6.1. Subjects

The study was conducted in Mumbai, India on 30 children in the age range of 8 to 12 years. The participating children were selected from 3 special classes for children with autism and intellectual disabilities. The subjects consisted of nonverbal and minimally verbal children with autism. As per records their psychometric performance placed them in the range of severe to moderate intellectual disability. The schools they attended provided speech and language intervention but the intervention was not AAC based. After selection all children were pre-assessed on Functional Language Assessment Scale (FLAS). Subsequently, they were randomly assigned to experimental and control groups so that each group had 15 children. The experimental group received PECS intervention for 15 sessions of 30 minutes each. The control group continued with the language intervention provided by the school.

6.2. Instruments

The researchers used PECS intervention and Functional Language Assessment Scale as instruments. A brief description of both is given below.

- *PECS Intervention*: The intervention consisted of the first 3 phases of PECS, namely, picture exchange, expanding spontaneity, and picture discrimination. PECS phases were taught

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using such techniques of applied behavioural analysis (ABA) as prompting, shaping and reinforcement.

a. Phase 1 taught a child how to communicate by exchanging a picture card for a desired item. This phase was taught by seating the child at a desk with a communicating partner. Another adult was asked to provide prompts to the child while the exchange happened. Only one desired object and its corresponding picture card was used in this phase. The desired object was shown to the child. As the child reached for the object, e/she was guided to pick up the picture card and give it to the communicating partner in order to get the object.

b. Phase 2 introduced distance between the child and the desired object. The child now learned to seek out the picture card of the desired object and take it to the adult for exchange. This phase shaped the child's responses by slowly increasing the distance between the picture card and the communicating partner.

c. Phase 3 required the child to learn to select the picture of the desired object from a set of pictures. Initially it was taught by introducing only one distractor picture with the picture of the desired object. As the child learned to pick up the right picture, more distractors were introduced. For some children this incremental complexity in task was difficult to master, while others learned it soon. Some preferred actual photos of objects to their graphic symbols.

- *Functional Language assessment Scales:* Two instruments were developed by the authors for measuring the acquisition of receptive and expressive language skills. The Functional Language Assessment Scale (FLAS) and Functional Language Assessment Scale (for Parents) or FLAS (P). The FLAS consisted of a list of items categorized as food items, classroom items, household items, names of common animals and play items, and verbs. The items were selected after an extensive review of curriculum for language and communication used in special classes within schools in Mumbai. The authors involved classroom teachers of children with autism to share the language intervention goals for their children. Additionally, parents were consulted for input on functional communication needed at home. After the content was validated by domain experts, the instrument was pilot tested. Since the children ranged between 8-12 years, the FLAS included a level of complexity in items to address the variety in functioning levels of the children. It contained a total of 80 items. Both receptive and expressive language skills were measured on a 4-point scale of 'Correct Response (CR), 'Response with Verbal Prompt' (RVP), 'Response with Gestural Prompt' (RGP), and 'Response with Physical Prompt' (RPP). Whereas 4 points were allotted to a CR and a RPP was given a score of 1 point. The combined maximum score attainable on FLAS was 640 and the minimum 160. The FLAS (P) was designed as a rating scale to be used by parents of children in the experimental group at post intervention condition. The scores on FLAS (P) were correlated with that on FLAS. The FLAS (P) followed the structure of FLAS in that it measured the development of functional communication through receptive and expressive language skills. Only those items that reflected communication needs at home were retained in FLAS (P). While the number of items were reduced in FLAS

(P) to 50, they were categorized and scored in the same manner as in FLAS. For details of FLAS structure and sample of items included in it please refer to Table 1.

6.3. Procedure

The intervention commenced after assessing the children's baseline functional language skills on FLAS. All 30 children were underwent the assessment before being randomly assigned to experimental and control groups. The assessments were done following the steps given below.

- For assessment of receptive language, a child was asked to pick up the picture of a named item from a group of 2-3 pictures. If the child selected correct picture without any prompts he/she was allotted 4 points. A prompted response was marked anywhere between 3 and 1 depending on the level of prompt required by the child.
- Since the research was conducted on nonverbal or minimally verbal children with autism, expressive language was measured in terms of the child's ability to match a picture to a given object. A child was shown a real object or its model and asked to pick up the picture from a set of pictures that represented the object. Scoring was similar to that for receptive language.

Once the participating children were assigned to experimental and control groups, the parents of experimental group children were shown how to use FLAS (P), and then asked to record their child's response to each item with respect to receptive and expressive language. The parents were provided pictures and models where real objects could not be used. The intervention began once the assessment process was completed. As stated earlier, only 3 phases of PECS training was considered for intervention. Each child received 15 sessions of intervention of 30 minutes duration. A description of intervention steps is given below.

a. As PECS is based on the principles of ABA, determining the motivator for a child was important. Hence, parents and teachers of experimental group children were consulted for this. A list of reinforcers to be used in subsequent sessions was made.

Receptive Language				Items	Expressive Language			
CR	RVP	RGP	RPP		CR	RVP	RGP	RPP
				Food items				
				· biscuit				
				· chocolate				
				· wafer				
				· apple				
				· banana				
				· samosa				
				Classroom items				

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Receptive Language				Items	Expressive Language			
CR	RVP	RGP	RPP		CR	RVP	RGP	RPP
				· Bag				
				· Book				
				· crayon				
				· desk				
				· pencil				
				· Paper				
				Household items				
				· Bed				
				· Chair				
				· toothbrush				
				· plate				
				· spoon				
				Animals & Play items				
				· Cat				
				· Dog				
				· Cow				
				· Blocks				
				· Ball				
				· Bat				
				Verbs				
				· To eat				
				· To sit				
				· To drink				
				· To run				
				· To sleep				
				· To Jump				

Table 1. FLAS structure and sample of items

b. The initial sessions aimed to help a child learn how to communicate. The first session began by showing the child the desired item, and encouraging him/her to pick up the matching picture. Since the children wanted the reinforcer, they could pick up the corresponding picture easily. At this point only one picture card was introduced. For children who required assistance to understand the concept of exchanging the picture for

what they desired, another adult prompted them to give the card to the communicating partner who held the desired item. Once the children learned the process of exchanging picture card for desired item they were shown other items and their corresponding pictures. Both correct and prompted responses would be followed by a reinforcer. This ensured that a prompted response shaped into correct response as the sessions progressed. The selection of items for a given session was based on the child's level of functioning as pre-tested on FLAS.

c. Once the children learned social interaction by exchanging picture cards for items sitting on a desk with a communicating partner, the intervention moved to the second phase of PECS training. The researchers introduced distance between the picture card and the communicating partner. Now the cards were either kept on a nearby table or stuck on a board. The children were expected to pick up the card and take it to the communicating partner. They were taught persistence by increasing the distance from the partner with desired item, so they learned to walk across the room to complete interaction.

d. Distractor picture cards were introduced during the third and last phase of training. Different picture cards served as distractors for teaching a child to select the target picture. The cards consisted of pictures of items included in the FLAS. Children's responses were shaped though the required level of prompts. Initially this was done sitting on a desk with the communicating partner. As the children learned to give correct response, distance was reintroduced in the session. Hence, the children were expected to select the target picture from a set of pictures on a board and bring it to the adult for the interaction to be completed.

While the children in the experimental group received PECS training for 15 sessions, those in the control group continued with the language intervention program provided in their schools. After intervention period all children were post tested on FLAS. Parents of experimental group children were asked to reassessed their children on FLAS (P). Figures 1-6 show some intervention sessions.

Figure 1. Introducing a desired food item with matching picture

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Figure 2. Learning to match object to picture

Figure 3. Exchanging picture card for desired food item

Figure 4. Selecting target picture from a group of pictures

Figure 5. Introducing verb cards

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Figure 6. Introducing distance between picture and desired object

7. Results

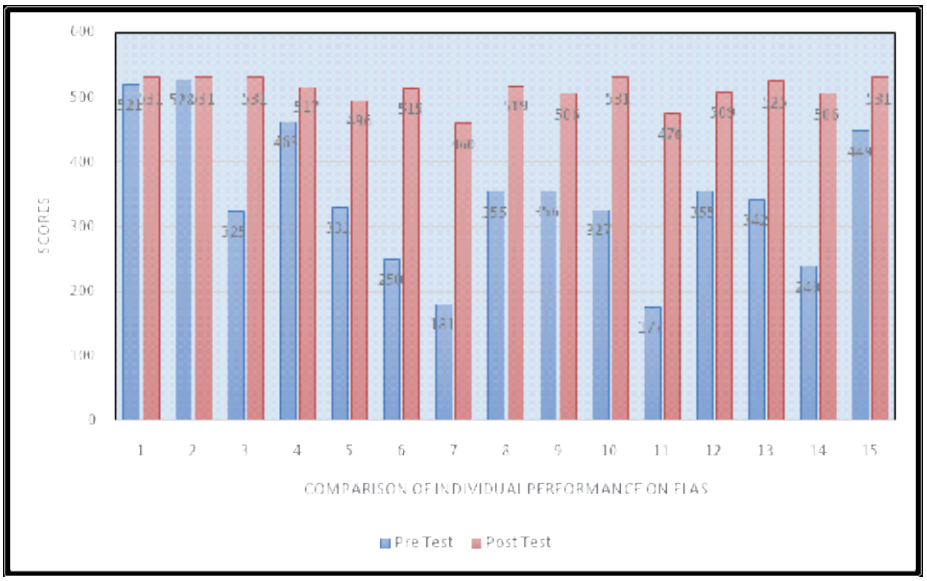
The study aimed to determine the efficacy of PECS based AAC intervention on development of functional language abilities of children with autism. The children under PECS condition showed quantitative change in their social interactions. A comparison of their composite mean score on FLAS at baseline with that at post intervention showed a significant difference (refer to table 2). As the selection of the children was random, the data was analysed using t-test.

Condition	N	Mean	r	t-value	df	Significance
Pre-test	15	346.66	0.72	6.80	14	P<.001
Post-test	15	512.26				

Table 2. Comparison of pre and post-test composite mean scores of experimental group on FLAS

The effect of PECS intervention was evident to people who interacted with the children in the experimental group. They noted the difference in the children's ability to communicate meaningfully. Statistical analysis of data supported this observation. The average score at baseline (346.66) showed a significant increase post intervention (512.26). Each of the 15 children in the experimental group benefitted by the intervention. This led to the large

difference between pre and post mean scores. The positive effect of training on the children is clear when their pre and post-test individual scores are compared (Figure 7).



As may be seen from Figure 7 that all children gained from the intervention, though some gained more than others. This may be understood in terms of the initial differences that existed among the children due to factors such as age and intellectual levels.

Functional language skills were measured through receptive and expressive language on FLAS. The mean scores on these component skills were compared. The baseline average score on receptive language (224.2) was significantly lower than that at post intervention (329.53) as indicated by the derived t-value (7.05; $p<.001$). From figure 8 it is evident that all children improved their performance from pre to post test. However, in comparison with others the observed gain was not as much in two of the children.

With respect to expressive language skills, the children's base line mean score on FLAS was 121.8. After 15 sessions of intervention their performance was observed to have improved. They had learned to use picture or symbols to convey their wishes and desires. They were able to engage in more meaningful social interaction. This was also supported by their post-test performance. The average score on FLAS (182.73) was significantly higher as indicated by the derived t-value (6.01, $p<.001$). This suggested the positive effect of PECS on communication ability. Figure 9 presents the details of pre and post-test individual performance on expressive language skill post intervention.

While the experimental group children received PECS based intervention, those in the control group continued with the intervention provided by their respective schools. At the end of intervention period all children were reassessed on FLAS. The second objective of the study

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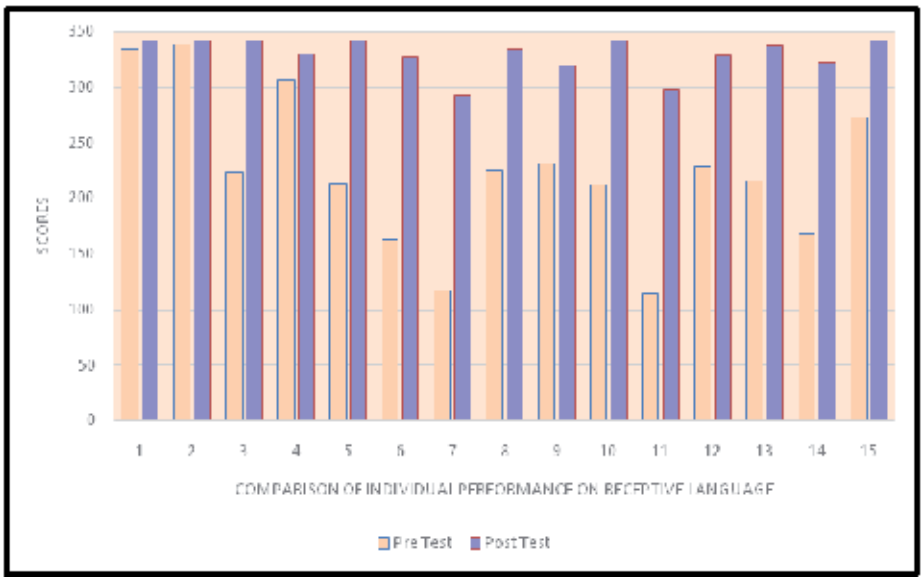
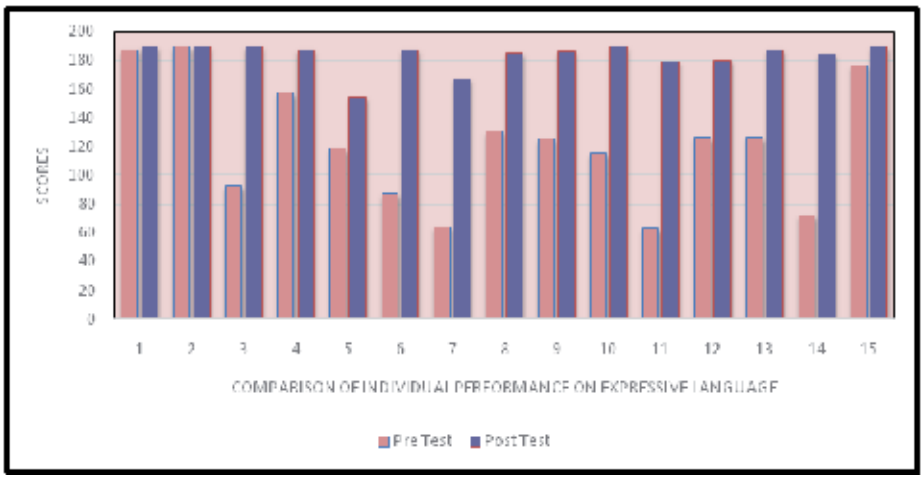


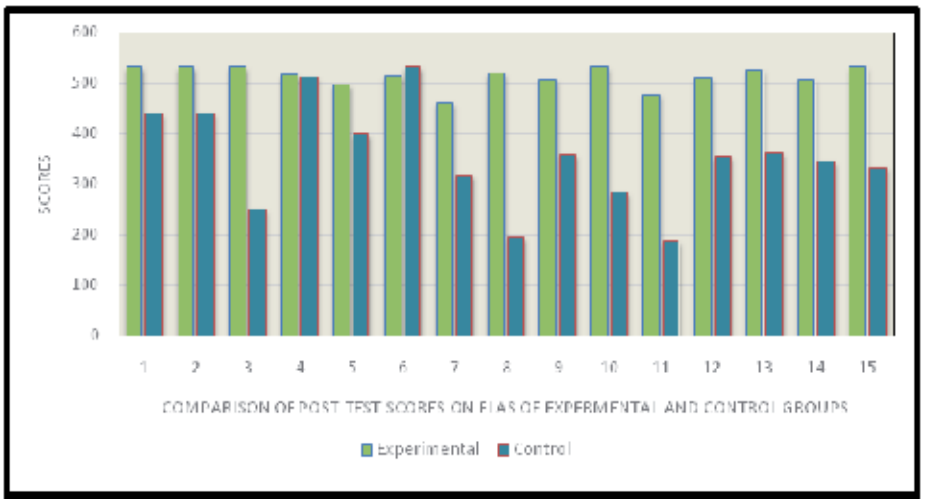


was to compare the post intervention performance of experimental group children to children in the control group. The difference was analysed for statistical significance (Table 3.)

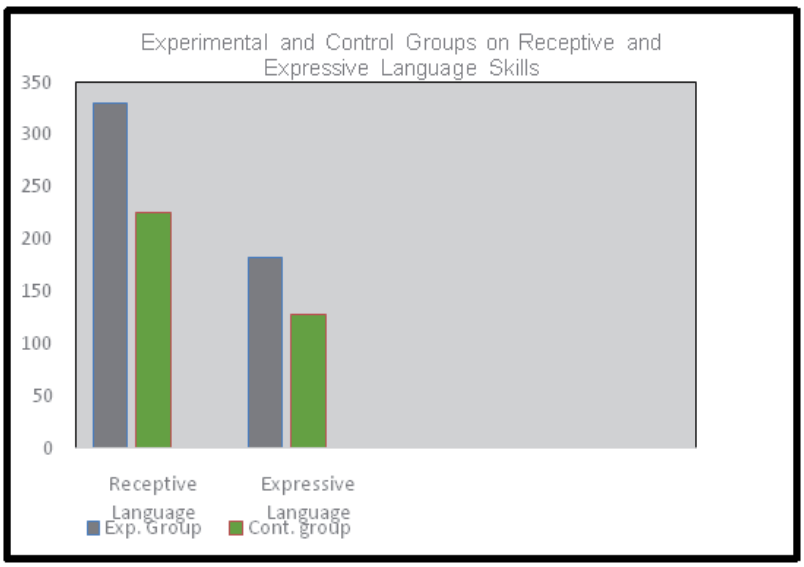
Groups	N	Mean	t-value	df	Significance
Experimental	15	512.26	5.92	28	P<.001
Control	15	353.13			

Table 3. Comparison of post-test composite mean scores of experimental and control groups on FLAS

The resultant t- value (5.92, p<.001) was highly significant. This indicated that PECS based intervention was effective than traditional intervention methods for children with autism.. Figure 10 shows the quantitative difference in performance of children in experimental and control groups.



Every child except one in the experimental group performed better than his/her counterpart in the control group. Some experimental children scored significantly higher than their control group peers. A similar trend was seen when mean scores on receptive and expressive language skills were compared (refer to Figure 11)



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The children in the experimental group performed better on FLAS component skills. But the difference was more in receptive language. This might be due to the limited number of intervention sessions. Due to the short duration of intervention, the experimental group children could not demonstrate similar gain in both receptive and expressive language skills. However, in order to ensure that acquisition and demonstration of newly acquired functional communication ability was not limited to intervention setting, the experimental group individual scores on FLAS was correlated with the respective scores given to children by their parents on FLAS (P). The parents administered FLAS (P) on their respective children at the end of the intervention period. Their children's gain in communication skills was reported by the parents. When FLAS (P) scores were correlated with scores on FLAS using Product Moment method, a high correlation ($r = 0.89$) resulted between the two sets.

8. Discussion

Among the various difficulties faced by individuals with autism, communication has been described as being at the core. It is believed that one third of all individuals with autism may never acquire oral expressive language sufficient to meet their daily needs [3]. It is imperative that they learn to use an alternative and augmentative mode for communication. As mentioned earlier, there are a variety of AAC systems available for children with disabilities. Selection of a suitable system must depend on its ability to respond to the unique features of a specific disability. One of the first communication difficulties with autism is with development of paralinguistics [25]. They do not understand the underlying meaning of a message that are embedded in the speaker's facial expression, body language, eye gaze and tone of voice. Learning to understand paralinguistics is important for development of receptive language. In a typically developing toddler paralinguitics emerge as a consequence of parent-child interactions. The parent smiles and waves a milk bottle before the infant, and asks in a high pitched tone if the infant wants milk. The infant looks at the smiling and nodding parent, and understands that something pleasant is going to happen. This is the premise that was used in PECS intervention. The communicating partner showed or pointed to a picture of the object that was desired. When the picture was exchanged the child was given the object with a smile and a nod from the communicating partner. Besides motivating the child to communicate, these paralinguitics provided social meaning to the exchange. Children with autism are visual learners. Research on graphic symbol learning indicates that symbols with iconicity are easier to learn [26]. The symbols used during the PECS intervention resembled their referents. The children could learn to identify and exchange them easily for desired items. The significant increase in children's receptive language skills post intervention could be attributed to this. Research also suggests that children with autism are more interested in inanimate objects than in human interaction [12]. They are able to process better when information is presented in static form. Pictures and symbols are inanimate and provide static information. The use of PECS as an AAC system in this study responded to the learning preferences of the selected children. PECS was designed specifically for children with autism who have limited verbal ability [27]. It addressed the difficulty children with autism have in social initiations. Teaching

a child to approach an adult and request for a desired object using a picture not only improved communication but also developed social interaction. Successful outcome of each attempt reinforced a child's communicative behaviour. The performance of the experimental group children on FLAS was significantly higher than those in the control group. The control group children also attended school and received speech and language intervention. Notwithstanding that they belonged to the same age group, the intervention goals would essentially consist of teaching similar language concepts, the control group children did not demonstrate gains equal to their experimental group counterparts. The principles of applied behaviour analysis is central to the PECS program. The ABA methods such as rewards and prompts are systematically used to shape a child's verbal behaviour though out the program, and much more rigorously in the initial phases. The ABA methods were used during the intervention period. This adherence to ABA principles might not be existing in the language interventions given to the control group children. Hence, as the children were not frequently rewarded or guided to produce correct response of identifying pictures, their gain on receptive language was below the children who received PECS training. Similarly, with respect to expressive language skills, in the traditional intervention setting the emphasis was on naming the picture orally. This might have been impacted their learning as the control group children like their peers in the experimental group were nonverbal or minimally verbal. The positive gains by the experimental group might be attributed to PECS training. That the change in ability to communicate was beyond the intervention settings was evidenced by parents, and borne by the positive correlation between observations made by the researchers and that by the parents.

9. Conclusion

Difficulties in social relationships and interactions have been the defining features of autism. Therapists and teachers frequently use augmentative communication systems with children with autism to support development of interactive behaviour. AAC systems follow a topographically based taxonomy. Some are selection-based systems in which each response is topographically identical and others are topography-based systems in which each response is topographically distinct [28]. PECS being a selection based system follows a topographically identical (e.g. card selection and exchange) pattern. It suits the literal thinking ability of a child with autism. The pictures and symbols are static, literal and clear, and enable children with autism to process information easily. The outcome of this study substantiate the findings of previous researches supporting use of PECS as a suitable augmentative communication system for children with autism.

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Chapter 11

A Conceptual Model for Empowering Families in Less Affluent Countries Who Have a Child With Autism

Sayyed Ali Samadi, Hadi Samadi and Roy McConkey

Additional information is available at the end of the chapter

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1. Introduction

International experience has demonstrated that children with ASD can be helped and that families are crucial to the success of any interventions. In less affluent countries families play an even more crucial role given the dearth of professionals trained in ASD and appropriate support services [23]. In such countries, indigenous research is crucial to fully appreciate the needs of families and the most relevant means of empowering them to face the challenges posed by their child's condition. The outcomes of these research endeavours can then guide practitioners and policy makers in devising services best suited to local needs. Conceptual Models (CMs) are critical both to guide and validate the style and direction of research studies that are undertaken as well as synthesising key factors in shaping the type of support services provided for families. In this respect CMs have the potential to integrate research and practice.

The reason for considering CMs in any scientific field is to provide an explanation for existing relationships among the phenomena under investigation and to provide insights that may lead to the discovery of new relationships [32]. A Conceptual Model (CM) can be considered to be both as a synthesis of extant knowledge on the topic but also a guide for further studies. Sometimes the phenomena under investigation are so complex that no one CM can exclusively provide the necessary guidance. Research on families-specifically families who have a member with disability-fit into this category. It is the main objective of this chapter to discuss and demonstrate how facing new problems in the course of an evolving programme of research, encourages researchers to further develop their initial CM in order to arrive at a more comprehensive account of the phenomena they are investigating: a necessary outcome in order to guide practitioners in new areas of work such as Autism. Otherwise the risk is that the services they deliver – either as an individual clinician or within a service system such as education – is based on incomplete and out-dated models. The chapter draws on a series of studies

undertaken by the first author initially for his doctoral thesis but continued in his post-doctoral research. As a clinical psychologist, he had previously worked in services for persons with intellectual and developmental disabilities on assessment and rehabilitation programmes.

The study started with two main aims: 1) to enhance current knowledge on the impact of taking care of a child with ASD on family dynamics in Iran; and 2) to help parents in reducing negative effects of raising a child with ASD through short educational courses and extending their social network through providing opportunities for meeting each other. He first undertook a survey of parents' experiences in Tehran to having a child with ASD [21] and how the personal impact on families differed from those with a child who had intellectual disabilities [27]. From this study, an introductory training course on ASD for parents was devised and evaluated [25]. The longer –term impact of such a course was also assessed and the contribution that mutual support from other parents can make to maternal well-being in particular [15]. Further resource materials to inform and guide parents were developed – DVDs, educational packs and the provision of educational materials [27].

2. Identifying appropriate conceptual models

There is no unique scientific method to guide the process of empirical enquiry. Likewise, there is no distinctive conceptual model that can be applied in all research programmes of family studies. So, the aim of this chapter is NOT to build up an all-embracing model in such a complex area as family environment. No one model would be sufficiently comprehensive that it could guide all future research. However, without adopting some form of CM no research could be done and so, adopting a CM is the first and indispensable part of research that no researcher could avoid even if they never make explicit the CM that underpinned their study which in fact frequently happens.

But how does a researcher choose among the competing CMs that are available and which are likely to prove suitable for other cultures? Again, there is not a single and simple guideline to help the researcher's choice. This is a tricky and potentially fallible step and one that has to be informed by the chosen topic of the investigation, the extant literature on it and the experiences gained personally by the researcher and in consultation with practitioners and families who have the lived experience of the chosen phenomena. It is some consolation to know that the CM initially chosen often is found to have shortcomings when it is put into practice. Abandoning the chosen CM and adopting another one is not a good recommendation most of the time; especially when the chosen CM has enabled us to deal with certain aspects of the problem. The better solution is to extend the CM to encompass newly identified issues. By offering an example around parental empowerment that might be useful to others, we aim to show how the formation of a more complete CM can be achieved. In so doing, we hope to draw out the ways in which this case study could assist practitioners and also the future research questions that can emanate from it.

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3. Parental empowerment

In developing countries parental empowerment is a relatively new term in the literature on children with developmental disabilities. Yet involving parents in the process of promoting their child's development seems to be the most rational solution to the lack of support and services for this group of children and their families. Even in developed and more affluent societies, parental empowerment is a growing concern as [18] point out. Financial constraints and changing ideologies have expanded parents' roles to include the jobs of "information seeker, problem solver, committee member, public educator, political activist and, most importantly, spokesperson for the needs of their children".

Empowerment has been defined as "an intentional, ongoing process … through which people lacking an equal share of valued resources, gain greater access to and control over those resources" (Cornell Empowerment Group, 1989, p. 2 cited in [19] The word '*intentional*' refers to the psychological aspects of empowerment; '*ongoing process'* refers to the likely up and downs that will be encountered as well as the need for persistence of over time; '*lacking an equal share of valued resources'* refers to the societal aspects that disadvantage families and '*greater access to and control over'* summarises the intended outcomes.

The first challenge was to find a CM that could be adopted so as to empower parents of children with ASD in Iran. Part of the difficulty with research on topic of parental empowerment is that it is context and culturally dependent [35]. This makes it a real challenge to find a universal model of parental empowerment.

However there are some general criteria that can guide the choice among available CMs. Simplicity, wideness of scope and easiness of applicability may be among these criteria (see [16] for the virtues of a good theory). However, such criteria may be too general; appealing more to philosophers of science and can appear trivial especially in assisting practitioners in their choice of CM.

The following criteria were used to select appropriate CMs for research into parental empowerment in Iran:

- *Concept of disability*: the CM had to reflect current thinking about disability, such as that reflected in the International Classification of Functioning, Disability and Health (ICF) [34].
- *Social Cultural issues*: the CM had to consider the impact of social context, cultural influences and attitudes;
- *Compatibility with family centred approach*: the CM had to be compatible with family centred approaches as international experience has identified this as key to effective intervention for children with developmental disabilities.

We now examine each of these in more detail.

4. Concepts of disability

ASD is predominantly conceived as a medical condition based on DSM or ICD definitions. The medical model tends to believe that the curing or managing of disability generally or completely, revolves around identifying the illness or disability from an 'in-depth' clinical perspective involving doctors, therapists and psychologists. The irony is that ASD even in the medical sources is defined based on its behavioural manifestation rather than clinical symptoms. Sole reliance on a medical condition sits outside modern conceptions of disability that acknowledge environmental influences such as family and society on a child/person's level of functioning. These may be particularly crucial in developing countries with their poor service infrastructures at local and national.

The International Classification of Functioning, Disability and Health (ICF, WHO, 2002) is an updated framework for the description of health and health-related states. The classification is focused on health and health-related domains based on what a person with a health condition can do in a standard environment compared to what they actually do in their usual environment (comparing the level of capacity to the level of performance). Thus social and environmental factors can have a major influence on a child's level of functioning in addition to any medical and disability condition.

The ICF also embodied the thinking in the bio-psycho-social frameworks which have been proposed in disability and mental health in which different biological, psychological, and social influences are brought together [8]. As Engel argues there is a reciprocal rather than a linear relationship between all these three main factors. According to this model, although a specific disability may require primary attention at the biological level – such as hearing impairment-it will also have an impact on psychological factors and both factors in turn may influence the social system of the person with disability and their parents. Thus ICF provides a comprehensive view of factors involving health, illness and health care and explains and understands individual behaviour in particular contexts.

5. Social and cultural factors

[1, 2] ecological framework of the different systems that impact on a child's development, could also help researchers and practitioners to better understand the situation of parents who are taking care of a child with ASD. He posits five different systems that can influence childhood development: the Microsystem, Mesosystem, Exosystem, Macrosystem and Chronosystem. A change in any one of these components can cause a change in the other components. Microsystems are those closest to the child-such as family and school-as they directly impact on the child. These Microsystems are interrelated and together form a higher level system: the Mesosystem. However these take place within an Exosystem of community services and supports that in turn is influenced by the wider cultural Macrosystem, including ideologies, laws, economic and social policies and religious attitudes. All of these systems and the interactions between them can change over the course of a child's life which is captured in the concept of the Chronosystem.

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As [33] argued, in an ecological model the main emphasis has to be on "fixing" the multiple ecological environments, rather than "fixing" the child with disability and having him/her fit into different social layers of family, community and society, which is the aim of the medical model. This suggests a shift of attitude to change the focus away from the child with disability as an independent entity towards a more global view which covers both children and their families. According to an ecological model, the focus is on a transformed ecology in which children with different types of disabilities can develop by using their skills in interaction with a responsive environment [33].

6. Family-centred interventions

There is also a shift from child-focussed interventions to family-focussed interventions. Family-centred practice is an umbrella term for both a philosophy and a method of service delivery consisting of a set of values, skills, behaviours and knowledge that recognises the centrality of families in the lives of their offspring. It puts family life, the strengths, needs and choices of people with a disability and their families as the focal point of service planning, development, implementation and evaluation. It is grounded in valuing the uniqueness of every person and family, and a commitment to partnering with families and communities to support children and young people with developmental delay or disability to learn, grow and thrive.

Family-centred approaches value the strengths and resourcefulness of all families and aims to support and encourage families in their efforts to meet the special needs of their child with a disability and of the parents in ways that are defined as independent, functional and appropriate [4].The efficacy of family-centred practice has been well demonstrated in affluent countries [7] and applied across all developmental disabilities but may be less well developed in ASD.

With these criteria in mind, the three most promising frameworks for family empowerment were found to be: 1) Bronfenbrenner's theory on human ecology [1, 2], 2) the McMaster Model of family functioning [9, 10, 11], and 3) Enabling and Supporting Families [6]. Although other frameworks have been applied in family research, they were considered to be insufficient for the purpose of the research study undertaken in Iran. For example, the Lazarus Theory on Stress and Coping (Lazarus, 1966 cited in [14] had been used in many studies on parental stress and coping. Although this theory conceptualizes stress as an outcome of the relationship between individuals and their situation as parents of a child with disabilities, it emphasises more the personal rather than the social side of stress and coping.

7. Amending the adopted model and combining with other CMs

The three identified models raised a fundamental issue. How would the researcher choose between them and which one should he choose? Were these CMs rival or complimentary to one another? In fact the answers came as part of an evolving process during the course of the

research. The most credible solution was to try and combine the three available conceptual models. In addition he also had to supplement the model to elaborate the concept of empowerment.

Initially Bronfenbrenner's theory on human ecology seemed sufficient as it brought together the insights from the other two approaches and provided a general picture of society with respect to its different layers in order to explain interactions between the components of the microsystem level and wider society. However our literature searches allied with the authors' experiences identified some limitations. Although this model stresses the relationships between various components within different social layers, it does not help us to fully explore and understand the relationship among the family members.

Thus the McMaster family functioning model was used as an extension of the ecological model. The main reason for adopting the family functioning model was to consider the family as the unit of analysis in the research. Although Bronfenbrenner's theory is based on systems theory, inherently it is an *individualistic* approach whereas McMaster theory has a *holistic* perspective and focuses on the family and the impact of disability on all members of the family – notably mothers and fathers. The main focus is on present problems not past origins which can be considered a particular concern for clinicians and practitioners. The emphasis is for family members to address present concerns, resistances, or blockages so as to find solutions for their problems. When using the McMaster approach, the practitioner functions as a catalyst, clarifier and facilitator. The goal is to help family members to identify and solve problems themselves.

However the Family Functioning model alone was insufficient in understanding how this problem solving process might be done. The addition of Dunst's family support model further extended the model by including the types of support – formal and informal – that are beneficial to families. But important as this was in identifying the range and level of supports across systems, in itself it did not focus on the process of empowerment a point we will come back to later.

A word of caution relating to merging CMs. In extending a basic CM to cover some merits of another one there should be some semblance in their background and overlaps between them. The CMs in this study recognised the core role that family relationships had within other systems such as the extended family, school and religious systems. These levels of similarity provided a basis for extending the ecology model to encompass aspects of the McMaster, Enabling and Empowering Families CMs.

Within each of these domains specific aspects that researcher had found to be especially relevant for parents' empowerment in Iran were highlighted. Moreover it is the combination of these different perspectives that is the main and novel feature of the proposed model in this paper.

Also it could be argued that we should separate the questions of our research at the outset and answer them in the context of separate and suitable conceptual models. Sometimes this may be a good recommendation. However, in some instances, especially in times of dealing with complex phenomena such as parental empowerment, a more comprehensive understanding of the subject will not occur by separating the questions that are actually deeply related and

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answering them in unrelated CMs. Our suggestion is that in such cases expanding the chosen CM to encompass other related questions is a better strategy.

8. Focus on empowerment

As Shultz et al., 1995, suggests empowerment can exist at three main levels: individual, organizational and community level. This became apparent in the different stages of the research programme.

Each of the three mentioned CMs has its own advantages for dealing with one of Scultz's levels. A variation of a "family systems model" is the McMaster model of family functioning (MMFF), described by [10] in the mid-50s. This outlines the basic concept of family functioning [17] and is based on the theory that the primary function of the family unit is to provide a setting for the development and maintenance of family members on the biological, social, and psychological levels [10]. Over a period of thirty years this model has evolved and the reformulations of it have tried to overcome some of the problems that emerged in the initial application of the model [17]. It facilitates empowerment at an individual level. Empowerment at this level entails psychological processes such as parental wellbeing, coping strategies and self-esteem.

Likewise an understanding of the socio-political environment, which includes knowledge of the laws and an appreciation by parents of their rights and responsibilities with respect to their situation helps with organizational empowerment. This level of empowerment enhances goal-directed actions by members of a group or organization. A model plays an important role at this level of empowerment. This was provided through the model of Enabling and Empowering Families. In this CM available sources of help are also important. [5] argue that a better relationship between parents, service providers and professionals increases the level of empowerment. Iranian parents in these studies were asking for more and improved professional services for their children and themselves. Therefore, at this stage of research, examining the service delivery-related factors that influence family empowerment was particularly helpful.

Finally at the broad level of community, empowerment reflects actions taken by a group of people to improve life in their society. The ecological model clearly explains this concept and defines approaches for helping families to strengthen their abilities to provide their children with experiences and opportunities similar to other children with regular development. Parents were asking for development-enhancing qualities above the individual or organizational level and were hoping to change the dominant attitude of the society and the stigma that resulted from having a child with ASD. This happened when a group of parents who were participants of the studies went on to form a non-governmental organisation for Autism to lobby for better services and to provide mutual support to families.This was the first Iranian nongovernmental association in this kind.

9. Further additions to the model

There were still aspects in family empowerment that even the extended CMs could not deal completely with, notably how educating families produced changes in them. This needs additional conceptual insights which were provided by [13] and [12]. Although their theories had been initially developed for nursing education, the attractive aspect was the emphasis that education is more than knowledge acquisition and should lead to action. [13] suggested that learning through understanding one's own situation and abilities, is built around the processes of *enlightenment*, *empowerment* and *emancipation*. In the educational sessions parents understand "who they are", i.e., the "Enlightenment". The second process helps parents to "change" who they are, i.e., "Empowerment". Following this, the third main dimension is presented, i.e., "Emancipation", the process which helped parents to "become" what they wanted to be. This highlights the importance of education in bringing about changes in parents and their activities so that they have their own voice in changing the attitudes of their society. On the other hand relying solely on this model of empowerment would imply that the process of emancipation occurred for all parents to the same extent which was not true. For example the Parental NGO faced different system problems which caused serious crises for both the NGO and the members. Thus the broader model that had evolved was needed to account for the individual variations that remained and which were evident after as well as before the training such as the nature of the disability, family dynamics and community reactions. Again, it must be noticed that in extending a CM the auxiliary theories should have commonality with the main CM, or at least be consistent with it. Thus enlightenment, empowerment, and emancipation concepts can be construed as an elaboration of the family functioning model. In this model the primary function of the family unit is to provide a setting for the development and maintenance of the family members on the biological, social, and psychological levels. To be able to provide the necessary bases for family development, the family's needs and desires must be known. Parental awareness about their needs could be obtained through information provision, exchange of experience with other parents and letting them have their own voices to talk about their ideas and to explain things from their own perspective. Family enlightenment, empowerment and emancipation will be obtained by improving family functioning and their communication with one another along with fostering the emotional health of its members through information provision, exchange of experience and having their own voices through their own advocacy. Equally these three concepts could help us in understanding the improvement of family functioning levels through providing more opportunities for being influential in their society.

Figure 1 presents the resulting model to emerge from the research and development programme. Here we draw out the ways in which this model could assist practitioners and also identify further research questions that emanate from it.

Finding theories and models of family programmes is not a big challenge. The challenge is to adopt them in a way that is suitable to use in the context of the reality of the life of families and children with developmental disabilities in different societies. Similar approaches could be adopted to guide the development of clinical practice and services especially in less affluent countries. A useful starting point is the model that has evolved in Iran albeit within the context

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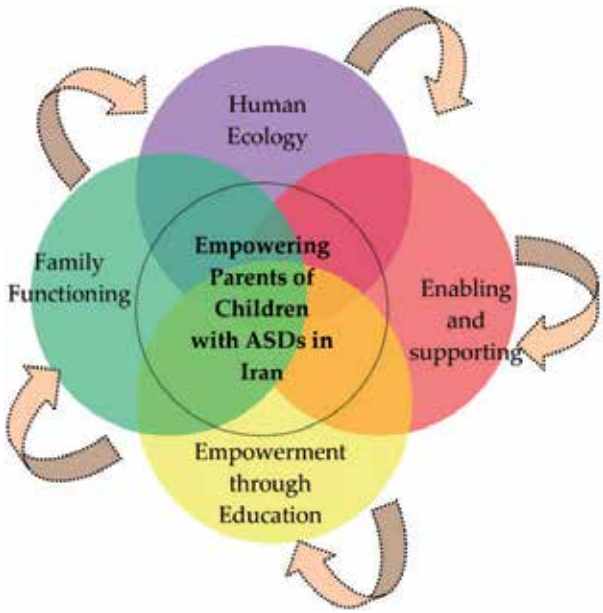

Figure 1. The final model which was used to answer the research questions that emanate from the thesis on "Parental Empowering".

of research. In recent years this process has begun and various strategies have been tested along the development of resources to support these new styles of working.

The following are some of the key components of service provision based on the integrated conceptual model.

- The focus should be on families and not just the child. Professionals visiting the family at home is one means for living this message even though initially it may go against cultural norms.
- Any assessment of the child needs to be informed by family interactions he or she experiences, the learning opportunities provided to the child and the possible social and environmental barriers impeding the child's development.
- Family–centred therapeutic interventions for ASD are devised which are undertaken mainly by families in home settings rather than by professionals in clinics.
- Knowledge transfer and the sharing of professional expertise is essential and can be done through the preparation of DVDs and books. Two books on Autism has been published in Farsi [22, 30].
- Training courses are devised and offered regularly to parents. One aim of such courses is for parents to learn from one another as a group on six to eight occasions.
- Parental advocacy is promoted and in this respect, the involvement of fathers can be especially helpful.

- Greater public awareness of ASD is promoted through parental advocacy, use of media and briefing for community leaders.

In sum, the model envisages a community-based, family centred service based on partnership working among all the stakeholders.

Equally this model generates further research questions. Chief among them are the following:

- Are children with ASD who experience these styles of services more socially included within their families and community?
- If they are included, does this reduce their symptoms of ASD – are they socially more communicative with fewer behaviour management issues?
- Are the children able to gain entry to mainstream schooling and what supports are needed to sustain their placements?
- Can schools incorporate elements of this model by becoming more family and community-focussed?
- Do parents who experience this model show sustained improvements in their family functioning and emotional wellbeing?
- How effective is this model for families living in rural settings?

10. Conclusions

Parents in most countries realise their important role in supporting themselves and their children despite financial constraints and changing ideologies [19] but in practice in the developing societies, their role is not clearly defined and their presence is not welcomed by clinicians and professionals. In these societies based on the dominant service provision for children with developmental disabilities, parents themselves preferred to act passively. In the case of ASD in Iran, parents still need to struggle to be trained and confident enough to be acknowledged and valued and to be recognised by the society as an integrated group. If the needs of families of children with ASD are to be met through parental empowerment, it seems that a more co-ordinated and coherent CM is needed. Since such a CM has not yet been developed, the family researchers, especially those who study more complicated families, such as a family of children with ASD, have to choose among the available CMs. The experiences which were mentioned here have also required other conceptual models and it could be argued that they have further validated the researcher's choice of framework in different studies on parental empowerment. The complex nature of empowerment has contributed to the adopted approach.

The nature of the phenomena under investigation urged the researcher to adopt different CMs. As the research went on, it became evident that the adopted CM had some limitations in dealing with aspects of the empowerment process in parents of children with ASD in Iran. In this case the adopted CMs need expansion each time to justify the findings. This expansion

should be done with the aid of other conceptual models that are consistent with each other, and could cover conceptual shortcomings. Therefore this chapter could be considered as an attempt to specify a model specific to ASD within a tradition that incorporates social ecology, family functioning and parent empowerment.

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Chapter 12

Evidence-Based Management and Intervention for Autism Spectrum Disorders

Karola Dillenburger

Additional information is available at the end of the chapter

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1. Introduction

Autism Spectrum Disorder (ASD) is diagnosed along a continuum of behavioural variants in social communication and repetitive behaviours [96]. Most individuals on the autism spectrum also experience differences in sensory perception. Some individuals on the spectrum are 'high-functioning' and able to cope in every day environments, while others are severely affected, non-verbal, and may have co-occurring diagnoses, such as intellectual disability, epilepsy, and/or obsessional, conduct, or mental health disorders. These individuals require substantial support, caring and careful management, and evidence-based, effective interventions.

ASD diagnosis can be detected from as early as 6-months to 1-year of age, although it is more common that children are aged 2-3 years before diagnosis is affirmed. Frequently, higher functioning individuals are not diagnosed until adolescence, or even adulthood. Present figures indicate that approximately 1:50 children are affected worldwide [97], with parent reported prevalence rates even higher in some countries, e.g., 1:38 (2. 6%) in South Korea (Kim, Leventhal, Koh et al., 2011) and 1:29 (3. 5%) in the UK, based on data of 11-year old children (n=13, 287) from the Millennium Cohort Study [19]. Similar prevalence rates have been found across racial, ethnic and socioeconomic groups; it seems that boys are affected more frequently than girls (estimated ration of 4:1), although this may be due to under diagnosis in girls.

2. Etiology

The exact etiology of ASD remains unknown even though genetic, immunological, neurological, neurotoxins, electromagnetic radiation, and allergenic causes have been investigated. Early theories of maternal unresponsiveness have been discredited as mentalistic and sexist,

while recent neurological studies have shown physical differences in early brain growth and functioning. Sibling and twin studies point to the possibility of genetic links. Ultimately, it is likely that ASD is caused by a combination of genetic and environmental risk factors [11]. In fact, it is to be expected that one day we will be able to differentiate symptomatology along the spectrum much more precisely and different 'causes' will be linked with different manifestations along the autism spectrum.

General Practitioners (GP) are the first port of call for most parents who are concerned about their children's behaviour. A referral is made to an assessment team, commonly lead by a pediatrician working in collaboration with a team of allied health professionals. A full diagnosisis based on behavioural observations and caregiver reports of their behavioural observations [19]. Although presently, there are no medical tests, ASD remains a medical diagnosis that requires a medical as well as educational response.

The Vice President for State Government Affairs of Autism Speaks, the world's largest autism charity, Professor Lorri [87] made this point clearly when arguing for health cover:

> Autism is diagnosed by a doctor, not a school principal. Treatment is prescribed by a doctor, not a teacher. Here are some things autism families deal with daily: swallowing aggression, teeth grinding, feces eating, depression, tantrum, drooling, elective mutism, food refusal, food theft, genital stimulation, hallucinations, hyperactive behaviour, hyperventilation, inappropriate vocalizations, insomnia, public disrobing, rectal digging, seizure behaviour, self-injurious behaviour, tongue protrusion and vomiting. Does anyone think these should be treated in our school classrooms? (p. 1)

Of course not everyone agrees. Proponents of the neurodiversity movement [48, 58, 66] argue that autism represents a neurological difference that should be celebrated rather than treated with interventions. [44] maintain that these arguments are valid with regards to rights, recognition and acceptance, however, they rightly argue that 'only a narrow conception of neurodiversity, referring exclusively to high-functioning autists, is reasonable' (p. 20).

3. Economic impact

For 'low-functioning' individuals with ASD, the lifetime cost to society is estimated to bein excess of £1. 4 million and these figures are similar internationally [7]. Of course, the cost for quality of life for the individual and their family is much higher. For example, 86% of parents of children with disabilities have to pay above average childcare costs and 72% of these families have given up work or reduced their working hours, because of childcare problems [9] and only about 15% of adults with ASD are in gainful employment [79]. The potential positive impact of effective interventions is enormous.

It is not surprising, therefore, that the intervention market is booming [17, 32]. As governmental investments into ASD services are increasing, fad treatments abound. In fact, the struggle for a slice of the market has been called the 'Autism Wars' [31]. Primary care, allied health, social

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care, and education professionals have a key role to play in protecting families and individuals affected by ASD from fads and ineffective, controversial, or even dangerous treatments that are peddled by self-proclaimed autism experts for commercial reasons [15].

4. Interventions

Given that there are no medical indicators for ASD, it is not surprising that currently there are no pharmacological treatments for the core symptoms of autism. There are, however, pharmacological treatments for some of the co-occurring symptoms, but due to lack of evidence of effectiveness and potentially serious side effects, the National Institute for Clinical Excellence [64] advises against the use of pharmacological interventions.

There are some commercially available intervention packages. However, commonly they are very expensive and make unsubstantiated claims and promises of recovery or 'cure' for autism. These claims are predatory on vulnerable parents, especially since there is generally very little evidence of effectiveness. The very few studies that exist for some of these commercial packages are usually not very rigorous and/or conducted by people who have a financial interest [38].

Some interventions have been developed and are frequently used or recommended by allied health professionals despite the fact that, after a thorough review of all available research evidence was carried out by the large team of multidisciplinary professionals for National Autism Centre [63], these interventions have been categorised as *unestablished*. For example, Sensory Integration Therapy is recommended widely by occupational therapists [9], yet there is evidence that it has very little or no effects and can even be counterproductive or detrimental [55]. Sensory Integration Therapy is classed as not recommended also by the Australian Department of Families, Housing, Community Services and Indigenous Affairs (FaHCSIA) [74].

Facilitated Communication is another *unestablished* treatment [63] that is still in use, despite the fact that it is highly controversial and has been exposed as being based on deception [57] and has the potential of causing harm [56].

Virtually all interventions that have been categorised as *established* are based on knowledge and applications of the scientific discipline of behaviour analysis [63, 89]. Even some of the most ardent doubters or opponents of applied behaviour analysis (ABA) have come to the realisation that behavioural interventions are the key to enhancing quality of life for individuals on the autism spectrum and their families across the lifespan [40, 41, 47, 60, 95].

It is important to know that the term 'behaviour' when used by behaviour analysts refers to anything we do and therefore includes feeling and thinking [16].

5. Evidence base

The evidence for ABA-based interventions spans all valid and recognised research methodologies, including Single-System Design (SSD), Randomised Controlled Trials (RCT), Meta-analysis and Sequential Meta-analysis, Systematic Reviews, Social Validity studies, Neuroscience studies, and Cost-benefit analysis.

Single System Designs (SSD) include reversal designs, multiple baseline designs (across behaviours, settings, or subjects), changing criterion designs, and alternating treatment designs [46]. In SSD studies internal validity is achieved by each participant serving as his/her own control, while external validity/generality is achieved through numerous replications of carefully described SSD methodologies.

Hundreds, if not thousands, of Single-System Design (SSD) studies have been published evidencing the effectiveness of ABA for individuals with autism [22]. While most of these studies are published in flagship journals, such as *Journal of Applied Behavior Analysis,* increasingly other mainstream journals publish SSD evidence for ABA-based interventions, for example, the *British Journal of Special Education* [15].

A good example of an SSD is Garcia-Albea, Reeve, Brothers, and Reeve (2014), who used a multiple-probe design across participants to teach 4 boys with autism to initiate and participate in social interactions without vocal prompts from adults. The procedure involved the use of a script and script-fading procedure. The boys quickly learned to talk independently about a whole range of relevant things in their environment without the help of adults. While this kind of research methodology lends itself particularly well to the action-based researcher/scientist-practitioner model inherent in ABA, it can be usefully employed in a range of different settings [49].

Randomised controlled trial (RCT), sometimes held up as the 'gold standard' for evidence of effectiveness of interventions, originated from medical research. RCTs were developed to compare outcomes for one group of people who receive a certain type of medication (treatment group), to that of another group of people who are not receiving the same medication, i. e., who may have received a placebo or 'treatment as usual' (control group). The basic assumption underpinning RCT is that, if both groups of people are well matched, any differences that are observed after the intervention are due to the intervention [37].

While RCTs may have their utility in relatively clear-cut medical research, there are many problems when they are used in social care or educational research, not least the ethical dimension of withholding a potentially beneficial treatment from the control group. Of course, there are safeguards, such as cross-over designs or the Hippocratic Oath to 'do no harm' [90].

However, some of the main drawbacks in autism research are that, for RCT results to be valid, all members of the 'treatment group' have to receive the exact same treatment and this has to be held stable for the agreed duration of the intervention. Of course, when interventions are based on a functional analysis of behaviour, as is the case in ABA, they are tailored to the needs of the individual, i. e., they are person/child-centered. Data-based decisions are made with

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regards to intervention adjustments, that are implemented immediately, for ethical reasons, in order to avoid harm and enhance treatment effects [14]. These kinds of progressive, systematic, individualized, data-based intervention revisions and adjustments would invalidate RCT data (see Single-System Designs).

Of course ABA (i. e., the application of the scientific discipline of behaviour analysis) itself cannot be assessed via RCTs, yet some specific intervention packages, such as Early Intensive Behaviour Interventions (EIBI) or the Early Start Denver Model, have been assessed in RCTs. A good example is Howard, Sparkman, Cohen, Green, and Stanislaw [39], who evaluated 29 pre-school children who received intensive behaviour analytic intervention (treatment group) and two matched control groups of 16 children each, receiving either intensive or non-intensive ''eclectic'' interventions. While the scores for cognitive, language, and adaptive skills were similar at intake, at follow-up the treatment group had statistically significant higher mean standard scores in all areas. These data were confirmed at the 2 year follow-up [40].

Other RCTs or quasi-experimental control studies have compared Treatment as Usual with ABA-based interventions, such as specific commercially available intervention packages [34), high vs low intensity ABA-based interventions [30, 59], or waitlist controls [67].

Meta-analysis and *sequential meta-analysis* are increasingly used to give a summary of multiple small n studies that provide individual participant data, with the expectation that combining these data (commonly calculated in effect sizes) will allow for the identification of patterns and thus increase statistical powerto show that treatment effects are not due to measurement error, variation in sample, etc. *Sequential meta-analyses* are conducted where enough cumulative knowledge is available through meta-analysis to draw convincing statistical conclusions about effect size. Of course as in all research, there are a number of issues related to researcher bias and declaration of interest, however, over recent years meta-analyses have become a welcomed addition to the evidence-based practice literature.

With regards to autism interventions, a recent overview of meta-analyses [77] found that early intensive ABA-based treatment was significantly related to enhanced outcomes (effect sizes 0. 30 to > 1). Further meta analyses [22, 23, 24, 72] and a recent sequential meta-analysis [54] have confirmed these findings [1].

Systematic reviews are based on detailed searches of data banks with clearly defined inclusion/exclusion criteria. Usually teams of multidisciplinary experts summarise selected studies, such as RCTs, single-system research design studies, and meta-analyses. Given the wide reach of evidence covered in systematic reviews, they have gained a strong place in evidence-based practice in ASD.

The number of systematic reviews of ASD interventions has risen recently [77]. By-and-large ABA-based interventions, in particular Early Intensive Behavioural Interventions (EIBI), are endorsed by systematic reviews. A good example of a comprehensive systematic review was carried out by the large scale multidisciplinary team of the National Autism Center [63] ; 11 interventions were designated as established, of these all but one are explicitly based on ABA; 22 intervetions were categorised as emerging, most of these were also based on ABA. All other systematic reviews came to similar conclusions [6, 36, 70, 75, 91].

The review by [43] is the notable exception, in that it does not fully concur with these conclusions. Howlin et al. concluded that 'this review provides evidence for the effectiveness of EIBI for some, but not all, preschool children with autism' (p. 20). Given that this review is frequently cited in the UK as a basis against the roll-out of EIBI for all children with ASD who need it [42], it is important to note here that Howlin et al. misinterpret a number of important points. First, it is in the mathematical nature of all group average data (such as those calculated for RCTs) that some individual data are above while others are below the average; such is the nature of group averages (see also [77]; second, Howlin et al. 'cherry pick' results by ignoring the fact that obviously some children must do extremely well, otherwise the group average would not be what it is. Thus, Howlin et al. contradict themselves in their conclusions. First they call for large sample comparisons and group averages (i. e., RCTs) and then they do not accurately interpret group data.

In a subsequent paper, Howlin and colleagues [99] report extremely poor long-term outcomes in a 40-year follow-up study of children diagnosed with autism at the Institute of Psychiatry/ Maudsley Hospital, London between 1950 and 1979. Intriguingly, they explicitly link these findings to the fact that none of these children had received early intensive behavioural interventions and claim that EIBI is available now. Praising the potential positive effects of EIBI stands in contrast to their earlier conclusions [42, 43]. It will be interesting to see how this new evidence will translate into advice given to government bodies.

Given that group average scores are neither sensitive to individual differences nor offer sufficient generality, most behaviour analytic researchers prefer to rely on replicated single-system designs (SSD) instead of group averages [14, 18, 29]. Clearly, SSD research data cannot be ignored and should find their rightful place in future reviews of autism intervention guidelines, such as NICE Guideline 170 [64].

Social Validity studies assess the social significance, appropriateness, and importance of treatment goals, procedures, and intervention effects [93]. Social validity measures are increasingly becoming integral part of research into interventions in ASD [27, 53].

A number of studies have shown clear evidence of high social validity of ABA-based interventions, especially those that include parent participation and training [18, 92]. Interestingly, while there is evidence of increased parental stress in families affected by ASD [10, 17], there is evidence of parental stress reduction when effective interventions for children are in place [17]. This is also true for education staff [26].

Neuroscience studies, including MRI scans are useful tools to bolster evidence-based practice in particular in the area of ASD, where the plasticity of the brain during early childhood constitutes an important focus of intervention [11]. There is evidence of differences in brain activity between individuals diagnosed with ASD and those who do not have an ASD designation [13, 35].

There is further evidence that early behaviour analytic intervention can lead to measurable change in brain activity [12]. For example, [28] found that ABA-based interventions not only lead to behavioural improvements, with some optimal outcome individuals becoming

'indistinguishable' from neuro-typical peers, but that they also lead to improved neurological development, i. e., neurological plasticity allowing for compensatory development.

Cost-benefit analyses are an important way to substantiate evidence of effective interventions. A recent study estimated the annual 'cost of autism' between £0. 8-1. 4+ million per lifetime depending on the level of functioning; these costs were similar in UK and USA [7] and in other parts of the world [61, 71].

There is evidence that effective ABA-based interventions can reduce this cost substantially in the long-term, i. e., $1+million per year [45]. However, due to the fact that intensive interventions generally are rather costly in the short-term, there has been resistance to their implementation. The key question is how effective high-quality programs can be delivered in a more cost-effective sustainable model, without losing out on effectiveness [1].

All of these studies supply ample evidence of the effectiveness and efficacy of ABA-based interventions, in achieving individual potential in a full range of areas, including intellectual, social, and verbal, functioning, ASD symptomatology, and challenging behaviour.

On the basis of this evidence, ABA-based interventions are now widely endorsed in the USA, Canada, Australia, and some European countries. On a federal level in the USA, for example, Medicaid now covers ABA-based interventions and the Affordable Care Act covers behavioural health treatments [83], which include ABA-based interventions generally, and is not restricted to ASD diagnosis.

6. Endorsement

In the USA, interventions for individuals with ASD that are based on ABA are endorsed as medically, as well as educationally, necessary and covered by health insurance in the vast majority of States [2]. In fact, they are now considered 'treatment as usual' [28]. As early as 1999 the [84] endorsed ABA-based interventions:

Thirty *[now 45]* years of research demonstrated the efficacy of applied behavioural methods in reducing inappropriate behaviour and in increasing communication, learning, and appropriate social behaviour. (p. 164)

More recently, [94] recommended

> that principles of applied behaviour analysis (ABA) and behaviour intervention strategies be included as important elements in any intervention program for young children with autism. (p. 33)

[8] recognized that:

> in areas such as social engagement, language, coping, and reduction of difficult behaviours… Applied behavioural analysis is usually needed to assist a child to gain skills and reduce negative or undesirable behaviours. (p. 10)

The Federal U. S. Office of Personnel Management responsible for all federal government employees concluded that ABA-based interventions should be covered not only for educational but also for medical reasons:

> based on ample scientific and empirical evidence, ABA therapy qualifies as a medical treatment, rather than purely educational. [5], p. 1)

In Canada, ABA-based interventions are supported, for example by the Ontario Department of Education Policy/Program Memorandum [73] that support[s] incorporation of ABA methods into school boards' practices. . . The use of ABA instructional approaches may also be effective for students with other special education needs. (p. 1)

The Maine Administrators of Services for Children with Disabilities confirmed their support in the Report of the Autism Task Force [6]

> It is important to note that ABA is frequently perceived to be synonymous with discrete trial teaching. However, ABA is comprised of a broad scope of empirically derived behavioural principles used in interventions. (p. 25)

Despite this general endorsement of evidence-based behaviour analytic interventions across most of the English speaking world, the highly controversial approach taken by governments across the UK and Ireland is to support an 'eclectic' approach. There are no clear guidelines as to what an 'eclectic' approach entails and not a single study is published anywhere to show the effectiveness of an eclectic approach being equal or superior to ABA-based interventions [14]. In fact, [21] and [39] findings show clearly that ABA-based interventions are superior to an eclectic approach. Individually tailoring behavioural interventions to match child characteristics is key to effectiveness [82].

Yet in the UK, the National Institute for Clinical Excellence's [64] response to stakeholders, who asked for ABA-based interventions to be included in the NICE guidelines for the management of children with ASD, was the following:

In the review of evidence, the Guideline Development Group found no evidence to support ABA, and therefore could not make a recommendation about ABA. (pp. 5& 8)

They also asserted that:

> NICE clinical guidelines are based on the best quality evidence and are developed according to rigorous and robust methodologies. The developers were unable to identify high quality evidence of effectiveness of the ABA approach in managing children and young people with autism. (pp. 5 & 8)

This view is informed mainly by relatively few, but well rehearsed anti-ABA arguments that continue to circulate misinformation and misleading anti-ABA propaganda. As [33] points out:

> The most concerning issue affecting the quality of practices and policies in the helping professions is the play of propaganda, which misleads us regarding what is a problem, how (or if) it can be detected, its causes, and how (or if) it can be remedied. Propaganda is defined as encouraging beliefs and actions with the least

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> thought possible. Censorship is integral to propaganda including hiding well-argued alternatives and lack of evidence for claims. Evidence-based practice was developed in part because of misleading claims in the professional literature. If propaganda is an integral part of our society, we cannot escape its influence. But we can become aware of it, encouraged by ethical obligations to avoid harming in the name of helping. (p. 302)

7. A 'new idea'

Anti-ABA propaganda generally comes from people not trained in the science (e.g., [41, 47]. Censorship comes in the form of excluding behaviour analysts from review bodies [14] or ignoring data presented to review panels [68]. As a consequence of this exclusion, ABA remains a 'new idea' in the UK, despite its extensively documented history and evidence base accessible in the English language.

The German philosopher Alfred Schoppenhauer (1788-1860) recognised that:

> All new ideas pass through three stages. First, they are ridiculed. Second, they are violently opposed. Third, they are accepted as being self-evident.

This is true for the evolution of the arguments by ABA opponents [15]. First, they ridicule ABA as' one approach for autism', while promoting the rather ill-defined eclectic approach. Of course, one could argue that the eclectic approach is one approach as it precludes any other approach, such as the dual approach taken in Germany, where psychotherapists are trained in either behaviour therapy and psychotherapy, and the service user has the choice which service they prefer to use [17]. In reality then, eclecticism is 'one approach' to autism intervention. When opponents of ABA state that they do not want one approach for all, they cannot at the same time say that they promote the one approach called 'the eclectic approach'.

There are of course further problems with eclecticism.

- Staff training in all possible autism treatments is impossible. Training and skills of eclectic practitioners necessarily remain limited to a certain number of preferred interventions. The decision about what to include/exclude in an eclectic treatment package therefore is not based on the child's needs but on the practitioner skills.
- There is no coherent theoretical knowledge base and the potential for conflicting interventions means that synergy effects cannot be controlled.
- There is no evidence of effectiveness.

On the other hand as mentioned earlier, ABA is not 'one approach to autism' [16], it is the application of the scientific discipline of behaviour analysis.

> ABA aims to discover and understand the underlying principles of behaviour with the function of a particular behaviour considered in the design of behaviour change interventions. Interventions are designed for the individual, recognizing that the function of behaviour varies based on complex combinations of variables. [6], p. 25)

There is nothing wrong with using one approach, if this 'one approach' is science [15]. Countless procedures have been developed from the science of behaviour analysis, many specifically for ASD, e.g., Discrete Trail Teaching (DTT); Pivotal Response Training (PRT); Natural Environment Training (NET); Verbal Behaviour Approach (VB); while other procedures have been developed for more general applications, e.g., Functional Analysis and Functional Assessment; Preference Assessments; shaping, forward chaining, backward chaining; differential reinforcement of low or zero rate and/or incompatible or alternative behaviours; Time-out from Positive Reinforcement (TOR); etc. . Some of these procedures have been combined into comprehensive packages for autism, such as Early Intensive Behavioural Interventions (EIBI) or Early Start Denver Model (ESDM), while others are used more generally, e.g., Programmed Instruction, Generative Instruction; Peer Tutoring; Habit Reversal Training; etc. Given that the science of behaviour analysis underpins all of these programmes/procedures and continuous data-based decision making is part and parcel of ABA, new procedures and progammes are developed continuously to meet the individual or group needs of service users.

ABA has been further ridiculed and accused of intending to change the person, while others pride themselves for accepting the person for who they are [69, 80]. In fact, the targets of ABA-based interventions are socially relevant behaviours, linked to cultural and personal norms and preferences [4]. The curricula are agreed with individuals with ASD and/or their caregivers. They are generally based on wide-ranging target behaviours, including life skills, such as dressing, toileting, attending; social skills, such as playing or imitation; academic skills, including attending, reading, drawing, writing, and maths, and work/employment based skills, including interviewing or team work.

Basically, the aim of ABA is to enhance all skills necessary to lead a fulfilled life for individuals who would otherwise be limited in the quality of life they experience. These are the same aims that most parents have for all of their children, irrespective of a diagnosis. As such, ABA does not intend to 'change the person', but to enhance skills and help individuals to break down barriers to learning and achieve their full potential. After all, enhancing skills development increases choice.

Once a new idea can no longer be ridiculed, the second point Schoppenhauer made comes to play: the new idea is opposed. In the case of ABA, this refers to statements such as there is no evidence to support ABA and therefore no recommendation can be made [64]. We have outlined the wealth of evidence in favour of ABA-based interventions earlier in this chapter. Given that behaviour analysts commonly are not included in review bodies, at least in Europe, this mountain of evidence generally is excluded from reviews [68].

When the evidence can no longer be denied, the opposition turns to the behaviour analytic scientists themselves, stating that research conducted by behaviour analysts is biased and therefore not to be taken seriously. The idea, that it is objectionable that scientist conduct scientific research in their own subject area is rather intriguing. Given that it is against ethical guidelines of all social and health care as well as education professionals to work outside their own area of expertise [90], clearly, multidisciplinary practice and interdisciplinary research teams in ASD, should routinely include behaviour analysts, not least because others are not qualified to make authoritative statements about behaviour analysis [16].

Once ridicule and opposition are not longer tenable, the third point of Schoppenhauer's concept of the evolution of a new idea comes to play, when finally, new ideas are considered self-evident. Intriguingly, this is now starting to happen with regards to ABA. There is evidence of a claim that all teachers and psychologists use ABA techniques. However, being able to conduct one or two behavioural techniques [16] clearly does not equate to training in applied behaviour analysis to international standards [3]. For example, clinical psychology training typically includes (under Psychological Therapies) 'competency in two evidence-based therapeutic approaches including CBT and one other (e.g. psychodynamic, systemic, social constructionist)' [76]. Other professionals commonly receive no training in behaviour analysis and either none or very little training in ASD [19].

8. Staff training

A Board Certified Behaviour Analyst (BCBA®) has received fully approved training in the science of behaviour analysis either at Masters or doctoral level, including at least 270 hours of course work and 1500 hours of supervised practice in ABA [3].

While NICE [64] did not make any recommendations regarding ABA or staff qualifications, they recommend a 'social-communication intervention' that includes play-based strategies with parents, carers and teachers to increase joint attention, engagement and reciprocal communication in the child or young person.

Table 1 offers a direct comparison of the basics of ABA-based interventions that were stipulated by the [8] and the NICE [64] recommendations.

	Basics of ABA-based interventions	**A Psychosocial intervention (NICE, 2013)**
Curriculum decision	The curriculum is organized around typical developmental expectations; Individualized approach is used to determine developmental level of programme; Functional analysis identifies the communicative role of behavior; Language- and communication-intensive; Socialization and play are actively stimulated;	A specific social-communication intervention for the core features of autism in children and young people; Be adjusted to the child or young person's developmental level; To increase joint attention, engagement and reciprocal communication;
Methods	An individualized approach is used to select or develop developmentally appropriate methods; Procedures are based on applied behaviour analysis; Includes structured as well as natural environment training.	Includes play-based strategies; Include techniques of therapist modelling and video-interaction feedback; Include techniques to expand the child or young person's communication, interactive play and social routines;

	Basics of ABA-based interventions	**A Psychosocial intervention (NICE, 2013)**
Monitoring	A formalized assessment of skills (cognitive, language, socialization, adaptive behavior, fine and gross motor, and play) is conducted at regular intervals; Data are recorded to monitor progress and to troubleshoot; Assessment results are used as a guide for planning what skills to teach next; Integration of research and practice is used;	
Generalisation & Maintenance	Generalization and maintenance of skills are built into the program;	
Outcome targets	Mainstreaming opportunities with typically developing peers are built into the program; Transitional support is provided when the child leaves one program and moves to the next. The skills needed in the next situation are taught and support needed is considered;	Aim to increase the parents', carers', teachers' or peers' understanding of, and sensitivity and responsiveness to, the child or young person's patterns of communication and interaction;
Parent involvement	Parent training and family support are used; Education about options for intervention is provided; Training is culturally acceptable to individual families;	With parents, carers and teachers;
Staffing	Collaboration of all team members is used; Related services are included (i.e., speech, occupational therapy, adapted physical therapy, and/or augmentative communication); Ongoing teacher/therapist training is included to consider what new and experienced personnel need to know.	The intervention should be delivered by a trained professional. For pre-school children consider parent, carer or teacher mediation. For school-aged children consider peer mediation.

Table 1. Comparision of ABA-based interventions and NICE [64] recommendation

9. Conclusion

In a recent review for the Canadian Medical Journal, [1] summed up the evidence for ABA-based intervention in ASD when they stated:

> Current best practices for preschool-aged children with ASD include a focus on improving language, cognitive and adaptive skills using applied behaviour analysis (ABA) techniques. Applied behaviour analysis refers to the application of empiri-

> cally derived learning principles (i. e., the antecedent–behaviour–consequence contingency) to produce meaningful changes in behaviour. Such strategies are carefully engineered and implemented through a variety of approaches (e.g., discrete trial teaching to more naturalistic learning contexts) to teach skills and reduce problem behaviour. Applied behaviour analysis interventions can be provided in a variety of settings (e.g., home, specialized treatment centres, specialized or public schools) by a range of front-line therapists, ideally supervised by a psychologist or board-certified behaviour analyst who specializes in ASD. (p. 515)

It is, therefore, not surprising that increasingly reports link ABA-based intervention with optimal outcomes. Individuals previously diagnosed with ASD are now living independent productive happy lives or no longer meeting diagnostic criteria. Mukaddes, Tutkunkardas, Sari, Aydin, and Kozanoglu (2014) suggested that '[i]t could be concluded that a group of children with an autism diagnosis could lose the diagnosis of autism upon early intervention' (p. 1). [65] for example, report a strong statistical significance of early intensive behaviour analytic interventions for children previously reported to have optimal outcomes [28], while [85] report on reductions of restricted and repetitive behaviours and [85] focus on improvements in academic skills following early intensive behavioural interventions.

Evidently, ABA translates into evidence-based interventions that allow individuals with ASD to overcome barriers by ensuring choice, human rights, equality and true active participation. ABA helps achieve potential by cherishing the person for who they really are and, by accepting difference, it values the difference we can make in people's lives.

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Chapter 13

Understanding the Importance of the Evaluation and Treatment of Elevated Androgens in Autism Spectrum Disorder

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Additional information is available at the end of the chapter

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1. Introduction

Autism spectrum disorder (ASD) is a prevalent, life-long, neurodevelopmental disorder diagnosed in more than 1% of children in the United States (the most recent estimate exceeds one in 68 children) with strong gender basis towards males (one in 42 boys) relative to females (one in 189 girls) [1]. In addition to the diagnostic impairments specified in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria for ASD in socialization, restricted, repetitive patterns of behavior, interests, or activities, and communication, which must be present in the early developmental period, many individuals diagnosed with an ASD frequently have co-morbid aggression and severe irritability, hyperactivity, and repetitive behaviors, which can become a major source of additional distress and can interfere with functioning [2]. Similarly, others have observed the occurrence of co-morbid conditions among individuals diagnosed with an ASD as follows: hyperactivity (67%), sensory processing problems (85%), anxiety/fear (74%), behavioral problems (89%), and obsessive-compulsive behaviors (92%) [3]. These investigators described that behavioral problems and obsessive-compulsive behaviors were reported to be the most serious and problematic. In addition, investigators described that some individuals diagnosed with an ASD show significant deterioration in symptoms about the time of puberty [4]. Among the symptoms that worsened according to these investigators were disruptive behavior, destructiveness, restlessness, and partial loss of acquired social and academic skills.

In considering the aforementioned facts, it was previously hypothesized that male hormones (androgens) may play a critically important role in the clinical presentation of individuals diagnosed with an ASD and that reduction of androgens in individuals diagnosed with an

ASD would result in a significant amelioration of their clinical symptoms [5]. The purpose of this critical review is to examine evidence supporting the role of androgens in mediating ASD traits/symptoms, elevated androgens among individuals diagnosed with an ASD, and the observed important role for anti-androgen medications in treatment of ASD traits/symptoms.

2. Evidence for a correlation between elevated androgens and ASD traits/symptoms

Investigators have systematically evaluated measurements of androgens and their relationship with the clinical symptoms or traits defining or observed in individuals diagnosed with an ASD [6, 7]. Fetal testosterone levels were observed to be significantly inversely related to eye contact, quality of social relationships, vocabulary size, and empathy among typically developing children. By contrast, fetal testosterone levels were observed to significantly positively correlate with autistic traits, restricted interests, and systemizing behaviors.

It was also determined on a psychological testing basis that were significant differences among individuals diagnosed with an ASD in comparison to neurotypical males and females [6, 7]. The tests revealed that autism quotient (AQ), systemizing quotient (SQ), child autism spectrum test (CAST), embedded figures test, intuitive physics test, social responsiveness scale, quantitative checklist for autism in toddlers (Q-CHAT) scores revealed a pattern of ASDs > males > females. By contrast, empathy quotient (EQ), faux pas test, friendship and relationship questionnaire (FQ), reading the mind in the eyes, and social stories questionnaire (SSQ) scores revealed a pattern of females > males > ASDs.

Other investigators examined brain structure for evidence of an extreme male brain among individuals diagnosed with an ASD in comparison to neurotypical males and females [6, 7]. A pattern of extreme male brain structure with ASD > males > females for total brain volume and amgydala size was observed. By contrast, it was observed that the brain size was females > males > ASD for the perisylvian language areas, left > right asymmetry in planum temporale, and lateral fronto-parietal cortex. Furthermore, brain function patterns revealed females > males > ASD for default mode network connectivity, embedded figures functional magnetic resonance imaging (fMRI), and reading the mind in the eyes task fMRI.

Still other investigators examined the relationship between various diseases known to be associated with elevated androgen levels and ASD traits and symptoms [6, 7]. For example, individuals diagnosed with congenital adrenal hyperplasia (CAH) were found to have increased problem behaviors and increases in AQ scores relative to unaffected controls. It was even observed that some individuals diagnosed with DNA-confirmed CAH mutations and associated clinical and laboratory findings had a concurrent diagnosis of an ASD. As another example, individuals diagnosed with polycystic ovarian syndrome (PCOS) were observed to have significantly increased AQ scores, significantly impaired communication, socialization, and attention relative to unaffected controls. Finally, investigators examined bio-physiological and cognitive differences in children diagnosed with premature adrenarche (with elevated blood androgen levels) in comparison to on-time adrenarche [8]. Children diagnosed with

premature adrenarche in comparison to on-time adrenarche had significantly increased problem behaviors and attention problems, as well as significantly decreased skills in socialization, information processing, language/communication.

Other investigators have more specifically examined the direct relationship between hormonal treatment status and ASD traits/symptoms by examining various groups of transsexual individuals [9] and among individuals injected with testosterone in a double-blind study [10]. It was observed among various groups of transsexual individuals that compared ASD traits/symptoms using AQ scores derived from five groups: (1) n = 61 transmen (female-to-male transsexual individuals); (2) n = 198 transwomen (male-to-female transsexual individuals); (3) n = 76 typical males; (4) n = 98 typical females; and (5) n = 125 individuals diagnosed with an ASD [9]. Higher AQ scores were seen in transmen than in typical females, typical males, or trans women, but transmen had lower SQ scores than those individuals diagnosed with an ASD. Transmen displayed ASD-like symptoms/traits and were more comfortable socializing with male peers than female peers. Thus androgen treatment in transmen correlated directly with development of ASD symptoms/traits. Transmen had a higher mean AQ than typical females, typical males and transwomen, but lower than individuals diagnosed with an ASD. Transmen have more ASD traits/symptoms and may have had difficulty socializing with female peers and thus found it easier to identify with male peer groups. The importance of these findings being that direct hormonal treatment with androgen therapy in transmen directly correlated with their development of ASD traits/symptoms. It was also observed, among individuals injected with testosterone in a double-blind study, that these individuals manifested a significant increase in ASD traits/symptoms with impairment in their cognitive ability to infer emotions, intentions, feelings, and other mental states from observing the eye region of another's face [10].

3. Evidence for the effect of elevated androgens in ASD

Investigators have undertaken extensive evaluation of various measurements of elevated androgens in individuals diagnosed with an ASD. They described, among individuals diagnosed with an ASD, significantly increased frequency of genetic changes in multiple genes involved in sex steroid synthesis, transport, and/or metabolism, testosterone-related medical conditions (e.g., polycystic ovarian syndrome, breast and ovarian cancers, acne, etc.), and testosterone-related characteristics (e.g., tomboyism, etc.)[6, 7]. It was also reported that individuals diagnosed with an ASD had significant alterations in the timing of puberty (boys diagnosed with an ASD were observed to enter "male" puberty earlier, while girls diagnosed with an ASD were observed to enter "female" puberty later). Elevated androgen levels and significantly lower second to fourth digit ratios in comparison to neurotypical controls (a known marker of elevated fetal testosterone) [6, 7].

Investigators recently measured fetal steroidogenic activity in amniotic fluid samples for individuals diagnosed with an ASD in comparison to neuroptypical controls. Amniotic fluid samples taken from individuals subsequently diagnosed with an ASD in comparison to neurotypical controls revealed significant elevations in androgen levels [11].

Investigators previously described evaluating blood androgen levels among a large cohort of individuals diagnosed with an ASD using routine laboratory testing from the Laboratory Corporation of American (LabCorp) [12]. It was observed that individuals diagnosed with an ASD were observed to have significant increases in their blood levels of testosterone, free testosterone, dehydroepiandrosterone (DHEA), and androsternedione relative to laboratory provided reference ranges. Overall, it was observed among the various blood androgen attributes examined, that over 80% of the individuals diagnosed with an ASD examined were found to have at least one of the blood androgen attributes examined that exceeded the age- and sex-specific reference ranges provided by the laboratory.

Subsequently, other investigators evaluated the potential role of androgens among individuals diagnosed with an ASD in comparison to neurotypical controls by examining salivary levels of hormones among children from 3-4 years-old and 7-9 years-old [13]. These investigators observed significantly higher salivary concentrations of androgens among individuals diagnosed with an ASD relative to controls, and the anomalies were prominent in older male children diagnosed with an ASD. Among the specific types of androgens observed to be increased among individuals diagnosed with an ASD in comparison to neurotypical controls were androstenediol, DHEA, and androsterone, which, the investigators concluded were indicative of precocious andrenarche and predictive of early puberty. These investigators also commented that some of the androgens observed were significantly increased among the individuals diagnosed with an ASD relative to the neurotypical controls are known to neuroactive and modulate GABA, glutamate, and opioid neurotransmission with the potential consequence of affecting brain development and function. They may also contribute to ASD-associated pathobiology and symptoms such as elevated anxiety, sleep disturbances, sensory deficit, and stereotypic behaviors.

Similarly, other investigators examined hyperandrogenemia in male children and adolescents diagnosed with an ASD in comparison to neuroptyical controls and in relation to ASD severity by assessing serum androgen levels [14]. These investigators observed that androgen levels were significantly higher among individuals diagnosed with an ASD in comparison to neurotypical controls, and the elevations were observed to significantly correlate with ASD severity. Overall, it was observed among individuals diagnosed with an ASD that 36.66% had high serum free testosterone, 30% had high DHEA, 40% had high androstenedione, and 26.66% showed elevation of all androgen levels in comparison to neurotypical controls. These investigators concluded that hyperandrogenemia is prevalent among individuals diagnosed with an ASD, correlate with ASD severity, and studies should explore the use of anti-androgen therapy to treat such patients.

4. Treatment with anti-androgen medications in ASD

It was original hypothesized that given the significant correlation between androgen levels and ASD symptoms/traits that administration of anti-androgen medications to individuals diagnosed with an ASD would result in significant clinical improvements [5]. More recently

other investigators extended this previous hypothesis by suggesting that circulating hormone levels and the administration of testosterone and other hormones were found to predict behavior in individuals, but the effect was suggested to be one of "activation" or "fine-tuning" earlier organization of the brain [15].

Among the most-well studied anti-androgen medications are gonadotropin-releasing hormone (GnRH) analogues. GnRH analogues are synthetic peptide drugs modeled after human hypothalamic GnRH, and are designed to interact with the GnRH receptor and modify the release of pituitary gonadotropins follicle stimulating hormone (FSH) and luteinizing hormone (LH) for therapeutic purposes, and over a period of time will lower the release of FSH and LH from the pituitary leading to reversible suppression of androgen release [16].

The use of GnRH analogues in various animal model systems has been observed to significantly improve many ASD symptoms/traits, and the improvements observed were comparable to those for commonly used psychiatric medications for these conditions [7]. For example, investigators studied the effects of GnRH agonists and antagonists on anxiety and social behaviors in rats [17]. These investigators observed GnRH agonists significantly reduced anxiety and increased social behaviors in the rats, and the overall effects were comparable to those observed with diazepam. Other investigators examined the effects of GnRH agonists on obsessive compulsive behaviors in mice. In one study it was observed that a GnRH agonist was able to significantly reduce marble-burying behaviors, a model system for obsessive-compulsive behaviors, comparable to that observed with fluoxeteine administration [18], and in another it was observed that a GnRH agonist was able to significantly reduce marble-burying behaviors comparable to that observed with ritanserin administration [19]. Finally, investigators observed that GnRH agonist therapy significantly improved hyperactivity behaviors in mice [20].

In addition to studies of animal model systems demonstrating the improvement of ASD symptoms/traits by GnRH analogues, a number of investigators have observed similar phenomena in human populations. For example, investigators examined the acute gonadal suppression effects of GnRH antagonists on sexual and behaviors in a case-series of men [21]. It was observed the treatment resulted in significant reduction in outward-direct aggression in all of the treated men with some also experiencing reductions in anxiety and sexual desire. Other investigators reported on the use of a GnRH analogue to treat obsessive-compulsive disorder in a clinical trial [22]. During the course of the 48 week clinical trial, it was observed that GnRH analogue therapy was effective in significantly reducing the severity of the symptoms of obsessive-compulsive disorder. Another investigator described the use of a GnRH analgoue as a means to treat problems behaviors in men suffering from dementia [23]. It was observed that within 4 weeks of the start of therapy, verbal and physical aggression had decreased; activity disturbances such as agitation, pacing, and restlessness were markedly reduced; and a significant reduction in disruptive sexual behaviors was observed.

Investigators have reported on the successful use of GnRH analogues in the treatment of sexual problem behaviors/symptoms in individuals diagnosed with an ASD over several decades. For example, investigators described that administration of an GnRH analogue to an individual diagnosed with an ASD and sexual behavior resulted in significant suppression of the

patient's sexual behaviors [24]. Similarly, other investigators described the use of GnRH analogues in the treatment of individuals diagnosed with an ASD and central precocious puberty [25]. These investigators described that many individuals diagnosed with an ASD tend to have early sexual maturation, and they described a case-series of patients with precocious puberty ranging from 6 years and 9 months-old to 9 years and 6 months-old. Treatment with a GnRH analogue to help alleviate their symptoms of precocious puberty, especially given that these symptoms were not well-tolerated in the context of the individual's ASD diagnoses. These investigators concluded that treatment of sexual precocity should be considered among individuals diagnosed with an ASD not only based upon their bone age maturation and growth, but also their mental maturation.

Finally, investigators described the successful use of the GnRH analogue, leuprolide acetate, in the treatment of ASD traits/symptoms in a clinical trial of consecutive individuals diagnosed with an ASD with laboratory findings showing elevated androgen levels [26]. Each patient was clinically studied at base line and at the end of the study, to evaluate hyperandrogenemia behavior/symptoms including secondary sexual changes, facial and body hair, early growth spurt and aggressive behaviors. A clinical examination was undertaken for each individual to evaluate clinical symptoms/behaviors of hyperandrogenemia such as early growth spurt, early secondary sexual changes, body and facial hair, and aggressive behaviors at baseline and at the end of the study period for each child. Autism Treatment Evaluation Checklist (ATEC) evaluations were completed by the child's parents prior to beginning the protocol and at the end of the study period for each child. The children received 15 mg of leuprolide acetate depot by intramuscular injection every 28 days. This dose was supplemented with a daily subcutaneous injection of leuprolide acetate so that each child received a total initial starting doses of 50 ug of leuprolide acetate/kilogram of body weight-daily. The children were monitored, and increased subcutaneous doses of leuprolide acetate or oral anti-androgen medication were administered to those children who exhibited persistent laboratory/clinical signs of elevated androgen as clinically indicated. The participants were enrolled in the study for a minimum of 2 months and a maximum of 7 months. Each child underwent laboratory testing at baseline and again after approximately 3 of treatment. Treated children were observed to significantly improve from a median baseline score of 87 (70th percentile of autism severity) to a median score of 63 (40-49th percentile of autism severity) by the completion of the study. Significant improvements among treated children when evaluating baseline measurements in comparison to those obtained at the end of the study period, were observed in the specific areas of sociability, cognitive awareness, and behavior. Additionally, trial participants having independent assessments by school evaluators showed significant improvements in general school skills mastered and significant improvements in the frequency and severity of disruptive/oppositional behavior at the end of the treatment period relative to baseline, despite the fact that the evaluators were unaware of the child's participation in the trial.

Comparison of clinical evaluation at baseline with evaluation at the trials conclusion showed significant reductions in hyperandrogenemia evidenced in clinical symptoms and the associated behaviors (early secondary sexual changes, early growth spurt, body and facial hair, and aggressive behaviors). A significant decrease in serum testosterone levels was demonstrated

by laboratory testing, and the treatment protocol did not significant adversely affect kidney, thyroid or liver function tests.

Since their study employed therapeutic agents designed to lower androgen levels, and significant decreases in androgen levels were observed, the researchers concluded the treatment protocol studied presented a novel method to significantly reduce autistic-like behaviors. Further, the study reported that significant autistic behavior improvements (i.e., improvements in hyperactivity and attention, better sleep patterns, and increased socialization) occurred within days of the treatment with leuprolide acetate. Finally, the study concluded that leuprolide acetate significantly ameliorated clinical behaviors/systems of hyperandrogenemia including aggressive behaviors,, early secondary sexual changes,, body and facial hair, and early growth spurt among children diagnosed with an ASD.

Other investigators reported that the administration of leuprolide acetate therapy to nearly 200 individuals diagnosed with an ASD [12] resulted in significantly lowered androgen levels very significant overall clinical improvements in sensory/cognitive awareness, socialization, and health/physical/behavior skills. Leuprolide acetate treatment resulted in significant clinical ameliorations in aggression, self injury, abnormal sexual behaviors, hyperactivity/impulsivity, stereotypy, and/or irritability behaviors in many individuals diagnosed with an ASD. Minimal adverse clinical effects to the therapy were seen, and there were with few non-responders.

Children were administered an intramuscular injection of 15 mg leuprolide acetate depot every 28 days and supplemented with daily, subcutaneously injected leuprolide acetate, so that children were started on a dose of 50 μg of leuprolide acetate/kilogram bodyweight/day. Children were monitored as successive doses of leuprolide acetate were administered for persistent clinical/laboratory signs of increased androgens, and subjects were treated with additional subcutaneous injections of leuprolide acetate dosing and/or an oral anti-androgen medicine as clinically necessary.

Children examined in the study were on the therapy for a minimum of 2 months and a maximum of 7 months. Laboratory testing was conducted on each child at baseline and at approximately 3 months of treatment. Among the children treated in the clinical trial, there was a significant overall improvement from the 70th percentile of severity (median baseline score = 87) at baseline to the 40-49th percentile of severity (median end of study period score = 63) at the end of the study. In the specific areas of sociability, cognitive awareness, and behavior, there were significant improvements among treated children when evaluating baseline measurements in comparison to those obtained at the end of the study period. Additionally, for specific subjects participating in the clinical trial having independent assessments by school evaluators, who were not aware of the treatment status of the child, there were significant improvements in general school skills mastered and significant improvements in the frequency and severity of disruptive/oppositional behavior at the end of the treatment period relative to baseline.

When comparing the clinical examinations undertaken for each child at baseline and at the end of the study period, significant reductions in clinical symptoms and the associated

behaviors of hyperandrogenemia (such as early growth spurt, early secondary sexual changes, body and facial hair, and aggressive behaviors) were noted. Laboratory testing revealed a significant decrease in serum testosterone levels. It was observed that the treatment protocol did not significant adversely affect kidney, thyroid or liver function tests.

As a result, the investigators concluded, since their study employed therapeutic agents that were designed to lower androgen levels, and significant decreases in androgen levels were observed, the treatment protocol presented a novel method for helping to significantly reduce autistic-like behaviors. Furthermore, the investigators reported that in some of the children examined, significant autistic behavior improvements (i.e., better sleep patterns, improvements in attention and hyperactivity, and increased socialization) occurred within days of the administration of leurpolide acetate. Finally, the investigators concluded that leuprolide acetate administration significantly helped to ameliorate clinical symptoms/behaviors of hyperandrogenemia such as early growth spurt, early secondary sexual changes, body and facial hair, and aggressive behaviors that may be observed among some children diagnosed with an ASD.

Subsequently, other investigators described their clinical experience following the administration of leuprolide acetate therapy to nearly 200 individuals diagnosed with an ASD [10]. Leuprolide acetate administration significantly lowered androgen levels and resulted in very significant overall clinical improvements in socialization, sensory/cognitive awareness, and health/physical/behavior skills, with few non-responders and minimal adverse clinical effects to the therapy. Leuprolide acetate administration also resulted in significant quantitative clinical ameliorations in hyperactivity/impulsivity, stereotypy, aggression, self injury, abnormal sexual behaviors, and/or irritability behaviors in many individuals diagnosed with an ASD.

Recently, investigators have purposed clinical guidelines for the evaluation and treatment of androgen dysfunction in individuals diagnosed with an ASD[7, 27]. It is important when considering medicines such as leuprolide acetate for the treatment of individuals diagnosed with an ASD, to consider that such therapy is not intended to deprive the individual of their sexuality nor alter their normal developmental trajectory. Instead, the initiation of such therapy is designed to regularize a process that was proceeding in an abnormal fashion and producing adverse effects. Thus, the use of anti-androgen medicines, such as leuprolide acetate, can safely improve the health of the individual diagnosed with an ASD by reducing in the frequency and intensity of their ASD traits/symptoms

In considering the in-use safety of GnRH analogues in the treatment of individuals diagnosed with an ASD, they have been on the market for many years, and many individuals have received GnRH analogues for many years to treat conditions such as prostate cancer, female reproductive problems, and premature puberty without serious adverse effects [7]. Studies of individuals receiving GnRH-analogue therapy for many years in the treatment of premature puberty reported that GnRH analogue administration was not associated with long-term reproductive dysfunction. The patients had normal menarche normal ovarian function etc. No impaired physical development was observed. The patients had normal body composition, normal body mass index, normal bone mineral density, etc. No reduction in the secretion of

sex hormones in men and women was observed [7]. In 2009 the American Academy of Pediatrics issued a consensus statement describing that GnRH analogues are generally well tolerated in adolescents and children. Systemic complaints such as hot flashes or headaches occur occasionally but are usually short-term and do not interfere with therapy [28].

In previous long-term follow-up of individuals receiving GnRH-analogue therapy in the treatment of premature puberty for many years, the studies reported that GnRH analogue administration was not associated with long-term reproductive dysfunction (normal ovarian function, normal menarche, etc.); impaired physical development (normal body mass index, normal body composition, normal bone mineral density, etc.); or reduced secretion of sex hormones in women and men [7]. The American Academy of Pediatrics in 2009 issued a consensus statement describing that GnRH analogues are generally well tolerated in children and adolescents, and systemic complaints such as headaches or hot flashes occur occasionally but are usually short-term and do not interfere with therapy [28].

Furthermore, when considering the safety profile of GnRH analogues among individuals diagnosed with an ASD, it is important to evaluate them in the context of currently used psychotropic medicines. For example, risperidone is currently approved by the US Food and Drug Administration (FDA) for the treatment of individuals diagnosed with an ASD. Investigators recently reported on the long-term treatment effects of risperidone on prolactin levels, sexual side-effects, and bone mineral density in pubertal boys diagnosed with an ASD [29-31]. The individuals diagnosed an ASD examined were physically healthy 10 to 20 year-old males chronically treated with risperidone for an average of 52 months (range 16 to 126 months). It was observed when comparing individuals chronically treated with risperidone in comparison to individuals not treated with any antipsychotic medicine, hyperprolactinemia was present in 47% of the chronically treated individuals in comparison to only 2% of the individuals not treated with any antipsychotic medicine. In addition, gynecomastia and sexual dysfunction were present in 43% and 14% of the individuals chronically treated with risperidone in comparison to 21% and 0% of individuals not treated with any antipsychotic medicine. Individuals chronically treated with antipsychotic medicines who developed hyperprolactinemia were compared to individuals not treated with any antipsychotic medicine and had no hyperprolactinemia. The patients treated with antipsychotic medicines had significantly lower lumbar spine bone mineral density scores, higher percentage of body fat, and a lower biochemical bone marker carboxyterminal cross-linking telopeptide of bone collagen. Finally, it was observed among individuals chronically treated with antipsychotic medicines who developed hyperprolactinemia in comparison to individuals not treated with any antipsychotic medicine who did not have hyperprolactinemia had significantly lower testosterone levels.

5. Conclusion

The present critical review provides evidence for hyperandrogenism as a significant feature among ASD. Further, many studies have shown a significant correlation between the traits/

symptoms of individuals diagnosed with an ASD and hyperandrogenism. Finally, the present critical review presents data from animal models and human clinical trials demonstrating that medication with anti-androgens significantly improve certain traits/symptoms exhibited by individuals diagnosed with an ASD.

The present critical review provides evidence for hyperandrogenism as a significant feature among individuals diagnosed with an ASD. Further, many investigations have revealed a significant correlation between the traits/symptoms of individuals diagnosed with an ASD and hyperandrogenism. Finally, the present critical review presents data from animal models and human clinical trials demonstrating that anti-androgen medications have the ability to significantly improve certain traits/symptoms exhibited by individuals diagnosed with an ASD.

In light of the high prevalence of individuals diagnosed with an ASD and the paucity of safe and effective medical treatments to help these individuals, anti-androgen therapy should be considered as it is an effective and relatively safe means to significantly help improve the adverse traits/symptoms exhibited by individuals diagnosed with an ASD. By directly targeting a traits/symptoms and/or biomedical indicators when elevated beyond the normal ranges, this therapy controls difficult traits/symptoms associated with high androgens such as self injurious behaviors and aggression, and, thus, contributes to the quality of the individual's life and the normalcy of the individual's home life.

It is recommended that all individuals diagnosed with an ASD should be screened for elevated androgens and elevated androgen-associated traits/symptoms as part of a standard initial clinical assessment. In addition, these same type of blood and clinical traits/symptoms should be assessed within the affected individual's family, so as to produce not only treatment options for the individual diagnosed with an ASD but also an understanding of why these conditions occur and who may be at risk. Finally, for those appropriate individuals diagnosed with an ASD, anti-androgen treatment should be offered.

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Chapter 14

ReAttach – The Exciting Development of a Promising Intervention for Autism Spectrum Disorders

Paula Weerkamp-Bartholomeus

Additional information is available at the end of the chapter

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1. Introduction

In our society, we usually *talk* about events that are happening around us. We do not usually reflect on the manner in which we *handle* and *process* these events. If there is an obstacle in our information processing, we notice that events that have happened in the past continue to influence our current functioning. For example, we cannot manage to forget past events. We become burdened if we are figuratively 'full' with the unprocessed information. ReAttach is an intervention in which people do not have to discuss their problems. This process is easier for people if they have difficulties communicating or expressing themselves, such as with many cases of autism. ReAttach assists with the collection of facts, impressions and events, which are later processed quickly to ensure that the process will not overwhelm the participants. During ReAttach, the therapist focuses on the *process* and not on the content of the information. The participants are asked to listen to the thinking assignments given to them during cognitive training. The subsequent insights that follow are the participants' own insights because they process information better.

2. February 2010: An experiment

Five years ago, I conducted an experiment that led to a drastic change in my work. Introducing a new intervention in the field of autism requires courage and determination. Accepting innovation requires an open mind and readiness to review pre-existing concepts. The name ReAttach was chosen because of the importance of the attachment theory [1] in my work as an educational psychologist. This name does not indicate that I think that autism is an attachment disorder, nor do I blame the parents of autistic chil-

dren. ReAttach emerged from the idea that we can learn from healthy child development and the manner in which healthy children process information, emotions and events. We therefore required a multimodal approach. On 26 February 2010 I was reading a manual for schema therapy [2], a book describing a treatment for adults with trauma and personality disorders. I tried to understand the authors' viewpoint and to integrate this viewpoint into the concepts that I have built from my own working experience. In my opinion, the behaviour patterns described in this book strongly matched the behaviour patterns of children with early maladaptive schemas. Children are able to cope with their stressful events during play if they have fundamental environmental support that provides them with the confidence and safety to work out their negative emotions through play. As an educational psychologist, for me, playing is processing [3]. Playing made me create an experimental treatment session in which I simulated the optimal conditions needed to process defensive excluded information through play. The results of this experimental treatment were positive, and I started to conduct practical research with traumatized adults. In July 2010, I realized that it should be possible to develop a special intervention for people with autism and to focus on cognitive training to improve information processing and daily life functioning. We made special adjustments for people with autism because we had to overcome their individual problems with arousal regulation and multiple sensory integration processing to be able to teach new social cognitive skills and to improve executive functioning. For the autistic children and adults who voluntarily joined the cognitive training the first results were amazing. We observed improvements in facial expressions and social cognitive skills, and high-functioning adults with autism reported that it felt as if the computer in their brain was updated and now contained multiple processors.

This process, which was the beginning of ReAttach for Autism, needed to be described in a protocol, and we needed to investigate how we could share this multimodal intervention with other professionals. Finally, we had to wait to determine whether the results would last after we ended the cognitive training. We started practical research and made improvements in the process of transferring the intervention to colleagues and during collaboration with parents and partners. In November 2012 I felt that there would be more options for strengthening the treatment process (i.e., information, emotions and events) if we could gather fragmented pieces of information stored in the long-term memory and reprocess this information in a coherent manner to reflect the following concepts: self, significant others and social. To reprocess information, the arousal level of a patient must be regulated slightly above the level of 'falling asleep' at the Alpha-Theta border (7-8 Hz). This arousal level is important for transitioning from deep relaxation, visualization, creativity, and learning to information acquisition from long-term memory [4, 5].

We currently work with two different arousal levels using the multimodal approach of ReAttach. We need a high arousal level for optimal information processing, good joint attention, active stimulation of multiple sensory integration and training social cognitive skills. To help participants with autism process information in a coherent manner, a near-sleep condition is required to access fragmented information that needs reprocessing. Both arousal

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levels might be reached by changing the tapping frequency at the back of the participants' hands.

3. The multimodal ReAttach approach

The ReAttach intervention involves individual cognitive training using multiple components with increasing difficulty, which allows the intervention to be adapted for children and adults. A brief overview of the therapy components is presented below to provide an impression of the complexity of the therapeutic skills.

4. Oxytocin

Physical contact stimulates the brain to produce the hormone oxytocin, which plays an important role in the bonding process and is a direct reward of social contact [6]. During ReAttach, gently and frequently tapping on the back of the participant's hand is used to manage arousal. The tapping helps the participant to release stress and negative thoughts, and it stimulates the participant to become involved in social interaction and joint attention. Joint attention is important to maximize the results of an intervention or cognitive training. Joint attention is considered to be a precursor of the theory of mind [7] and language development [8]. In ReAttach, we simultaneously combine a) external arousal regulation to gain, and maintain joint attention and b) oxytocin, administered through physical contact, to improve the social reward system. We hypothesize that this process optimizes the conditions conducive to further information processing and growth in individuals with autism.

There is another reason why tapping is involved. One goal of ReAttach is to stimulate multiple sensory integration processing to teach the multitasking skill. Gently tapping on the back of the participant's hand ensures the input of the essential tactile stimuli needed to stimulate the tactile sensory channel simultaneously with auditory and visual inputs.

The tapping is based on a natural method of making physical contact without overstimulating oxytocin production. If a parent comforts an upset child, we see the same kind of tapping on the back of the child. The result of that natural parental tapping behaviour is that the child's stress levels can be easily and naturally regulated by the parent [9]. To use the same technique during the ReAttach intervention, we chose a more professional attitude and transformed this arousal regulation technique by gently tapping on the hands of adults and children with autism spectrum disorders. If a participant with autism cannot bear the touch of the therapist even after an explanation has been provided, we provide additional instructions that enable the participant to perform the tapping himself (for example on the knees). We have learned that even children with tactile defensiveness responded well once we gave them the time that they needed to understand and to adjust.

A condition of safe attachment is required for the intervention. Therefore, we intend to work in the presence of a parent or partner unless the participant prefers to work alone.

5. Manage your own arousal

If we work with families, we start by teaching the parents how to manage their own arousal. We provide parents with a technique to lower their own arousal and the tools to help their children with stress and emotion regulation. To provide a good therapy session, the ReAttach therapist must manage his/her own arousal before addressing the participant.

6. Multiple sensory integration processing

People with autism experience difficulties processing information through more than one channel; they process sensory information atypically. Because of monotropism, people with autism store information in a fragmented manner. According to Bogdashina and Siebelink [10], children with autism have disrupted concept formation because of these sensory integration problems. I believe that we can teach them how to improve in this area. To build coherent concepts we must use multiple sensory integration processing. During optimal arousal under multisensory stimulation (tactile, auditory, visual), we can stimulate multisensory integration processing by requesting conceptual thinking.

7. Conceptual thinking

At approximately the first year of age, children become capable of placing coherent information into concepts. People with autism lack this ability. They continue to process incoming information in pieces; consequently, they do not create a coherent image of 'the self', 'the other', or 'the world'. Baron-Cohen believes that the social interaction problems of people with autism arise because of a basic inability to think about mental phenomena in terms of 'self' and 'other' [11]. It has been my experience that with ReAttach we can train people with autism to form concepts. During our cognitive training, we follow the same order of development that occurs in a young child [12]. We start with the concept of 'the self' – the name. Then, we train concepts of significant others, theory of mind and social concepts. Autistic individuals with average or high intelligence can start this training at the age of six and follow it through to completion. With low-functioning people with autism and with younger children, our purpose is to teach them to differentiate between 'the self' and 'the (significant) other'. At a later stage, we can try to train theory of mind and inter-relational concepts. We must adjust the intervention to the developmental stage of the participant.

8. Low arousal as a condition for reprocessing

Based on the theory proposed by Bogdashina, I assume that people with autism have an entire database of loose fragmented pieces stored in their long-term memories [10]. It is important

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to retrieve this information and piece it together. This training is possible during low-level arousal – a near-sleep condition [4, 5].

While the first process is still running, the therapist externally regulates the arousal in a soft and low tapping frequency, with a dimmed voice and attitude. Most children and adults like this condition; it makes them feel relaxed. Simple instructions are given to collect positive information from the long-term memory to reprocess it in a coherent manner. If a person with autism has a negative attitude toward himself and the world there will be many social interaction problems. After reprocessing the same person might have a more realistic coherent point of view and fewer social interaction problems. In many patients we have observed a reduction in aggression regulation problems, as well as less explosive behaviour, and we think that these findings might be the result of a more realistic and coherent understanding of themselves and the world. These findings strengthen the Baron-Cohen theory that many social interaction problems of people within the autism spectrum arise because of the inability to think in terms of self and others [11]. By teaching these concepts we can observe a significantly reduced number of social interaction problems.

9. An illustrative case study: The story of Jason

Jason, a 22-year old male, demonstrated development after undergoing ReAttach therapy four years ago. Jason was diagnosed with Asperger syndrome when he was eight years old. Despite his high intelligence level, it was obvious that something was wrong. Asperger's manifested itself in a typical manner. Jason himself describes some of the more prominent features of his condition before and after the ReAttach therapy.

'Before receiving the ReAttach therapy, I, for instance, had always had trouble signalling my own pain sensations. According to my mother, this was already apparent when I was young. As a baby, when I accidentally held my arm in a hot bath, I did not flinch. When I was a teenager, I broke my arm twice but did not hesitate to shake the general practitioner's hand with my injured arm, simply because I was unable to sense the pain this must have caused. The same goes for sensing hunger: it has always been difficult for me not to forget to eat.

Another example was trouble in both perceiving and showing emotions. I remember how my grandfather died when I was ten, and of course it was obvious to me that everyone was sad, as that is what most people are at funerals. However, it was very difficult for me to become aware of the way I felt myself. I remember thinking I had to feel sad too, but was not able to show empathy. Looking back, I notice how seeing someone crying was connected to the cognition of feeling sad, but the actual feeling never came.

When reflecting with my mother, it became clear that I was often absent-minded, and could completely focus on one activity, for instance playing a video game. In these situations, I completely lost track of time and the people around me. Simple tasks like walking the dog or doing the dishes were not executed, not because I was unwilling but because of the lack of overview.

The first time I was going to receive the ReAttach therapy, I was slightly sceptical of the improvements it could offer me. Afterwards, I realize that because I was not able to reflect on my own situation, I could also not see the skills that I lacked. Of course I was aware of my diagnosis, but that did not mean that I felt limited in my daily functioning. So far, I had lived a happy life. My results at school had been excellent; why bother improving?

It is impossible for me to fully describe my gain from ReAttach, not only because it comprises so many aspects but also because I lack a proper self-image from the first 18 years of my life. According to my relatives my social interaction skills have improved dramatically. Not only are my facial expressions more appropriate but people in conversation with me also feel better understood, and...I actually take part in a conversation.

Another big improvement is the ability to multitask in everyday life. Since ReAttach, I have been able to live on my own, get my driver's license, play in a band, maintain my social life with my roommates and friends, and undertake university study with an internship abroad, but above all I have been able to do these things with ease. I do not think I would have been able to, for instance, live on my own if I had not received the ReAttach therapy. I do think that it would have come with a lot more trial-and-error. This is the exact reason I would recommend the therapy to everyone: after a couple of almost effortless sessions my life has become so much easier, it would be almost foolish to not see what ReAttach could offer you'.

10. Transferability and cultural differences

Working in countries other than the Netherlands (e.g., India and Romania) has taught us that there are many different methods of expressing the meaning of ReAttach. I was pleased that my original intent to make children experience play was easily accepted and recognisable so many miles from home. I was also pleased with the commitment to participate in the cognitive training as we provided ReAttach to high-functioning adults with autism spectrum disorders and to parents. In a few weeks we will begin teaching a course for professionals in Saudi Arabia, and we are confident that we are able to make the adjustments that are needed to overcome communication problems and cultural differences. Autism does not discriminate in terms of intelligence, social economic status or culture; therefore, we want to include all families affected by autism.

11. Conclusion

The development of a new intervention is an exciting process that might take several years. Continuous practical research in the form of pre- post measurements has shown positive results and a publication about this practical research is in progress.

This illustrative case study of one of the first follow-up interviews, four years after the intervention, is promising. This young adult with Asperger syndrome has shown no signs of

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regression at all after ending the cognitive training. On the contrary he describes how he has been able to use his newly-acquired skills for his personal development and self-determination.

Future research is necessary and most welcome to explore the mechanisms that may underlie the improved daily function that has been observed in the children and adults with autism who have participated in our practical research. I can only speculate that for most individuals with autism, one or more components used in this multimodal ReAttach approach may lead to reliable improvements.

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My intention to contribute to the solution of problems in daily life functioning for people with autism has grown with the unconditional support of parents, children and adults with autism that were willing to participate in the innovation and practical research of ReAttach. Without their support it would not have been possible to make efforts or progress in the field of autism.

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Chapter 15

Meeting the Communicative Rights of People with Autism — Using Pictorial Supports During Assessment, Intervention and Hospital Care

Gunilla Thunberg, Magdalena Johansson and Julia Wikholm

Additional information is available at the end of the chapter

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1. Introduction

The main purpose of this chapter is to describe how assessment, intervention and hospital visits more generally can be managed to meet the communicative rights of people with autism spectrum disorders and improve aspects of activity and participation. A working model, built upon the United Nations conventions on the Rights of the child [1] and the Rights of persons with disability [2], using the principle of universal design [2] and augmentative and alternative communication (AAC) methods was developed within the project KomHIT-communication support in paediatric and dental care. An evaluation of this model in the form of a focus group interview with a multiprofessional team at a neuropsychiatric clinic will also be presented alongside with the examples of the pictorial supports that were used.

2. Communication problems and communication rights in clinical settings

2.1. Communication in children with Autism Spectrum Disorders (ASD)

Major advances have been made over the two past decades in understanding the social-communication difficulties of children with ASD, resulting in greater emphasis on early social-communication features in the diagnostic criteria. Most parents of children with autism first begin to be concerned that something is not quite right in their child's development because of early delays or regressions in the development of speech [3]. Problems with communication, in terms of both understanding and expression, are often said to be one of the main causes of

the severe behaviour problems that are common among persons with severe autism and mental retardation [4].

Although all persons diagnosed with autism have problems with communication, their type and degree vary a lot and the work of identifying different subgroups has just begun. It has been estimated that between one-third [5] and one-half [6] of children and adults with autism have no speech. However, more recent research results indicate that the proportion of non-speaking children with ASD is much smaller, approximately 14% to 20%, among those who received very early intervention [7]. In spite of the heterogeneity of language abilities in children with ASD, social-communication or pragmatic impairments are universal across all ages and ability levels [8]. Certainly, communication and communication problems are at the heart of what ASD is all about

2.2. Communication rights of persons with disability

All individuals, with or without disabilities, have a basic human right to influence their own living conditions through communication. The United Nations' (UN's) convention on the rights of persons with disabilities, has the purpose to promote, protect and ensure the full and equal enjoyment of all human rights and fundamental freedoms by all persons with disabilities, and to promote respect for their inherent dignity. (DS 2008:23) [2]. The convention is built on eight general principles, for example: individual autonomy including the freedom to make one's own choices, full and effective participation and inclusion in society and accessibility, and respect for the evolving capacities of children with disabilities and respect for the right of children with disabilities to preserve their identities. Article 25 postulates that health professionals are required to provide care of the same quality to persons with disabilities as to others and to take all appropriate measures to ensure access. According to article 21 this includes the freedom to seek, receive and impart information and ideas on an equal basis with others and through all forms of communication of their choice, including augmentative and alternative communication. Furthermore, the idea of "Universal design" is put forth, meaning that the design of products, environments, programmes and services should be usable by all people, to the greatest extent possible, without the need for adaptation or specialized design [2].

2.3. Communication and communication problems in health care situations

People with disability often have many health contacts. According to Mahon and Kibirige [9] children with disability more frequently are in need of health care and are cared for longer than children without disabilities. Due to the communication difficulties being part of the autism spectrum visits to health care or hospital stays can be very problematic. Children with ASD are particularly stressed due to lack of structure and predictability [10]. It is also difficult for the individual with a communicative disability to communicate with the staff and ask questions [10]. To a certain degree this is true also for other individuals, in particular those whose skills in the spoken and or written language that is used, are not enough, and also may lack knowledge of the culture of the health care system [11].

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Children also may have difficulties in understanding and communicating during health care situations. The UN convention on the rights of the child states that all children should be equally treated and have the right to freedom of expression, including the right to seek, receive and impart information and idea in all forms [1]. Research has shown that this is not always the case in within health care. Coyne [12] has shown that children sometimes have the feeling of being excluded, not receiving information or being involved in decisions and often talked to in a language which is difficult to understand. The same study shows that children feel less worried, calmer and respected when they are provided with information and asked about the care [12]. According to [13] this also leads to an increased feeling of control which in turn leads to improved compliance and more effective care.

This means that far more people, than those with communicative disability, are in need of better support to access information and communication within the health care system. To develop routines, procedures and materials within health care, based on the idea of universal design, should benefit all groups both with and without communication problems. This would also save time and resources in the efforts of providing equal care to all [11].

2.4. AAC to promote accessibility in health care situations

Augmentative and alternative communication (AAC) includes all forms of communication (other than oral speech) that are used to represent thoughts, needs, wants, and ideas. AAC can be used both as a support for comprehension and for production of spoken or written communication [14].

Project activities concerning use of AAC as a tool in hospital care seem to be going on in many countries. However, when it comes to research of the effects of these interventions, specifically regarding children, very little has been done. In a review of research regarding communication between nurses and patients with complex communication needs (CCN) undertaken by Finke, Light and Kitko [15], none of the twelve studies that were identified specifically concerned children. Another review that was found focused disabled children's experiences as inpatients [16]. The data, gathered from children, parents and staff in the eight qualitative studies that were reviewed, showed that communication was the overarching theme. Nurses reported that communication was difficult and that they did not have a consistent framework for involving the child in discussion and decision. The main conclusions comprised recommendations of giving the child information and appropriate involvement in discussion and decision-making and that the children's experiences with respect to this was not optimal. Despite the strong focus on communication in this review and the conclusions also pointing to the need of more training in communicative strategies, there is no mentioning or discussion of augmentative strategies or tools in this article. Beside these two reviews of communicative disability and hospital care, a pilot study published in 2013 report successful results using pictorial supports for children with autism in medical settings [17]. Two other studies report how AAC successfully can be used more generally in paediatric care. The first study was published by Costello in 2000 and presents the Children's Hospital Boston model of pre-operative AAC-intervention. This intervention prepares the children and the families for the expected period of loss of speech due to tracheostomy, intubation and/or use of ventilators during the postoperative care

at the Intensive Care Unit (ICU). The results of the evaluation were excellent in that almost all patients used the communication aids they had chosen and loss of speech was not seen as the major problem, in contrary to most evaluations of ICU care [18]. In the second study a picture board was provided as a means to answer questions of pain after surgery. The children's answers were more precise using AAC and the parents were very positive [19].

In spite of these positive reports more efforts are needed. This was evident in a study by Thunberg, Buchholz and Nilsson [20], where parents of children with communication difficulties were interviewed (among these also parents to children on the autism spectrum). The parents stated that hospitals should be better both in providing various forms of communication materials and also in adapting these to different children and different situations.

In particular the parents stressed the importance of direct communication between the medical staff and the children, and that staff need more knowledge about communication and use of AAC to manage this. The staff need to communicate with the child on the child's own condition and should therefore receive training in the use of alternative and complementary means of communication and also how to interact with children with communication difficulties [20].

Unfortunately there is no research on how children with ASD or other types of communication problems perceive medical care. However, there are studies showing that adults with communication difficulties are experiencing a lack of communication competency in health care. Just as parents of children with communication disabilities, adults states that medical care staff need greater knowledge of and training in communication strategies and the use of alternative means of communication [21].

2.5. KomHIT model — Communication support in paediatric and dental care

The KomHIT model – communication in care settings using communicative support and IT – has the overall purpose to improve the communicative rights of children with communicative disabilities during pediatric or dental care situations according to the Convention on the rights of persons with disability using AAC as Universal Design (article 3, United Nations, 2006). KomHIT therefore tries to implement AAC, mainly in the form of visual supports, generally to all or most children. This is important in today's care which often is slimmed with respect to time and resources, making it a challenge to implement procedures and methods that are exceptions to the daily routines. The basic idea is that "what is good for people with disability is good for everyone". When AAC or visual support is used generally, communication, clarity and safety is improved for everyone. This is particularly important for the group of children with disabilities and their parents who have another language-and/or cultural background. The model has been developed within a joint project involving both professionals and user organizations.

KomHIT consists of both educational resources and easy available communicative tools/ materials. A web tool has been created where pictorial communication material can be made, stored and searched by both professionals and parents (www.bildstod.se). The symbols that are available have been developed within different EU projects and can all be used for free, as long as they are not used commercially. This pictorial web tool www.bildstod.se can be said

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to constitute the main resource. The other web-resource (www.kom-hit.se) also shares information about (1) communicative rights according to the UN conventions on the right of the child and on persons with disabilities (2) project work and methods (3) relevant research (4) a video bank of illustrative video clips and links to external video material (5) a bank of educational resources and information about webb-based and campus-based courses and educations.

The educational model involves both campus-and web-based courses. Two basic packages for education has been developed. One to educate KomHIT communication mentors, and the other one to be used by the communication mentors in their job to guide and educate their colleagues. The education of mentors includes knowledge about communication, communicative disability, the UN convention on the right of persons with disability and augmentative and alternative communication strategies. This is given through lectures, video examples, role plays and exercises using and designing pictorial material and the web-resource www.bildstod.se. A choice of these resources are then provided to the mentor to pass on to their colleagues during meetings and/or educational activities within their clinics to implement the use of AAC/pictorial support. The majority of the educational resources are available on the KomHIT web site also to be accessed and used by other persons in need of communication support, specifically parents of children with communicative disabilities.

2.5.1. KomHIT model — A pilot study within day surgery

KomHIT was first pilot tested and evaluated on a day surgery ward at Queen Silvia Childrens' Hospital in Gothenburg, Sweden. All children/families were provided with (1) an invitation letter to the surgery ward with structured text and pictorial support, (2) a visual schedule with six pictures informing of the main events, (3) a communication board with 30 symbols to enable conversation on the topic of day surgery (figure 1). (4) A visual schedule book of 6 pages, depicting a vertical column of five photos/symbols each, showing the details of the procedures during the visit (figure 1). Information about the KomHIT project and the use of the materials was also attached to the invitation letter. The parents were instructed to point to the pictures while explaining and talking to the child about the hospital visit, and to bring the visual schedule along during the travel to the hospital. Upon arrival to the surgery ward the nurse used point talking to the pictures in the Schedule book explaining the procedures of the day. The child then could bring this book along during the day and remove the pictures one-by-one after finishing the different steps. Each nurse also had access to the same "day surgery communication board" as was sent to the family (to the right above), to be able to expand point talking beyond the book, specifically for children with more comprehensive communication problems.

A pilot study of this intervention was conducted focusing on the expected decrease in stress and anxiety [22]. Twenty-five children with communicative disability (about half on the autism spectrum) and their parents participated (seven in the intervention group, 18 controls). Children and parents were asked about their emotional state using the State-Trait Anxiety Inventory (STAI), for children adapted to the Talking Mats format, and samples of saliva were collected. Premedication was also checked. Due to the few participants that could be recruited

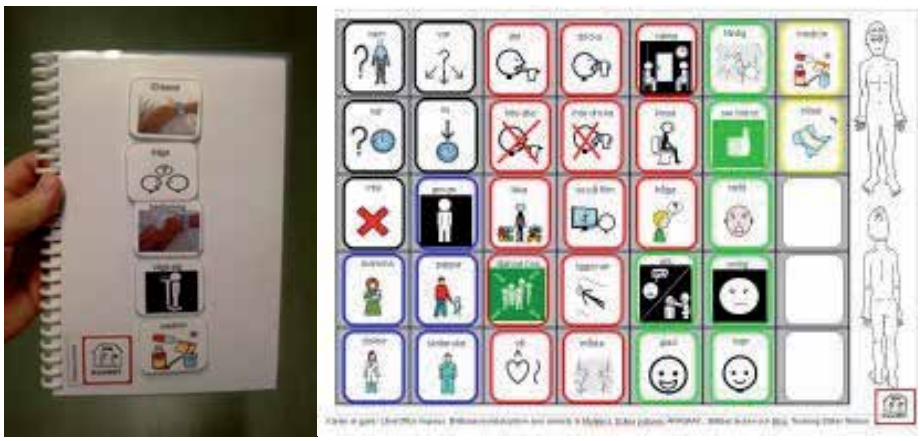

Figure 1. Examples of tools used within day surgery. To the left the visual schedule book of six pages depicting a vertical column of five photos on each side. The child removes the pictures one-by-one after finishing the different steps. This book was used for all children 2-8 years old and for older children with disability or language problems and/or being tense or anxious. The picture to the right shows a communication board that was used with children who needed more support during information and conversation.

during the intervention phase no statistical analyses could be done. The results were promising in that the morning cortisol levels were lower in the group of children who were provided with AAC and that none of these children were in need of premedication. No differences were seen in regard to the STAI results. It was discussed that this might be due to the adapted STAI being too rough a measure. In conclusion this pilot study indicated that the use of pictures can reduce anxiety in children with communicative disability during hospital care, but that more research is needed to prove this [22].

The following parts of this chapter describes the implementation and evaluation of the KomHIT-model in a Neuropsychiatric clinic, using AAC in the form of pictorial supports during assessment and intervention procedures.

3. The KomHIT-model using AAC during assessment and intervention within neuropsychiatry

3.1. Implementation of the model

The department that was involved in this study is part of the neuropsychiatric clinic at Queen Silvia children's hospital, a regional specialist hospital for children and adolescents in Sweden. This clinic mainly performs assessments and medical interventions for children and adolescents with suspected and diagnosed neuropsychiatric disorders. The main task of this particular department or team is to assess young (pre-school-aged) children, where the majority of the children have pervasive problems with communication. Due to the strong hereditary factor in neuropsychiatry several parents also have problems with communication.

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A comparatively large amount of the families also have another language and/or cultural background that complicates the understanding of information, instructions and also the health care system and Swedish society generally.

Two team members from this department, a speech-language therapist and a special educator, was enrolled in the development of the KomHIT model and was provided with the communication mentor education described above. In collaboration with the head of the department the planning of implementation was done. They started off by informing the staff about the overall purpose and methods of the KomHIT intervention and that they wanted to interview everyone about their processes, the need of pictorial supports and the design of these. After completing these interviews the designing of the supports or tools were done according to the wishes and ideas of the different team members.

The mentors had the opportunity to convene the staff to a kick-off – a half-day of training, going through convention texts, AAC methods and showing video clips of AAC-use in clinical situations. Each professional was provided with a folder with his/her own set-up of tools; visual schedules and dedicated communication boards and exercised the use of these in role plays. The two communication mentors also presented the general tools of the department; invitation letters with pictorial support, communication boards and visual schedules for waiting room communication, play activities and toilet visits, and finally visual support for identifying the different rooms. The materials that were developed are listed in the table below (table 1) and examples of these are displayed (figure 2).

The staff was asked to start the use of the visual tools and point talking immediately after the kick-off or as soon as possible. They were informed about the evaluation activities, a survey and a group interview, that was about to take place two months later and that it was important that they could participate in these.

3.2. Pictorial supports and examples

The materials that were developed are listed in the table below (table 1) and examples of these are displayed (figure 2).

Type of material	Aim/name	Short description
Invitation letter	Child invitation letter (figure 2)	Text and illustrating pictures. Sent home to the child
	Invitation letter with many appointments	Text and illustrating pictures. Sent home to the family
Visual schedule	Physician and nurse	Pictures to be selected and used on a visual schedule during the visit and that could be removed after finishing the different steps
	Sampling and measuring	As above – more specific for sampling: blood, weighing and measuring

Type of material	Aim/name	Short description
	Medication school	Pictures to be used within the clinic's medication school where the children are taught how to manage their medications
	ADOS	Pictures to support procedures and instructions in regard to ADOS assessment
	Speech-language therapist	Pictures to support procedures and instructions in regard to assessment and intervention
	Psychologist (figure 2)	Pictures to support procedures and instructions in regard to assessment and intervention
	Literacy testing	Pictures to support procedures and instructions in regard to assessment of reading and writing
Communication board	Large general (figure 3)	Larger board that could be used generally to support communication/conversation and other more specific tools
	Small general	Smaller board that could be used generally to support communication/conversation
	Small specific speech-language therapy	Smaller board to be used more specifically during speech-language therapy visits
	Doctor's bunch (figure 3)	A bunch of small boards to be used by the doctor to support communication/conversation
	Specific doctor and nurse board	Two smaller boards to be used more specifically during medical visits
Waiting room/ environment	Car play	Board to support car play communication
	Doll play	Board to support doll play communication
	Duplo play	Board to support duplo play communication
	Garage play	Board to support garage play communication
	Play House	Board to support Play house communication
	Reading story books	Board to support story book reading
	Choosing play activity	Board to support pay and choice-making
	Waiting room	Board to support waiting-room communication
	Cloak room	Board to support cloak room communication
	Schedule for clothing	Visual schedule for taking on/off clothes
	Schedule for toilet	Visual schedule for toilet procedures, available in two formats: less and more detailed
	Welcome instructions	Text and illustrating pictures to welcome patients and parents and provide instructions (available in different formats for the different waiting-rooms)
	Missed appointments	Text and illustrating pictures to inform about consequences of not cancelling booked appointments
	Symbols/pictures for visual marking-up	Symbols/pictures for marking-up rooms an functions on the clinic

Table 1. List of pictorial material that was developed on the Neuropsychiatric clinic

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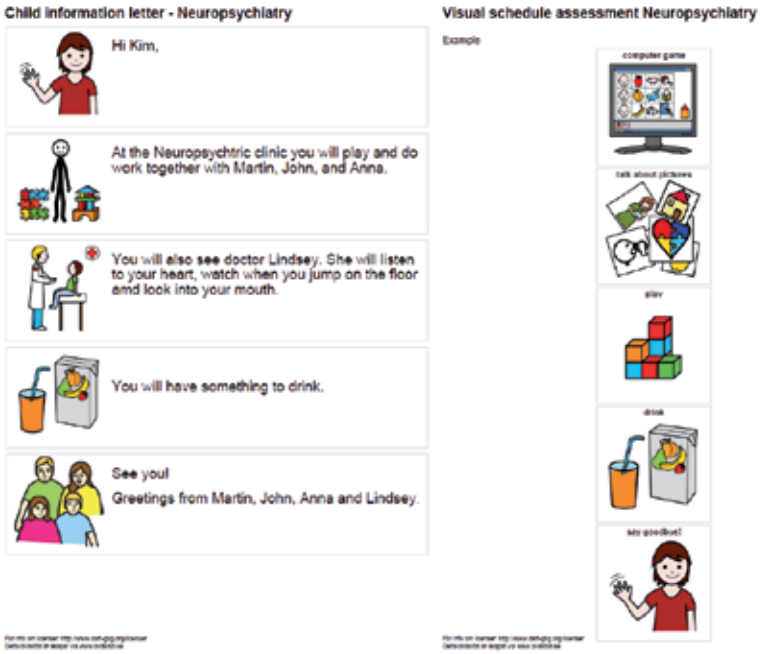

Figure 2. Examples of the pictorial materials listed above. To the left an invitation to the child. To the right a visual schedule for an assessment session. More material are available at www.kom-hit.se

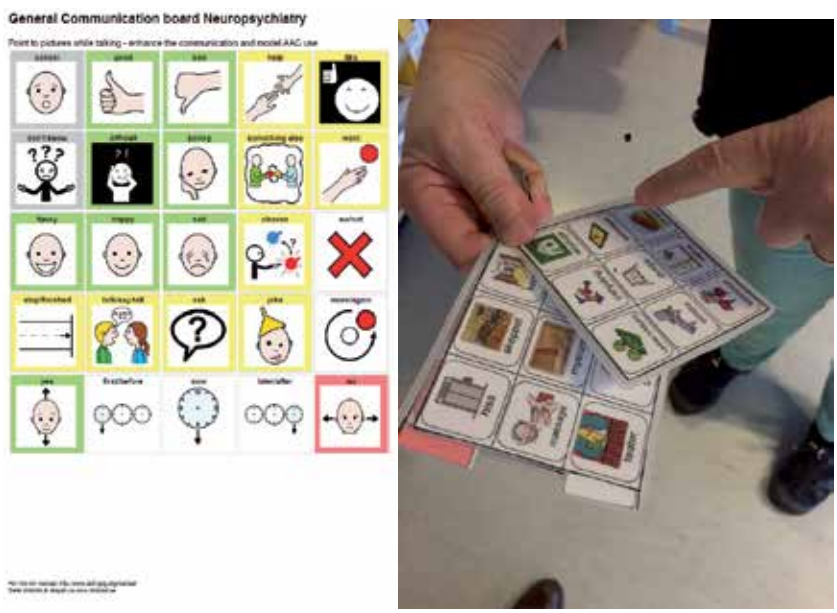

Figure 3. Examples of the pictorial materials listed above. To the left a general communication board to be used in different situations. To the right a bunch of boards dedicated for the physician.

4. Evaluation and results

The evaluation was done through a survey distributed to staff and parents at the department and through a group interview with staff members. The survey was part of the general evaluation activities that was completed on all clinics involved in KomHIT and will not be reported here. The group interview used a semi-structured format along the lines of focus group methodology [23] and a content analysis of the transcripts was carried out to identify categories and main themes [24].

4.1. Participants

The participants in the focus group study was recruited from the department working with young pre-school aged children on the child neuropsychiatric clinic at Queen Silvia Children's Hospital, a regional specialist hospital in Sweden. This department was selected since the vast majority of the patients had communicative problems, were in need of communicative support that was only occasionally provided before the intervention started. An invitation letter with information about the interview was distributed to the entire staff at the department. A group of six staff representing five professions was recruited. Participant data is presented in table 2.

Participant	Gender	Profession
P1	♂	Physician
P2	♀	Psychologist
P3	♀	Speech language therapist
P4	♀	Special educator
P5	♀	Nurse
P6	♀	Special educator

Table 2. Participants

The initial purpose was also to carry out a group interview with parents. Although many parents were positive to participate in such an interview this idea finally had to be put off due to practical problems.

4.2. Procedure

The group interview was carried out by the second and third author. One interviewer had the role as moderator and was responsible for introducing new topics and lead the interview, and also to hold a short summary at the end of the interview. The second interviewer was responsible for the sound recording and took notes during the interview. The sound recording was carried using an iPhone 4 with iOS 7 and a Samsung Galaxy S4 with Android version 4.3. A

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pilot interview was first completed to practice the allocation of roles and responsibilities. Four speech language therapy students was interviewed of how the speech language therapy program prepares the student for working life.

The interview took place at the neuropsychiatric clinic. The participants all filled out a consent form also containing a question about their earlier experiences of pictorial supports. An interview guide was used. The issues were linked to the survey the staff recently had completed and focused the health professionals', parents' and children's views about the KomHIT materials. The children's and parents' degree of anxiety and possibility to be active and to participate during care and through the use of pictorial support was also discussed. The guide was used as a support for the moderator to hold the group on focus and in presenting the issues. Open-ended questions were used. A stimulus material consisting of examples of the pictorial supports, was placed on the table to help the participants stay on focus [23]. The moderator redirected the discussions when they were considered as drifting away too far from the targeted topics. At the end of the interview, the moderator summarized what had been said and the participants were given the opportunity to make clarifications [23]. The interview lasted for approximately one hour.

4.3. Transcription and analysis

The audio recordings from the interview was transcribed ortographically. Focus was on content rather than interaction patterns. The transcription was done at Level III, which meant that the utterances were transformed to complete sentences that began with a capital letter and ending with appropriate punctuation. Unfinished sentences, repetitions and hesitations were removed. Pauses and laughter was not marked [23]. Transcription Level III was chosen to facilitate for the participants to read through the transcription. The authors transcribed half of the sound recording each and then read through each part of the transcription, and compared with the audio recording. As a final step the authors listened to and discussed the pieces that were difficult to hear until consensus was reached. In the transcripts, participants were given a code and the names of individuals and entities were removed. The transcription was sent to the participants who had the opportunity to read, review and then approve it. Participants had a week to come back with changes. Participants were only allowed to revise their own utterances. The revision process proceeded until the participants were satisfied. One of the participants clarified some opinions, but did not remove any information. No other changes were made.

Qualitative content analysis according Graneheim and Lundman [24] was applied as a method of analysis. In the present study manifest content, ie content that is expressed directly and does not need interpretation, was in focus. Each step in the analysis was conducted jointly by the authors. To get an overview and to obtain an overall impression the authors began by reading the transcript several times. The transcription was inserted into a table in a word processing program and then divided into meaning-bearing units. This meant that utterances involving several topics were divided into smaller units. Utterances that was on other topics or lacked relevant content was deleted from the analysis. In case of disagreement about this, the authors listened to the audio recording until consensus was reached. The meaning-bearing units were

then condensed with the purpose of obtaining the core without affecting the content. The next step was to code the condensed units. The codes were printed, spread out on a table and then grouped in different categories based on their content. As the last step in the analysis, the categories were grouped together to form themes. When disagreements arose the authors first consulted the transcription and as a next step the audio recordings and discussed until consensus was achieved.

Meaning-bearing units	Condensed units	Codes	Categories	Themes
I think it helps to play down also it is not so mysterious.	It helps in making it more concrete and less mysterious	The information letter demystifies	Preparation	Pictures before visit
But it is only within pediatric care you are thinking. Because I belive in geriatrics and in care for the elederly, as they get old, there must surely be. I believe this would be great.	I'm thinking of care for the elderly, when people are older this would be useful .	Pictures should be used within geriatrics	Pictures in other areas of care	The need of pictures in health care

Table 3. Overview of the process of the content analysis and two examples

Credibility in this qualitative content analysis concerns how well the themes and categories were consistent with the transcribed data. One way to show this that also was used in this text, is to present representative quotations from the transcribed material [24]. This means that the data processing is presented in an explicit and transparent way, which facilitates the examination of the credibility [25]. An external check of the analysis was also conducted [23]. A senior speech language therapy student read twenty percent of the transcription and compared the content to the analysis and the identified codes, categories and themes. The external assessor found that the identified themes and codes were in concordance with the text except for one utterance that the authors had excluded as not being relevant. This was taken into account by the authors, who returned to the audio recording to ensure proper assessment.

4.4. Result

The content analysis of the interview data resulted in 18 identified categories that could be merged into 7 themes. These were: pictures used preparatory before healthcare visits, pictures used during healthcare visits, design, use, guidance, reactions in children, and the need of pictures in health care (see Table 4). Each theme and the included categories are described below in the text and used as titles. Examples from the transcribed texts, printed in italics, are presented for the majority of the categories.

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Themes	Categories
Pictures used preparatory before health care visits	Support for parents
	Preparation
Pictures used during health care visits	Pictures in waiting room
	Impact on testing
	Learning
	Structure
	Participation
Development of materials	Digital pictures
	Form
Use	Developmental and pictorial level l
	Opportunities for use
	Pictures as a resource
Guidance	Health care professionals as models
	Generalisation
Reactions in children	Anxiety
	Interest
The need of pictures in health care	Previous need for pictures
	Pictures in other areas of care

Table 4. Themes and categories identified in the content analysis

4.4.1. Pictures used preparatory before health care visits

4.4.1.1. Support for parents

The staff thought that the pictures was a support for the parents. The staff expressed the opinion that the parents' anxiety seemed to be reduced when they had been provided with the invitation letter with pictures and then had more information about what was about to happen during the visit. The pictures seemed to serve as a tool for the parents to explain what will happen to their children. The staff expressed that the invitation letter could play an important role for parents of young children and also for parents with insufficient understanding of Swedish.

> *"... I mean it is a support for the parents as well, explaining to the children, in that they have access to the pictures, so in that way I believe it's very positive."*

4.4.1.2. Preparation

The nursing staff thought the invitation letter made both children and parents feel safe because they know what will happen and who they are going to meet. The staff experienced that the parents were more prepared and better informed. The invitation letter made the visit less mysterious.. According to the staff, several parents had expressed that they appreciated the pictorial invitation letter.

"We really enjoyed to look at the pictures and checked, what's going to happen, well who is this, and so on. I believe this actually is good."

4.4.2. Pictures used during health care visits

4.4.2.1. Pictures in waiting room

Only a few of the staff had used the waiting room boards, but told that some parents had commented that the pictures were funny and that the children liked them. These boards may not be have been used in the best interest of the children because the parents were not accustomed to the use of pictorial support. The staff stressed that in spite of this the pictures still were important in demonstrating an approach to support communication.

4.4.2.2. Impact on testing

Some of the staff felt that the use of pictorial support could influence the evaluation and testing results. The perception was that the pictures facilitated the testing too much so that the purpose of some of the tests could not be fulfilled. The staff expressed that during the assessment of the child's communication skill the pictures should be used to enable the child to participate in the test situation but not to communicate. However, in some test situations pictures could not be used at all. Pictorial support was considered to be easier to use in a treatment situation.

"I can imagine it [visual schedule] would affect the ADOS-result. One would think, but if he had not pictorial support how he had reacted when..."

4.4.2.3. Learning

Most children and parents were unfamiliar with the use of pictorial supports. The staff expressed that it was problematic that they saw the children only occasionally and too little to really have them understand the use of the pictures, specifically those at early developmental stages. The staff thought it was easier for the children and parents to understand the use of the pictures if they consistently were provided with pictorial support in invitation letters, waiting rooms and personal interaction. The staff thought the children could gradually learn the meaning if they were recurrently exposed to the pictures and if the staff used a rich body communication to assist the children's understanding.

4.4.2.4. Structure

The staff felt that they did not need to use the visual schedule so often, but that it was great to use with children who have attention difficulties. For these children, the pictures provide structure and help to focus. The children also are provided with a concrete idea of how far they have proceeded during the visit.

"... And said, yes, but we're going to do this, and lined up the pictures so that the child can imagine. Yes now we can remove this, now we can take that one away. Then they are assisted in coping".

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Staff however also had the opinion that the pictures sometimes made them less flexible. They felt that they had to stick to the schedule, even when it was less well adapted. When they used pictures that were not so specific, it was easier to change the order during the visit.

4.4.2.5. Participation

The picture schedule seemed to facilitate participation for some children during examination or testing. The pictures could be used to direct the children's attention to something and to have children who were restless to sit down. Staff discussed that the situation could be perceived as less demanding when pictorial tools were used. A picture schedule was considered to give children control over the situation. Through the use of images the children had freedom to express what they wanted to do. The images had enabled communication between children and the staff, and had been used by the child to ask questions.

> *"And a little control of the situation as well, then you do what he picture says, and will not come up with something else that I do not know what it is. And you have the freedom of saying, that and that, and that I do, but not this."*

4.4.3. Development of materials

4.4.3.1. Digital pictures

Having access to pictures using a smartphone or tablet was considered to simplify the work. Being able to find exactly the correct one quickly was seen as an advantage. Children who were not interested in pictures might think they were more funny and interesting if they were presented on a phone or tablet. However, the staff also discussed the risk that the tablet could be associated with gaming or play. Therefore alternate forms for presentation of the pictures are needed for different children.

4.4.3.2. Form

The group also discussed the size of the images and some thought that the images being used were too small. Size and degree of detail of the pictures differs on an individual basis. The nursing staff did not think that it was necessary to use a particular or specified picture/symbol system but that it instead was the way of thinking that was important.

4.4.4. Use

4.4.4.1. Developmental and pictorial level

The staff thought that the pictures they used right now worked best with the children at more advanced level of development. For children at earlier stages, it could be difficult to understand the picture and associate it to the activity. Options should be available that would be more easy to use for these children, such as photographs and objects. The staff had the idea, that to be able to use a picture as a resource, it is not necessary to have a full understanding of the picture. To be able to focus the picture is more important. The staff must be quick in deter-

mining whether pictures would work for a specific child. Staff expressed that it was difficult to find and use pictures for more abstracts concepts.

> *"... Sometimes it doesn't mean anything to the children, the young children /... /are sometimes on a concrete level..."*

4.4.4.2. Opportunities of usage

The staff discussed during which occasions the pictures were best used. Some had the opinion that the picture schedules were difficult and unnatural to use for testing or assessment. Instead they were considered to be easier to use during intervention and more concrete activities, such as weighing and measuring the child. In some situations pictures were not used at all by the staff, either because an enhanced use of body communication was considered sufficient or that the sometimes long experience of working with children with neuropsychiatric disorders made them manage without. On the other hand experience in using pictures was considered to facilitate the use of pictorial support:

> *"but I believe that it is good if you use it (pictorial support) continuously to feel comfortable and relaxed"*

The opinion of the staff was that pictures was a great resource for those children who had difficulties with eye-gaze contact. To jointly watch the pictorial aid could be a way to establish contact without the need of direct eye-contact. The transition from the waiting-room to the examination-room was also considered to be facilitated through the use of pictures.

4.4.4.3. Pictures as a resource

The staff thought that the pictures generally made their work with the children easier. The pictures were looked upon as a resource or a tool that could be used when there was a need, for example when they got stuck out of some reason. Pictures did not always help out in these situations, but on the other hand never did any harm either

> *."... It is a privilege to have this resource and it is such a useful aid..."*

4.4.5. Guidance

4.4.5.1. Healthcare professionals as models

The staff felt that they could act as models for the parents so they could observe how pictures could be used in interaction with their children in everyday life. When the staff used pictures, this no longer seemed so strange or dangerous. The staff expressed that the parents often became positive when they could see themselves how the use of pictures facilitated the staff's communication with their child.

> *"... And see that it actually increases, yes it may well increase the child's understanding and ability to come up with something and show..."*

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4.4.5.2. Generalisation

The nursing staff wished to have access to pictorial supports or tools for various activities and games to give to parents in facilitating generalization to the home environment. According to the staff, parents are in need of concrete support to be able start up in practice as soon as they showed that they wished or wanted to. This was also clearly expressed by the parents. The staff thought it would be easier to show how pictures could be used and to answer parents' questions if they could provide the parents with some ready-made materials.

> *"Because they [the parents] kind of kick-offs mentally and get concrete ideas after they have had the opportunity to start up with something."*

The staff had the opinion that the generalization to the pre-school environment often was good due to the fact that many pre-schools already used pictorial tools. The staff only had to encourage these pre-schools in enhancing their use of visual support and sometimes also demonstrate the use.

4.4.6. Reactions in children

4.4.6.1. Anxiety

The nursing staff believed that the pictorial supports decreased anxiety in both children and parents. In particular, the pictorial invitation letter was considered to reduce the child's anxiety in that the child was provided with information about what was about to happen that was easy to understand. Sometimes when a child was anxious or restless the staff also could get back to this letter and go through what was going to happen. The staff was convinced that clear information reduced anxiety in children with autism. They also believed that pictorial support should be used with an increased number of children since most children would benefit from this.

> *"... We do not know how much it reduces anxiety during some visits, I think. I think, for you, for example, you know when you to go to the nurse, 'oh they won't do anything that I don't allow, for example."*

4.4.6.2. Interest

The staff told that many of the children were very interested in the pictures. They were curious and perceived the pictures as fun and exciting. The staff expressed that the pictures added a sense of playfulness to the visits at their clinic.

> *"It gets a little bit more exciting and appealing to kids when pictures are used in some way. They become more curious..."*

4.4.7. The need of pictures in health care

4.4.7.1. The previous need for pictures

According to the opinions of the staff there had been a need for pictorial support on the clinic long before the project was started. Parents had asked for photos of the staff and for information

about what would happen during the visits. The staff had experienced difficulties in describing this in a concrete way, which now easily could be done using pictures in the invitation letter. The staff meant that texted information only, could not generate the same type of conversations between parent and child as now was the case. Without the pictures it was more difficult for the parent to explain to the child what would happen. Some of the staff had previously created their own pictorial support by drawing or using photos when they felt that this was needed.

> *"And there was a need for this because I used to say to the parents when I met them the first time that you can take a photo of me with your phone and show to the child..."*

4.4.7.2. Pictures in other areas of care

The staff believed that the use of pictorial support was something that had come to stay within health care. They expressed that pictures would be good to use outside of pediatrics, for example within geriatrics, and with people with aphasia.

4.5. Further research

To further investigate the role of pictorial support in health care and within neuropsychiatric clinical work, it would be interesting to do a controlled group study comparing both communication and other aspects of care with and without the use of pictorial support. Doing a similar study like this, but with a larger number of respondents and interviews with children, parents and health professionals from different clinics that strengthen and further develop these results, is also important. It would also be interesting to study and compare the results for different groups of children – of varying age, diagnosis, communication profiles-and for different activities and types of pictorial supports.

5. Conclusion

This study is one of the first that describes an intervention aiming at increasing the communicative rights of children within the autism spectrum during clinical assessment and intervention. The pilot evaluation in the form of an interview with the multiprofessional team provides valuable information on how work with pictorial supports can function in practice.

The staff was generally very positive and expressed that the pictorial supports facilitated communication. The materials made both children and parents better prepared for the visits and the clinical procedures. The children liked the concrete visual material that also seemed to provide them with a higher degree of control in the situation. The children were more focused when the pictures were used and both children and parents also seemed to be more relaxed. However, it also emerged that there are still shortcomings and that further development is needed. The staff expressed the opinion that it was easier to use the pictorial supports in concrete activities, such as medical procedures, compared to for example assessments. Children at really early stages of development could not benefit so much of the existing materials but instead probably are in need of a more individually adapted support, as are some

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other children as well. It was also possible to see that some opinions of the staff were contradictory. For example, it was expressed that they as professionals in the field did not need pictorial support very often, but that many more children than expected were in need of pictures. This might be a symptom of the fact that this was a new intervention that had not been used for long.

Finally and in spite of this, the staff expressed that the use of pictures "have come to stay", both at their own clinic but also elsewhere within health care. They meant that the number of people that benefit of the use of visual support are much larger than could be imagined.

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Aetiology

Chapter 16

Etiology of Autism the Complexity of Risk Factors in Autism Spectrum Disorder

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Additional information is available at the end of the chapter

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1. Introduction

Autism Spectrum Disorder (ASD), also currently known as autism, refers to a group of complex behavioral disorders of varying severity, characterized by manifestations noted in early childhood, usually before the age of three and defined as impaired social communication and presence of restricted interests and repetitive behaviors, compromising the entire life of the individual (DSM-5). The etiology is very complex and heterogeneous, with numerous causes described, and includes genetic, epigenetic, or environmental factors in isolation or associated. It aggregates in families with the heritability being estimated at 0.50, but the individual risk and to what extent this is caused by genetic factors or environmental factors remains unresolved. These factors probably interact at least in the majority of cases, and thus the assessment of individuals and genetic counseling is further complicated [124].

Valuable information is been gained through the identification of candidate genes, though case-control and association studies and more recently by comparative genomic hybridization and whole exome and genome sequencing. In the epigenetic area, mechanisms such as genomic imprinting, epimutations and methylation have been identified [133]. Copy number variations (CNVs) have gained prominence on the stage of the discovery of the causes of autism. The *de novo* CNVs have been reported in 7% of simplex families and ~2% in multiplex families. Moreover, hypomorphic alterations in some genes suggest oligogenic inheritance. Recently, discoveries employing large-scale whole exome sequencing (WES) showed that one gene alone is not able to confer significant risk for autism. Instead, the most probable hypothesis is the contribution of several risk variants that are scattered in hundreds of genes. There

are approximately 4,000 genes involved in molecular pathways, gene regulation and functional domains that may contribute to neurodevelopmental disorders. It is noteworthy that the same genes can cause different disorders leading to an etiologic overlap [35].

One other issue that has emerged recently is that a significant number of synaptic proteins directly or indirectly affect the structure and function of neurons, dendrites and synapses. Subtle changes in the dendritic and synaptic structures can lead to huge changes in information processing. Dendritic branches and spines are essential for the formation and plasticity of neuronal circuits but are interrupted in many neurologic disorders, such as autism. In many cases the same mutations are observed in unaffected relatives. This suggests the existence of a compensatory mechanism or other genetic or non-genetic causes [140].

New findings on the genetic etiology of autism have pointed to the participation of regulatory regions of transcription factors, the microRNAs (miRNAs), a class of noncoding RNAs of ~22 nucleotides that suppress translation by pairing with miRNA recognition elements present in the 3'untranslated region (3'UTR) of target mRNAs. Candidate genes and sites of miRNA targets have been identified from these. It is known that the expression of many genes involved in autism is regulated by miRNAs. Single nucleotide polymorphisms (SNPs) have been described as modulators or creators of new recognition elements of miRNAs. Therefore, there is a hypothesis that SNPs disrupting the interaction between miRNA and genes can lead to the aberrant expressions of genes implicated in autism, resulting in susceptibility to disease or pathogenesis in at least one subpopulation of affected individuals [149].

Although the involvement of genetic abnormalities in autism is well accepted, recent studies have indicated that there is a similar contribution of environmental factors. However, studies related to the environment, especially those regarding toxic products, have not been systematically reviewed yet, as many studies have limitations, including a lack of reproducibility, small sample size, retrospective design, bias between cases and controls and non-use of an appropriate autism diagnostic tool. Thus, in general, there is a potential involvement of some toxic products in complex genetic-environmental interactions which act synergistically or in parallel on the brain in a way that increases the likelihood of developing autism.

Moreover, although some studies suggest that autistic characteristics are due to central nervous system (CNS) dysfunction, there is evidence of autism-related abnormalities that are not related to the CNS, at least in some individuals. Hence, the metabolic system, immune system dysregulation and oxidative stress have also been implicated in the etiology [107].

Furthermore, other new lines of research also point to the importance of the so-called "brain-gut axis" revealing the central role of the intestinal microbiota in postnatal development and maturation of the immune and endocrine systems that, in turn, control CNS signaling, brain function and behavior [151]. But studies on this line must be carefully analyzed.

The low recurrence related to any one cause is one of the most intriguing aspects of the etiology, as is the difference in the proportion of affected between the genders, because men are four times more affected by ASD than women [27]. Additionally, there is an association between increased paternal age and risk for ASD. This finding may indicate that *de novo* mutations,

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which are more common in older men, may play a smaller role in the incidence of autism than the familial genetic load [73].

Investigating and understanding the etiology of autism is extremely important for families because it allows a determination of the recurrence risk, the possibility of detecting other associated medical problems, an assessment of the molecular nature and cellular pathophysiology, and potential therapeutic approaches. In this context, the aim of this chapter is to provide the reader with an overview of these possible causes and others that may contribute to autistic behavior.

2. Common chromosomal alterations: 15q11-q13, 16p11.2 and 22q11.2

In addition to well-established genic syndromes, a lot of cases of ASD present with numerical or structural chromosomal alterations visible by conventional cytogenetic techniques [164]. Due to the high number of cases and the type and location of the genes described, the association of some chromosomal regions is well established in autism including: 1q21, 2q37, 7q11.23, 15q11-13, 16p11.2, 17p11.2, 22q11.2 and 22q13. Rearrangements involving these regions are detected by GTG banding however more sophisticated molecular techniques are recommended. High-resolution whole-genome analysis with array-based technologies have revealed genomic imbalances in at least 10% of cases [170].

Chromosome 15 is reportedly the most common site of autosomal abnormalities in autism with the duplication of 15q11-q13 being the most frequently reported alteration. This region contains at least 30 genes, several of which have been associated to ASD, neurobehavioral disorders, cognitive deficits, hypotonia, language delay and seizures [141, 154].This region, known for its genetic instability, contains many low copy repeats and segmental duplications. It is known as a critical region for Prader-Willi/Angelman syndrome and has a complex pattern of paternal and maternal imprinting; it contains at least five paternally expressed genes (*MKRN3*, *MAGEL2*, *NDN*, *C15orf2*, *snoRNAs* and *SNRPN-SNURF*) and two maternally expressed genes (*UBE3A* and *ATP10A*). Furthermore, epigenetic factors regulating 15q11-13 have been implicated in the presence of autism [6].

The phenotype involving recurrent ~600 kb microdeletions and microduplications in the 16p11.2 region is characterized by a spectrum of neurodevelopmental impairments including developmental delay and intellectual disability, epilepsy, autism and other psychiatric disorders which are all subject to incomplete penetrance and variable expressivity. This deletion is observed in ~0.5% of autism patients, making this the second most common abnormality in this disorder [48, 156]. Losses in candidate genes in this region, such as *ALDOA*, *DOC2A*, *HIRIP3*, *MAPK3*, *MAZ*, *PPP4C*, SEZ6L2, and *TAOK2*, seem to contribute to the ASD phenotype [171].

The 22q11.2 deletion is one of the most commonly known interstitial deletions identified in humans, and with a frequency of around 1:4,000 live births in the general population, it is related to DiGeorge Sequence/Velocardiofacial syndrome [98, 132]. Recent studies suggest that

the high prevalence of autistic behaviors in children with 22q11.2 deletions should not be viewed only as ASD but as prodromal symptoms preceding the onset of schizophrenia [9, 132, 153]. Individuals with hemizygosity of the 22q11.2 deletion represent genetically identifiable cases of ASD. However, the 22q11.2 gene(s) responsible for ASD have not been identified yet. *Tbx1* is one of the candidate genes, possibly through its role in diverse cell types, including prenatally and postnatally generated neurons.

Several large chromosomal microarray studies have reported the prevalence of CNV variants in people with particular features (e.g., autism, schizophrenia, and epilepsy) but few studies have investigated the prevalence in the general population. In a screening of 6,813 consecutive cord blood samples from a predominantly French–Canadian population to assess genomic CNVs, 23 children were identified with alterations in 15q11-q13, 16p11.2 or 22q11.2. Longitudinal follow-up studies are needed to determine the clinical consequences of CNVs identified at birth [146]. Anyway, considering the important implications for genetic counseling, these regions must be evaluated in ASD patients.

3. Copy number variations (CNVs)

Dysregulation of gene expression of several genes/loci converging on the same networks (overlay) and/or combinatorial effects of different deleterious genetic variations appear to exceed a threshold and result in the autistic phenotype. In support of these ideas, strategies based on bioinformatics have identified many candidate genes, showing that ASD can be triggered by different types of genetic variations in many different genes, a phenomenon known as non-allelic genetic heterogeneity [74, 138, 105]. This model is more accepted; combines both common and rare variations posing risk for ASD, particularly those involving synaptic genes and genes involved in neurogenesis [138]. Thus it is assumed that people with ASD have a set of genetic variants that predispose them to abnormal development of brain structures involved in processing social information (the "social brain"). But it is known that there is no common pathophysiology in ASD. This may result from mutations in many different genes involved in different functions [138]. The kinds of variants that incline to autism and can involve several genes at the same time are the CNVs.

CNVs are microduplications or microdeletions resulting from insertions, deletions or translocations in the human genome that are observed in the general population and commonly found in genic regions in individuals with neuropsychiatric disorders. They can be inherited or *de novo*, frequent or rare with a frequency of less than 1% of the population. A substantial portion of autism cases appears to result from rare CNVs with variations larger than 100kb; they are more common in individuals with ASD than in the general population [33, 83, 118].

De novo CNVs have been reported in 5-10% of cases of idiopathic ASD. Many studies have revealed that some CNVs occur at significantly higher frequencies than others and some are exclusively observed subjects and not found in normal controls. This has allowed the identification of new candidate genes which have not yet been described in the Autism Chromosome Rearrangement Database, such as *GABRA5, GABRA3, GABRG3, UBE3A, E2F1, PLCB1, PMP22,*

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AADAT, MAPK3, NRXN1, NRG3, DPP10, UQCRC2, USH2A, NECAB3, CNTN4, LINGO2, IL1RAPL1, STXBP5, DOC2A, SNRPN, E2F1, AADAT, NECAB3, GPHN, dlg2, HPCAL1, BDNF-OS and *IL1RAPL1*, (http://projects.tcag.ca/autism/). The new risk loci for ASD have functions that suggest an important role in the function and architecture of the brain; one CNV could interfere with normal biochemical pathways and predispose to the disorder [27, 46, 95). CNVs associated with ASD and schizophrenia are also associated with cognitive problems in control subjects showing a probable variable expressivity of these changes [134].

Although structural variations, such as CNVs, play an important etiologic role in the development of ASD as has been proposed by several authors since 2006, most of the results of different studies are not considered in the clinical evaluation of children with ASD, probably due to the rarity of individual variants, the lack of coverage of probes in clinical microarrays, the lack of reproducibility of studies that present different findings and the difficulty to understand the biology corresponding to some variants even when they are significantly associated with ASD. Nevertheless, clinical guidelines suggest that microarray-based tests are the first step in the genetic analysis of children with ASD [128, 68]; however this is not feasible in most cases of low-income countries due to the high cost of these tests.

4. Cellular adhesion molecules (CAMs)

While the majority of genetic mutations currently linked to autism are rare variants that change the protein-coding sequence of synaptic candidate genes, regulatory polymorphisms affecting constitutive and alternative splicing have emerged as risk factors in other diseases, accounting for an estimated 40-60% of general disease risk [131].

Neurons communicate via synapses, mainly mediated by precisely controlled intercellular interactions. Interactions between presynaptic and postsynaptic cellular adhesion molecules (CAMs) drive synapse maturation during development. CAMs provide "bridges", that is, cell-to-cell connectivity between pre and postsynaptic sites. These transsynaptic interactions are regulated by alternative splicing of CAMs RNAs, which ultimately determines neurotransmitter phenotype. Failure to generate the appropriate CAMs can result in loss of activity-dependent neuronal plasticity, and risk for developmental disorders, including autism. However, it remains unclear as to how many and which proteins are involved in the synaptogenesis process [161]. The postsynaptic proteome of excitatory synapses of a mammalian brain contains over 1,000 proteins, indicating complex protein-protein interactions that occur both within and between synapses [15, 30, 32, 47].

Typically, CAMs are located at the center of synapse and contain three domains: an intracellular domain that interacts with the intracellular scaffolding protein, a transmembrane domain and an extracellular domain which interacts with other CAMs [101]. Intercellular interactions in synapses mediated by protein-protein CAMs are involved in recognition and alignment of pre and postsynaptic sites, transsynaptic signaling, the exact location of neurotransmitter receptors and release of synaptic vesicles. There are several families of CAMs that have already been recognized, including neurexins (Nrxs) and neuroligins (NLS), neuronal transmembrane

proteins rich in leucine (LRRTMs), N-cadherin/β-catenin, ephrins and Eph, SynCAM receptors and integrins [161].

The Nrxs and NLS contain an extracellular domain that participates in the pre and postsynaptic interaction and an intracellular domain that is involved in multiple functional interactions and regulatory processes. They interact with high affinity via their extracellular regions [135, 136]. Nrxs create extracellular protein-protein interactions with the intracellular signaling cascade. NLS binds to areas of postsynaptic density (PSD), proteins which are supported by glutamatergic synapses. In postsynaptic sites, the NLS/Nrxs interactions cause an increase in the PSD agglomeration recruitment of postsynaptic N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). Thus, the binding of Nrxs and NLS helps to align presynaptic and postsynaptic receptor release (Budreck et al., 2013; Mondin, Tessier, Thoumine, 2013).

LRRTM proteins are a group of type I transmembrane proteins containing extracellular leucine-rich repeats and a short cytoplasmic tail. They play a key role in the development and maturation of synapses, but are also directly involved in synaptic transmission and more complex behavior [87]. Contactins (CNTNs) provide a set of glycan phosphatidyl-inositol (GPI) Ig-CAM links containing six N-terminal Ig-like domains and four Fibronectin Type III domains. CNTNs play an important role in the formation of axon connections in the developing nervous system. For example, Cntn-1 and Cntn-2 are involved in axon growth and guidance, and Cntn-6 is expressed in the presynaptic region in the developing nervous system [169].

As most neurological diseases originate as a dysfunction of neural circuits whose function is highly dependent on the accuracy of cell-cell adhesions, there is increasing evidence connecting several neurological disorders with mutations or altered expressions of CAMs. For example, mutations in the *NLS* and *Nrxs* genes are found in patients with autism [136]. Therefore, research on the role of CAMs will help provide a better understanding of the underlying mechanisms of pathogenic neurological disorders [172].

5. Synaptic vesicles

Alterations in neurotransmission and its components, such as synaptic vesicles seem to be one of the keys in neurological disorders. Abnormalities in synaptic vesicle endocytosis and recycling may contribute with this type of disorder. Exoendocytic cycling of synaptic vesicles, which are organelles of 40 nm in diameter, is involved in neurotransmitter release. Hundreds of synaptic vesicles, filled with neurotransmitters are found in each presynaptic nerve terminal. When presynaptic plasma membranes depolarize, Ca2þ-channels open and calcium flows into the nerve terminal, triggering the exocytosis of synaptic vesicles and releasing their neurotransmitters into the synaptic cleft. Calcium binds to synaptotagmin, and after exocytosis, vesicles are re-endocytosed, recycled, and refilled with neurotransmitters. Recycling can occur by multiple parallel pathways, either by fast recycling via local reuse of vesicles, or by slower recycling through an intermediate endosomal [137]. Also, a critical step in presynaptic differentiation is the clustering of synaptic vesicles near neurotransmitter release sites, the active zone, where vesicle fusion and exocytosis of neurotransmitters occur. Synaptic vesicles

at presynaptic terminals store neurotransmitters from presynaptic neurons such as gamma-aminobutyric acid (GABA) and glutamate [133].

Many presynaptic molecules are involved in the regulation of synaptic vesicle release, including CAMs. The family of adaptor protein (AP) complexes, AP-1, AP-2, AP-3 and AP-4 mediates various types of vesicle formation and selection of cargo molecules for inclusion in these vesicles. The synaptic vesicle process involves AP-2/clathrin-mediated endocytosis [133]. The structural composition of synapses may be altered by mutations or deletions in other scaffold proteins, such as those of the Shank family, neurexin and NLS. These changes may result in an altered number of receptors such as mGluR receptors or changes in the composition of NMDA and AMPA, and affect component signaling in PSD. Dysregulation in the synapse morphology induced by structural alterations and disturbed signaling might converge and lead to disrupted long-term potentiation (LTP) formation and plasticity, and a specific decrease in excitatory signaling by various genetic mutations, environmental factors, or immune system alterations, which would lead to an imbalance in inhibition and excitation as a likely cause of autism [26].

The main excitatory neurotransmitter in the brain, glutamate, modulates the neuronal formation and synaptic strength in the early phases of development due to its role in neuronal plasticity and cognitive functioning [88]. Glutamate receptors are diffused throughout the brain, in the cerebellum and hippocampus, regions implicated in ASD pathogenesis [25]. Genetic alterations in glutamate signaling have been found in association with ASD through candidate gene screening and genetic association studies and an imbalance in excitation and inhibition with glutamate signaling is proposed as a mechanism involved in ASD during the early development stages, between one and three years of age [112].

There are two types of glutamate receptors, metabotropic and ionotropic. Metabotropic glutamate receptors (mGluR) are G-protein coupled receptors involved in intracellular signal transduction and can be divided into three groups: Groups I (mGluR1 and mGluR5), II (mGluR2 and mGluR3) and III (mGluR4, mGluR6, mGluR7 and mGluR8). Group I receptors activate phospholipase C. Groups II and III are negatively linked to cyclic adenosine 3′,5′-monophosphate (AMP) production, but they differ in agonist selectivity. Two Group III receptors, mGluR7 and mGluR8, are located within the presynaptic grid, whereas mGluR3 and mGluR2 are located on the preterminal axons. Ionotropic glutamate receptors form ligand-gated ion channels (LGICs) and are labeled according to their prototypical agonists: NMDA, AMPA and kainate [25].

Some studies have focused on the endocytosis, docking, priming, fusion and recycling processes that may play a role in intellectual disability and ASD, but the functions of several vesicle components remain unidentified and more studies are needed to understand these processes [133].

6. Cytoskeletal dynamics

The cytoskeleton forms the backbone of neuronal architecture and is essential for axon growth and synapse formation. The microtubule cytoskeleton has an active role during different

phases of neuronal polarization; microtubules and their stability determine axon formation, they maintain the identity of axons and they regulate the dynamics of dendritic spines. Once the synapses have been formed, the neuronal cytoskeleton supports maturation and maintenance, and so the synaptic cytoskeleton is essential for the stabilization and remodeling of synaptic connections [40]. Actin filaments are the predominant component of the cytoskeleton in dendritic spines [20]. Changes in these key molecules mediating that bind to actin and members of the Rho family of small GTPases, such as RhoA, Rac and Cdc42 can disrupt this process [69]. These proteins play important roles in synaptic functions, dendritic branching, the formation and maintenance of dendritic spines and the growth and differentiation of neurites [133]. Their genes include *OPHN1*, *MEGAP*, *OCRL1*, *ARHGEF6*, *ARHGEF9*, *FGD1*, *LIMK1*, *PAK3*, and *IQSEC2* [133].

It is known that genetic alterations in the pathways controlling local protein synthesis in neurons contribute to diverse intellectual disabilities and ASD. A set of cytoskeletal proteins has been reported as mutated in these individuals. The resulting disorders are called synaptopathies with dysgenesis of dendritic spines being a recurrent anatomical feature. These include factors that regulate the dynamics of the actin cytoskeleton, such as GAPs and guanosine factors [12]. Mutations in the tumor suppressor genes, *TSC1* and *TSC2*, are also connected to the ASD mutant proteins that seem to disturb the dynamics of the cytoskeleton and the structure of dendritic spines [61]. Moreover, the microtubule-associated protein, *KATNAL2*, has emerged as a risk factor for ASD [105]. But the best example of dendritic spine defects is Fragile X syndrome. This disease results from a loss of function of the RNA-binding protein, the fragile X mental retardation protein (FMRP), which regulates dendritic targeting of mRNAs and controls protein synthesis and mRNA decay in neuronal soma and at synapses. High-throughput screenings have revealed that a wide array of neuronal mRNAs is targeted by FMRP, suggesting that simultaneous dysregulation of many proteins contributes to the syndrome, including cytoplasmic FMRP-interacting protein 1 (CYFIP1) [38].

New research has revealed many interactions associated with brain disorders, opening up new perspectives to define regulatory pathways shared by neurological disabilities characterized by dendritic spine dysmorphogenesis.

7. Translational regulation and the process of ubiquitination

It has been seen that many synaptic proteins are critical to the formation and maintenance of proper synaptic function. The expression level of many of these proteins may be tightly controlled by the balance between translation and turnover. The growing number of developmental cognitive diseases, whose underlying cause is a defect in the regulation of either translation or turnover, suggests that the equilibrium between these opposing processes is a sensitive point in establishing normal cognition and behavior [36].

Ubiquitination, the covalent attachment of ubiquitin to a target protein, regulates most cellular processes and is involved in several neurological disorders. Many genes in the ubiquitin

pathway and neuronal proteins that are targeted by the ubiquitin-proteasome system have been linked to cognitive deficits [57, 82].

Studies have highlighted an important role for protein degradation by the ubiquitin proteasome system (UPS) in synaptic plasticity [126, 91]. These observations suggest that changes in synaptic transmission involve extensive regulation of the synaptic proteome. The synaptic proteome is also affected by nonsense-mediated mRNA decay (NMD) that provides a quality control linked to translation. NMD has a role in degradation of aberrant mRNAs with a premature termination codon and the regulation of the transcriptome [109]. CNVs and mutations in several genes associated to NMD such as *UPF3B, UPF3A, SMG6, EIF4A3, RNPS1* and *RBM8A* have been identified as probable causes or predisposing factors for neurodevelopmental disorders such as autism [5, 76, 108].

UPS consists of a group of enzymes, an ubiquitin activating enzyme (E1), an ubiquitin conjugating enzyme (E2) and an ubiquitin ligase (E3), which are associated with ubiquitin ligases and proteasomes to mediate protein degradation. The ubiquitinated target protein is subsequently shuttled to a protease complex known as the 26S proteasome and subjected to degradative proteolysis. They also play a role in the regulation of cell signaling and cell cycle progression, and are associated with cytoskeletal elements. Thus, posttranslational ubiquitination modifies protein function and triggers the subsequent degradation of ubiquitinated proteins by the 26S proteasome. Several components of the UPS are required for proper brain development, axon guidance, and the development and plasticity of synapses. It has been shown that protein degradation via the UPS controls the appropriate synaptic balance, maintaining optimum levels of the protein, thereby promoting functional balance [23].

Several studies have shown a crucial role of UPS in neuronal transmission. For example, mutations in *UBE3A* have been associated with ASD. *UBE3A* encodes an ubiquitin E3 ligase that contains a domain that catalyzes the ubiquitination of target proteins. A reduction in density results in defects in synaptic plasticity [57]. UBE3A regulates the development of excitatory synapses by controlling the degradation of activity-regulated cytoskeletal protein (Arc or Arg3.1). Arc is critical for long-term memory formation and essentially every form of plasticity, including LTP, long-term depression (LTD), and homeostatic scaling (Greer et al., 2010). It has been shown that UBE3A-deficient mice, express high levels of Arc in response to synaptic activity, which coincides with severely impaired hippocampal LTP [78, 133]. Also, Arc regulates the ionotropic glutamate receptor (iGluRs) expression and trafficking. Findings from various experimental systems implicate iGluR dysfunction in ASD [148].

8. miRNAs

As previously reported, CNVs are recognized as important genetic factors in ASD, with a high prevalence of *de novo* CNVs in sporadic and familial cases compared with control subjects. However, studies conducted so far have highlighted a pathogenic role of CNVs in terms of changes in dosage of encoding protein genes without bearing in mind the potential involvement of non-encoded RNAs, particularly miRNAs, even with the inherent difficulties of this

type of study [120, 150]. Generally these two themes (CNV and miRNAs) are investigated separately.

A few studies have investigated the transcriptome in ASD samples of postmortem brains and some of them used mRNA from peripheral blood of patients [1, 54, 71, 110]. More recently, disruption of miRNA expression has been repeatedly reported in microarray studies and it is believed to be linked to the pathogenesis of autism (Sarachana et al., 2010; [28, 55]. However, lymphoblastoid cells are not representative of neural tissue and very few miRNAs exhibit consistent deregulation between studies.

According to [93], miRNA loci are underrepresented in highly polymorphic and well-validated CNV regions. One study investigated the pathogenic role of miRNAs in autism by checking associations with *de novo* CNVs. Twenty-four miRNA genes likely to play a pathogenic role in autism were identified on chromosomes 1, 2 and 22. Two, *mir-HSA-4436b-1 and 4436b-HSA-mir-2*, appear to be strong candidates. Unfortunately, the targets of these miRNAs were not identified [94]. The difference in penetrance of the deleted/duplicated genes may be explained by a variety of factors including: (i) pre-natal exposure to environmental risk factors; (ii) the presence/absence of functional SNPs in genes that encode proteins related to susceptibility for autism; (iii) epistasis; (iv) epigenetic factors and (v) the number and type of genes encoding proteins co-existing in different CNVs and overlapping in the same miRNA.

The *HEY1*, *SOX9*, *miR-486* and *miR-181b* are some candidate genes. All of these are involved in the development and function of the nervous system, and some, such as *HEY1*, are involved in Notch signaling networks [55]. However, a systematic analysis of CNV-miRNAs based on their interactions with target genes identified other miRNAs such as hsa-miR-590-3p, hsa-miR-944, miR-HSA-570, hsa-miR-34a, hsa-miR-124, hsa-miR-548f, hsa-miR-429, miR-HSA-200b, hsa-miR-195 and miR-497-HSA. Moreover, the miRNAs related with CNVs can explain the difference in levels of the important genes that are controlled by them. These CNV-miRNAs can also harm the overall biogenesis and processing of all miRNAs by targeting key molecules in the miRNA pathway [150].

On the other hand, dysfunction of neuronal miRNAs can result in a number of neuropathological conditions. It has been reported that neural miRNAs and their target mRNAs are co-expressed, suggesting their participation in feedback mechanisms to connect the transcriptional activation with the control of local dendritic protein synthesis [145]. Interestingly, the functions attributed to miRNAs overlap with growth abnormalities, delays and the disruption of neuronal maturation observed in the brains of autistic individuals. Aberrations in the translational control of multiple mRNAs mediated by targets of each miRNA may lead to the difference in phenotypes observed in ASD. Moreover, multiple miRNAs may target the same mRNA leading to phenotypes resulting from the converging of several loci in CNVs. Thus, a change in expression or level of miRNA will affect the expression of target genes and might have a pleiotropic effect that would produce a more severe autistic phenotype. However, one can not underestimate the clinical relevance of the deregulation of a single or a subset of CNV-miRNAs. Based on this, it is clear that the characterization of this relationship may illustrate the complexity of the underlying neuronal development, function and dysfunction that will eventually help in the understanding and treatment of autism [150].

9. Chromatin remodeling

Chromatin is defined simply and collectively as genomic DNA associated to proteins within the nucleus. There is a vast assortment of chromatin factors dedicated to the DNA packaging and the enzymatic functions involved in changing chromatin states. Nucleosomes are the primary unit of chromatin organization with a histone core (H2A/B, H3, and H4) and linking subunit H1. They keep DNA condensed and regulated by only releasing genes into the open conformation when their accessibility is needed [81]. Interestingly, disruptions in chromatin regulator genes are frequently the cause of neurodevelopmental and neuropsychiatric disorders. Chromatin regulators are widely expressed in the brain, yet symptoms suggest that specific circuits are altered when they mutate [143]

Chromatin regulator genes are also altered by *de novo* mutations in a small proportion of ASD cases. They are involved in various cellular processes such as transcriptional regulation, cell cycle regulation, genomic stability and DNA damage repair, but it is still unclear how mutations in chromatin regulators lead to behavioral phenotypes. Following deletion models, it is suggested that mutations that affect chromatin regulators can lead to ASD because they are "global regulators" that are placed on top of a hierarchy of regulators. The regulators interact with many genes and pathways, and thus disruption can simultaneously affect multiple target genes. Furthermore, it is proposed that these genes may also act as phenotypic capacitors, protecting processes of genetic development and environmental perturbations [138].

Methylation of the genome in certain areas appears to remodel chromatin and consequently the genes that are in this region. The regulation of each histone modification requires specific enzymes that add or remove the methyl or acetyl group. Several mutated genes associated to ASD encode histone demethylases, including *KDM5C*, a demethylase of histone *H3K4* implicated in gene repression and *JMJD1C*, a demethylase of histone H3K9 implicated in hormone-dependent transcriptional activation. Furthermore other genes involved in specific chromatin remodeling, such as *SMARCC1*, *SMARCC2*, *ARID1A*, *ARID1B*, *CHD8*, *CHD1*, *CHD3*, *CHD75*, and *ATRX*, have been described as mutated in rare cases [66, 77, 81, 105, 114, 111].

10. Epigenetic: genomic imprinting, epimutations, histone and DNA methylation

Epigenetic is a term used to refer to features of organisms, such as DNA and chromatin modifications, that do not involve changes in DNA sequence. The effects of environment on the phenotype are generally mediated through epigenetic mechanisms. These mechanisms, such as DNA methylation, can become programmed (e.g. imprinted). Genomic imprinting is a unique phenomenon wherein genes are expressed in a monoallelic way, and the choice of which allele is expressed is determined by the parental origin of the allele. Disruptions of the epigenome are called epimutations. Some of these appear to be corrected by normal germline-

specific epigenetic reprogramming and are therefore not transmitted transgenerationally, but others are not corrected and are transmitted over multiple subsequent generations [97].

Epigenetic mechanisms act on chromatin accessibility to transcriptional regulation. Then, they regulate DNA structure and gene expression that can be influenced by exposure to environmental factors. The most studied are the methylation of genes and modification of histones. Interestingly, epigenetic abnormalities are associated with several neurodevelopmental diseases. The connection between ASD and epigenetic comes from the identification of genetic mutations in imprinted regions and genes that control epigenetic processes. As cited before, among the most common chromosomal alterations in ASD are duplications of the imprinted region 15q11–13, which is maternally inheritable [96].

There are several possible explanations for the involvement of imprinted genes in autism. The imprinted brain theory of autism suggests that autism is a disorder of the extreme imprinted brain and would be caused by imbalances that involve increased effects of the 'paternal brain' relative to the 'maternal brain'. Imprinting has been hypothesized to explain the gender difference through the proposed action of unknown paternally imprinted loci on the X chromosome. Also, as mentioned, autism has been strongly associated with chromosomal abnormalities in the imprinted region of chromosome 15q. This includes the Angelman and Prader-Willi syndromes, as well the 15q duplication syndrome, which occurs in up to 5% of individuals with ASD. Imprinted genes may also contribute to autism indirectly as targets of other genes such a regulatory connection between *MECP2* (the gene associated with Rett syndrome) and the imprinted gene *UBE3A* (associated with Angelman syndrome). Besides this, imprinted genes are candidates for association with autism because of their functional haploid state. This feature may make them extremely vulnerable to rare mutations because the gene may be inactivated. Moreover, a single epigenetic change may lead to loss of imprinting, leading to biallelic expression and to gene dysregulation [173]. Both genetic and environmental factors can affect the imprinting process and alter the level of expression of genes. But the full contribution of genomic imprinting to the risk for autism is still unclear.

The imprinted genes are expressed in several types of tissues but are highly expressed in the brain. Human neurons require extensive methyl modifications throughout development and postnatal life. Several important posttranslational modifications of histone core subunits within nucleosomes involve methylation, an epigenetic mechanism. Recent unbiased genome-wide analyses have turned up a multitude of novel candidate genes that encode nuclear factors implicated in chromatin remodeling, histone demethylation, histone variants, and the recognition of DNA methylation. Both histone and DNA methylation patterns are highly dynamic processes in the early development phase that correlate with dynamic changes in cell lineage and differentiation events. Interestingly, mutations in autism have been found in several genes encoding proteins involved in demethylase reactions, that is, reactions that remove methyl groups from histones or DNA [81].

The mechanism of action of the *SHANK3* gene (also known as ProSAP2) is an example of this phenomenon in ASD. The three members of the SHANK family, *SHANK1*, *SHANK2* and *SHANK3* are expressed in different regions of the brain. *SHANK3* is strongly reported to be involved in the etiology of autism since several mutations have been identified in a particular

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phenotypic group of patients. *SHANK3* regulates the structural organization of dendritic spines and is a binding partner of NLS. It codes a synaptic scaffolding protein enriched in PSD of excitatory synapses and plays important roles in the formation, maturation and maintenance of synapses. Haploinsufficiency of this gene is related to the 22q13.3 deletion syndrome (known as Phelan-McDermid syndrome), a developmental disorder which is characterized by severe language and speech delay, hypotonia, global developmental delay and autistic behavior. It is possible that loss of one copy of this gene makes the nervous system more vulnerable to degeneration in the long term and less able to recover after psychiatric and somatic events. Five CpG-islands have been identified in this gene, and tissue-specific expression is epigenetically regulated by DNA methylation. Much evidence in animal models has shown that *SHANK3* variants are expressed in the developing rodent brain with expression being regulated by DNA methylation of intragenic promoters [39, 147].

[75] reported that mothers of autistic children show significantly lower levels of methylfolate and methionine, two essential precursors for methylation in DNA compared to a control group, but methylation-inhibiting protein levels and S-adenosylmethionine (SAM), adenosine, and homocysteine were elevated. SAM has a role in the DNA methyltransferase reaction, which produces S-adenosylhomocysteine (SAH) and methylated DNA. The SAM/SAH ratio is considered to be an indicator of DNA methylation potential.

Additionally, oxidative stress in brain cells caused by environmental and genetic factors leads to decreased activity of the methionine synthase enzyme which participates in DNA methylation processes. When the activity of this enzyme is impaired, affected individuals can exhibit attention deficits and other signs, including autistic behavior symptoms due to defects in the expression of genes controlled by this epigenetic mechanism [42, 104]. Therefore, environmental factors may also activate intracellular pathways during embryonic development, causing epigenetic changes in neural function that would explain the relationship between environmental signals and the genome in the regulation of individual differences in behavior [166].

A study in Sweden with 208 autistic children showed an association between advanced paternal age and an increasing risk for ASD in offspring. Autistic-like traits in the normal population are associated to both young and advancing paternal age and the autistic similarity in twins seems to increase with advancing paternal age. Exposure to toxic agents during life, *de novo* mutations in germ lines and epigenetic alterations are correlated factors [72, 90]. Advancing age in mothers has also been reported as a risk factor for ASD [116].

Thus, epigenetic alterations may be the biological targets through which environmental factors can cause autism. Imprinted genes may be associated with autism because they are involved in brain development and also because they may be more vulnerable to genetic or epigenetic mutations. Some features of ASD are highly consistent with epigenetic dysregulation such as the discordance between monozygotic twins, parental origin and the gender-dependent effects of some alterations. The cause of autism is not just by congenital genetic defects but can also be caused by environmental factors via epigenetic factors, with epigenetic modifications being affected by environmental factors including fetal exposure to drugs.

11. Environmental factors

11.1. Toxicity during neurodevelopment

Although the involvement of genetic alterations in ASD is clearly accepted, new studies point to a similar or even greater contribution by environmental factors, particularly environmental toxicants. Toxic chemicals cause dysregulation of the developing human brain by interacting with the genome or through direct toxicity.

The developing human brain is exceptionally sensitive to injury caused by toxic chemical exposure with several developmental processes being highly vulnerable. The dissemination of chemical industrial agents in the environment is important contributor to the call "global silent pandemic of neurodevelopmental toxicity" [63]. An estimative by U.S. National Academy of Sciences (NAS) shows that 3% of all neurobehavioral disorders including ASD, attention-deficit hyperactivity disorder and dyslexia are caused directly by exposure to environmental toxics and that another 25% are caused by interactions between environmental factors and inherited susceptibility [103].

About 80,000 new synthetic chemicals have been developed in the past 50 years, but only about 20% was screened for potential toxicity in early neurodevelopment. The human fetus is susceptible and not well protected against industrial chemicals, because the placenta does not block the passage of all toxicants from the maternal to fetal circulation. The individual's brain is unique and individual variability in genetic susceptibility can influence responses to environmental toxicants [62, 79, 106].

Exposure to many environmental toxicants has been correlated to autism including pesticides, polychlorinated biphenyls, solvents, toluene, toxic waste, and heavy metals such as mercury, lead and arsenic, besides exposure to automotive air pollution [115, 132, 152]. On the other hand, there was a false indicative association between these disorders and vaccines such as the measles, mumps, rubella vaccine and thimerosal-containing vaccines against diphtheria, tetanus and pertussis vaccine. One meta-analysis, combining the results of five previous studies involving 1,256,407 children with five case-controlled studies with a further 9,920 children show that there was no relationship between vaccination and autism [144].

There is thus strong evidence that the relation between environmental and genetic factors may converge to neurotoxic mechanisms that could lead to behavior disorders. But what kind of biological mechanisms would be involved in the causation of autism due to toxic agents? Epigenetic mechanisms are known to affect the subsequent gene expression in the brain as has already been described in this chapter. Toxics can lead to a modification in epigenetic gene expression, resulting in methylation, histone modification or changes in non-protein-coding RNA [60]. However, possible individual susceptibilities to toxicants implicated in ASD, including altered detoxification, genetic factors, oxidative stress, altered neuronal development, epigenetic mechanisms, synaptic function, hormonal factors, etc., may amplify the effects of toxicants during the prenatal and early postnatal periods [123]. The susceptibility to effects of environmental toxicants needs more attention and studies.

11.2. Oxidative stress

ASD also can be characterized by some physiological abnormalities, such as oxidative stress and immune dysregulation/inflammation. Many of the behavioral and cognitive features of ASD appear to arise from dysfunctions of the brain but studies have documented physiological abnormalities in organs other than the brain [122].

Many studies have reported genetic variations in glutathione-related pathways associated with autism, such as lower concentrations of reduced glutathione (GSH), higher levels of oxidized glutathione (GSSG) and a decrease in the GSH/GSSG redox ratio, along with a lower mitochondrial GSH reserve in individuals with ASD compared to controls [19, 2952, 65, 75 , 121]. Moreover, ASD severity has been correlated with lower GSH levels and markers of increased oxidative stress [2, 56, 123]. Oxidative stress studied in postmortem brain samples from individuals with ASD demonstrated low levels of GSH, the major cellular antioxidant, oxidative damage to proteins, lipids and deoxyribonucleic acid (DNA) as well as alterations in the activity of enzymes important for redox metabolism [123, 142].

Adaptive responses to oxidative stress were shown by [102], when significantly lower methionine synthase mRNA levels and lower homocysteine and cystathionine concentrations were observed in the frontal cortex of the brains of ten individuals with autism compared to ten controls.

Also it is possible that the reduced transportation of folate into the brain as a consequence of the folate receptor alpha autoantibody or mitochondrial dysfunction could reduce the methylation process and glutathione metabolism. Many findings reported for the brain (oxidative damage to lipids, protein and DNA, glutathione abnormalities and reduced function of enzymes essential in oxidative stress regulation) have been found in the blood, immune cells and cell lines from individuals with ASD, raising the question of whether these findings are specific to the brain or whether they represent a more general process [53, 123].

11.3. Immune system

Dysfunctional immune activity, both innate and adaptive, can impact neurodevelopment, cognitive function and behavior, suggesting a profound effect on neurodevelopment. Some studies in individuals with ASD have reported evidence of immune dysregulation and inflammation related to ASD, including disruption of genes of the immune system with elevations of tumor necrosis factor-alpha (TNF-α) in lymphocytes and amniotic fluid, alterations of immune proteins, and increased levels of cytokines, expression in genes related to immunity and microglial cell activation in brain tissue [113]. The expression of inflammatory genes in brain tissue was studied by [163], who reported that nuclear factor-kappa β expression in the orbitofrontal cortex was increased in individuals with autism compared to controls.

Microglias, a type of glial cell, are the resident macrophages of the brain and spinal cord. They therefore act as the first and main line of active immune defense of the CNS and participate in immune surveillance of the CNS and synaptic pruning in normal neurodevelopment. They are activated to eliminate some agents and damaged cells via phagocytosis, but, they may increase inflammation if chronically activated by releasing proinflammatory cytokines and

free radicals [41]. Changes in microglial morphology and gene expression are seen in many psychiatric disorders and neurodegenerative diseases, such as Alzheimer's, Parkinson's, Multiple Sclerosis and autism. [100] and [165] reported that microglias in the dorsolateral prefrontal cortex were frequently located closer to neurons in ASD individuals compared to controls. Another study with autism showed microglial activation in the cerebellum, brainstem, corpus callosum, fusiform gyri, superior temporal gyri, anterior cingulate, orbitofrontal, and parietal lobes [139].

Proteomic analysis indicates that the levels of many immune proteins in plasma, such as cytokines, chemokines, complement proteins, adhesion molecules and growth factors are altered in ASD [113]. Increases in plasma levels of pro-inflammatory cytokines [interleukin (IL)-1β, IL-6, IL-8 and IL-12p40] as well as macrophage migration inhibitory factor (MIF) and platelet-derived growth factor (PDGF), have been reported in ASD [11, 64].

Alterations in immune mediators can occur at an early stage of development and might alter NMDA and NMD receptor-mediated excitatory synaptic transmission and plasticity, which is relevant to ASD (Escobar et al., 2011). These immune mediators may be related in LTP which is involved in synaptic plasticity in learning and memory processes. IL-1 influences many molecular components of LTP, such as NMDA and AMPA receptor signaling and glutamate release. IL-6 is involved in the generation of LTP and an increase in IL-6 leads to a reduction of insulin-like growth factor (IGF)-binding protein 3 and IGF1 [43, 117]. Furthermore, other cytokines, such as IL-18, IL-1b, and TNF-α, act on AMPA and NMDA receptors in different ways [25].

Increases of pro-inflammatory cytokines (including TNF-α, IL-6 and granulocyte-macrophage colony-stimulating factor), a T helper cell type 1 cytokine (interferon gamma) and a chemokine (IL-8) were reported in postmortem frontal cortex brain samples of autistic individuals, but no significant differences in T helper cell type 2 cytokines were identified (IL-4, IL-5, and IL-10) [86]. The cytokines IL-2 and IL-4 have been shown to influence repetitive and cognitive behaviors. Mice treated with IL-2 showed an increased "climbing behavior" that is thought to denote repetitive behavior, a pattern of behavior that is characteristic of ASD.

There is evidence suggesting a role of immune dysfunction in ASD symptoms, but further investigations should be carried out to clarify these findings because it is still unknown whether these changes are a primary cause or a secondary consequence of neuronal deficits.

11.4. Microbiota and autism

Gastrointestinal (GI) disorders are a comorbidity of autism and interestingly have a strong correlation with disease severity [7, 16]. Thus, a growing number of papers point to the importance of the so-called "brain-gut axis", revealing the central role of the intestinal microbiota (the new name of "microflora") in postnatal development and maturation of the immune and endocrine systems for control signaling in the CNS, brain function, and behavior [51; 158].

Individuals with ASD often suffer from GI illnesses, e.g., diarrhea, constipation, bloating, and gastroesophageal reflux [22, 3]. The composition of the microbiota is influenced primarily by

genetic factors, age and diet [80, 168], although the interactions between these are multifactorial and not well defined yet [21].

Thus, several studies have been conducted in an attempt to profile the microbiota in ASD compared with healthy siblings and controls [4, 51, 59]. While some authors have reported little or no differences in the composition of the intestinal flora between children with ASD and their unaffected siblings, the imbalance in the intestinal microbial composition in samples of ASD has been identified, especially when compared to controls [49, 50].

Analyses of the feces of patients with ASD have revealed that the microbiome of ASD is significantly different to controls and consists in over 1,000 different species compared to unaffected children. Of the phyla, patients with autism have underrepresented *Firmicutes* and actinobacteria, especially bifidobacteria, and over-represented *Bacteroidetes* and proteobacteria compared to control individuals [49, 51, 119].

Interestingly, non-autistic siblings often presented intermediate microbiota profiles between ASD and controls [49, 155], possibly due to genetic factors, but also as a reflection of shared environmental conditions. These studies are complicated by the fact that autistic individuals often receive medications such as antibiotics and are often on special diets or have repetitive eating habits, both of which can alter the composition of the microbiota [89].

Interestingly, although *Bacteroidetes* are over-represented in ASD feces, the presence of the genus *Prevotella* and other fermenters, albeit in lesser amounts, has been described in the gut of children with ASD. *Prevotella* do not only have the ability to synthesize vitamin B1, which attenuates the ASD symptoms, but it is also considered a central niche to maintain the structure of the intestinal microbial community of healthy humans [10, 13, 162]. Moreover, *Propionibacterium* and *Clostridium* that are over-represented in the intestine of ASD, produce propionic acid, a short-chain fatty acid capable of passing the gut-blood-brain barrier thereby changing neurophysiological processes by binding to acetyl-CoA and acetyl-carnitine which are involved in mitochondrial lipid transport. Recent experiments have shown that administration of propionic acid in young mice causes mental retardation with cognitive disabilities, innate neuroinflammatory response and restricted, repetitive behavioral, symptoms consistent with autism [53, 92]. Propionic acid induces behavioral and functional alterations in the brain of animals. Most likely, the presence of this acid alters mitochondrial function. Taken together, these reports support a view that the metabolism of proteins and the host/pathogen relationship is altered in patients with autism [99].

Few studies have considered a deregulated metabolism of fecal levels free of amino acids in autism. Certain amino acids, in particular glutamic acid (Glu), act as neurotransmitters in the center of the CNS. An excess of Glu leads to neuronal cell death and plays an important role in the pathophysiology of several neuropsychiatric disorders [127]. High levels of Glu were found in fecal samples of autistic children [37]. As it has a role in brain development, the findings support the hypothesis that glutamatergic neurotransmission is involved in ASD [130].

The microbiota might also be involved in the etiology of the disease via interactions with the immune system. Some of the possible mechanisms described above are likely to involve

changes in the global balance of the entire microbial community, while others may be exercised by certain bacteria. More studies are needed to clarify whether the gut microbiota in fact plays a role in ASD. These include prospective studies to address the issue of cause and consequence, and intervention studies aimed at modulating the microbiota with probiotics or dietary interventions. The right profile, the categorization of patients and control groups, with the application of molecular techniques to verify the profile of fecal microbiota and urinary metabolome will corroborate the underlying relationship between gut microbes and the host [34].

Some authors believe that the action of microbiota may have much wider effects on the physiology of the host than originally thought, and emerging evidence shows that it may include modulation of brain activity and behavior. Differences in the composition of the microbiota between individuals with ASD and healthy controls were identified in several studies, both based on bacterial cultures and on molecular methods [18]. However, changes in bacterial diversity that were reported in one study [51] were not confirmed by another [158]. The direct comparison between studies is complicated because different methodologies are employed and study groups may not be directly comparable due to the heterogeneous nature of ASD [89]. However, if the differences in gut microbiota between autistic children and controls are one of the causes of the disorder or the result, could have implications on the diagnosis, treatment and prevention [37].

Nevertheless, despite the substantial amount of data, it is not possible to clarify whether the results represent the presence of a causative agent, or reflect a consequence of treatment, or whether they are nothing more than confounders. This has to be considered and caution is needed before recommending "miracle diets" to the child and family that may only increase the anxiety in respect to symptom improvement.

12. Etiology and mechanisms of sexual differences

It is well known that ASD affects more males at a ratio of 4 boys:1 girl. Some studies suggest that gender differences in phenotypic presentation, including less severe manifestations of restricted and repetitive behaviors in girls, seem to affect this ratio. Genetic studies show that girls seem to be more "protected" from the effects of inherited and *de novo* variants that cause ASD than boys. This suggests that genes that participate in sexual development and/or sex hormones, particularly testosterone, may modulate the effects of genetic variations in the autistic phenotype [157].

Despite the fact that ASD is more prevalent in boys *de novo* mutations are also more frequent in girls with ASD. The female protection theory fits in with the model of loss of robustness. According to this model, besides the variations between individuals, there is a difference in the average degree of robustness of the brain between males and females. According to this hypothesis the development of the female brain is more robust, and this may explain the higher rate of severity of behaviors when *de novo* mutations are present in girls with ASD. The brain can also be more vulnerable compared to other organs because it is a complex organ that

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develops later in life and is mainly composed of terminally differentiated cells. In the first year of life, the brain may be particularly sensitive to reduced robustness because social development depends on signals from the environment [138].

Although neurodevelopmental systems evolved to be robust, they can be vulnerable to disturbances in a specific subset of genes called phenotypic capacitors [85]. Phenotypic capacitors are genes that act against disturbances and thus contribute to the robustness of the phenotype. Thus, phenotypic capacitors, when operating normally, can prevent the development of diseases such as ASD, even in patients exposed to genetic and environmental risks. This means that girls are less likely to develop ASD, but when they have, they tend to have a more severe phenotype [138].

There seems to be unknown factors that "protect" females from ASD [157]. Recent genome studies showed that, on average, women with ASD have more mutations than men, including single nucleotide variants (SNVs) and CNVs [74, 84, 105]. Furthermore, *de novo* CNVs in females were larger and included significantly more genes than males [84].

Moreover, not all genes in the inactive X chromosome are inactivated, and the genes that escape X inactivation in females are revealing some interesting insights into gender differences related to chromatin. *KDM5C* and *JARID1C* are genes that escape X chromosome inactivation (160). In addition, the gene encoding O-linked N-acetylglucosamine (O-GlcNAc) transferase (*OGT*) which regulates chromatin remodeling factors is less expressed in males than in females and the expression is reduced further by prenatal stress [70]. These sexual and epigenetic differences must be investigated further in respect to the protective effect of the female gender in autism [81].

Recently, gender-specific gene expression obtained from the transcriptome of normal human brain development using a bioinformatics approach suggested that male-biased genes are enriched for the processes of extracellular matrix formation/glycoproteins, immune response, chromatin, and cell cytoskeleton. These pathways have been repeatedly implicated in autism and demonstrate that autism candidate genes are also enriched for these pathways. Furthermore, the development of the male brain may be naturally more susceptible to environmental factors as its normal development is more strictly dependent on the immune system [167].

A gender-dependent difference in the incidence of neural tube defects has been described. It was speculated that these defects are due to a synergistic effect between the gene expression of *SOX9* and *Barx1*. *SOX9* is an essential transcription factor for skeletal development, but it is also involved in the development of the male phenotype [14], thus contributing to the increased risk of autism in males. Interestingly, a study showed up-regulation of *SOX9* in autism [55].

On the other hand, altered behaviors in ASD are often related to a “more masculine” pattern of behavior linked to testosterone. However, although current levels of steroid hormones appear to be altered in patients with autism, the data indicate that prenatal testosterone by itself does not seem to be sufficient for the disorder to develop [125].

Differences between individuals with an atypical karyotype (monosomy X or Y or X-polysomy) and those with a typical karyotype are often interpreted as being significant for the

difference in susceptibility between genders. However, it is likely that many of the differences arise because of hyperexpression or hypoexpression of genes in pseudo autosomal regions that escape X inactivation, thereby being similarly expressed in men and women with a typical karyotype. The addition or loss of an X or Y chromosome, which leads to altered protein levels that are atypical or typical for both men and women, cannot explain the gender difference in ASD. However, some genes on the X chromosome are not in these regions and have no corresponding functional alleles on the Y chromosome, and escape X inactivation in some circumstances [125].

Moreover, the *SRY* gene is mapped in a region on the Y chromosome and can also directly regulate the gene monoamine oxidase A (MAOA) that is located in the Xp11.3 region and encodes a key enzyme in the breakdown of catecholamines and other monoamines. SRY can directly affect transcription in the brain [159]. As individuals diagnosed with ASD are found with changes in catecholamine and metabolite levels in the dependent activity MAO-A and autism severity is associated with child and maternal MAO-A genotypes, the disruption of the synthesis of catecholamines may be modulated by the gender-specific *SRY* gene associated with ASD. Several genes on the Y chromosome are expressed in the brain. Since this leads to a specific expression of gender in the brain, these genes, some of which play a role in catecholaminergic functions, are candidate genes for the increased susceptibility to ASD in males. An investigation of the role of these genes will possibly clarify the gender-specific mechanisms underlying ASD and thus help in the understanding of the etiology of ASD [31, 125].

Another factor that may contribute to the skewed gender ratio in ASD is parental age. Increased parental age is known to increase the risk of a child with ASD [45] and there are some indications that parental age affects the gender ratio of children diagnosed with ASD [125]. The male-female ratio dropped from 6.2:1 in under 30-year-old parents to 1.2:1 in parents older than 44 years old [8]. This finding may be related to the higher frequency of *de novo* mutations which are more common in older men and seem to play a minor role in the gender bias in the incidence of familial ASD. However, it is still not clear whether this effect is true for simplex families, which are most representative of ASD in the general population [125].

13. Conclusion

Thus, considering all that has been studied about ASD, it is difficult to conduct a comprehensive analysis about the etiologic complexity, without running the risk of over or under estimating some factors. On consulting the available literature on ASD, there is an impression that all can cause autism. The truth is that everything that affects the CNS system can interfere with mental health and this opens up a universe of possibilities. The gene expression, immune susceptibility and environmental stressors, even those that affect men more than women, need to be organized using a multidisciplinary approach in order to explain what actually happens in normal CNS development within the first three years of life. From there, the goal is to have a method of comprehensively analyzing each particular case to try to obtain specific treatment. While this is not available, it is interesting to investigate the most common risk factors and give support to the patients and families in order to improve their quality of life.

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Chapter 17

Possible Endophenotypes in the Search for Genetic Risk Factors in Autism Spectrum Disorders

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Additional information is available at the end of the chapter

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1. Introduction

Autism Spectrum Disorders (ASD) are complex neuropsychiatric conditions characterized by stereotypic behaviors and conspicuous deficits in social communication. It has been demonstrated that there is genetic and clinical heterogeneity in these disorders. Inherited and/or de novo genetic factors, as well as environmental and epigenetic components have been shown to be involved in the etiology of ASD. Among the common comorbity are epilepsy and seizures, gastrointestinal problems, depression, anxiety, hyperactivity (including ADHD), Tourette syndrome, phobias, dysmorphic features, and psychotic disorders [1-5].

The etiological role of genetic factors in ASD has been evaluated by twin studies; the concordance found in monozygotic pairs is higher than the concordance in dizygotic twins (36 to 91% versus less than 32% [6]). Concordance estimates for both types of twins have been reported to be higher if the analyzed phenotype is ASD as opposed to narrow phenotypes [7].

Heritability of ASD has been estimated to be as high as 90%, although a more recent report suggests that it may be about 19-35% in males and 50-63% in females [8]. While some cases are considered sporadic and have been associated with mutations, others are familial and may tend to be associated with relatively common genetic variation [9].

Genes related with synaptic development, signaling, chromatin remodeling, transcription, methylation, neurotropism, and neuroptrotection are probably involved in ASD. These genes may include some that code for neurexins, neuroligins, shanks, reelin,

integrins, cadherins, contactins, and neutrophins. Linkage and association with ASD have been described in different regions of autosomes that harbor candidate genes (Table 1, figure 1) [10-17]. In addition, as table 2 shows, the X chromosome has also been implicated in ASD (Table 2, figure 1) [18-20].

Gene symbol	Product
SLC25A12	Solute carrier family 25 member 12
OXTR	Oxytocin receptor
GRIK2	Glutamate receptor ionotropic kainate 2
RELN	Reelin
MET	MET protooncogene
FOXP2	Forkhead box P2
CADPS2	Calcium dependent activator protein for secretion 2
EN2	Engrailed 2
CNTNAP2	Contactin-associated protein-like 2
BDNF	Brain derived neurotrophic factor
SLC6A4	Solute carrier family 25 member 4

Table 1. Genes frequently linked or associated with ASD in autosomes

Gene symbol	Product
NLGN4	Neuroligin 4
NLGN3	Neuroligin 3
FMR1	Fragile X mental retardation protein
MECP2	Methyl CpG binding protein 2

Table 2. Genes frequently linked or associated with ASD in the X chromosome

Besides Fragile-X syndrome, other single-gene disorders are sometimes associated with ASD. Rett syndrome (MECP2 gene) is an autism-related condition. Tuberous sclerosis (TSC1 and TSC2 genes) may account for 1 out of 10 cases of ASD. Furthermore, 50% of individuals with Smith-Lemli-Opitz syndrome (DHCR7 gene) and 10% of those with phenylketonuria (PAH gene) may have ASD; in addition, adenylosuccinase deficiency, characterized by psychomotor delay, is often comorbid with epilepsy and autistic features [17, 21-23]. As described earlier, epilepsy is a common comorbidity in patients with ASD, and it has also been associated with region 15q11.1–q13.3 (ubiquitin-protein ligase E3A gene,UBE3A), TSC1 and TSC2 genes, MeCP2, CNTNAP2, SYN1, Fragile X syndrome, 1q21.1, 7q11.23, 16p11.2, 18q12.1, 22q11.2, and 22q13.3 (SHANK 3 gene).

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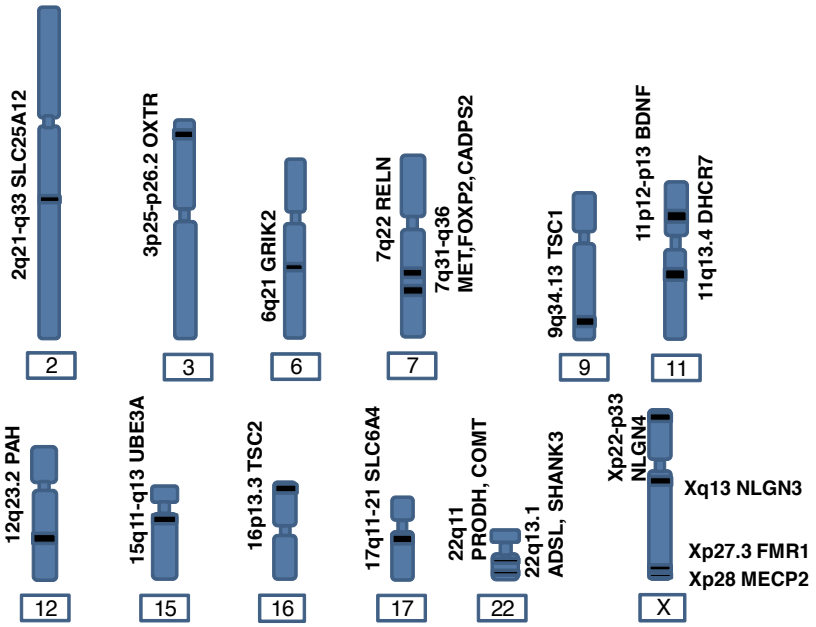

Figure 1. Chromosomal regions frequently linked or associated with ASD

Chromosomal anomalies such as deletions, duplications, inversions, balanced and unbalanced translocations, and aneuploidies have been described in some children with ASD [24]. For example, deletions on region 22q11-q13, which is associated with velo-cardiofacial syndrome, have been identified in about 1% of children with ASD; besides SHANK3, this region harbors two genes that have been associated with ASD, that code for proline dehydrogenase (PRODH) and catechol-o-methyltransferase (COMT) [25]. According to a meta-analysis, copy-number variants and truncating mutations in SHANK genes may be present in almost 1% of patients with ASD (SHANK1 in 0.04%, SHANK2 in 0.17%, and SHANK3 mutations in 0.69%) [26].

De novo chromosomal deletions or duplications have been identified in about 7 to 10% of patients. The 15q11-q13 chromosomal region, that includes a locus for the Prader-Willi/Angelman syndrome, is affected in 1% to 4% of children with ASD. Moreover, the phenotype of a supernumerary chromosome 15 includes autistic features such as developmental delay, mental retardation, neurological signs and behavioral disturbances. A 3.7 megabase deletion (Smith Magenis Syndrome) or duplication (Potocki-Lupski syndrome) on the 17p11.2 region is also associated with ASD [27]. Likewise, deletions on the short arm of chromosome X (NLGN4 gene) and an inversion on 7q (at common fragile sites) have been implicated in ASD [28].

Specific environmental and epigenetic factors have also been associated with ASD. For example, advanced paternal age at conception of the child, especially in non-familial cases, could impact the vulnerability to these disorders with de novo mutations [29, 30]. In addition,

errors in DNA methylation during spermatogenesis may affect the next generations. Recently, it was found in a mouse model that older fathers had a significant decrease in methylation in genomic regions associated with the control of transcription. Indeed, the expression of developmental genes implicated in ASD was dysregulated in the offspring of old fathers [31].

Other non genetic factors that have been associated with ASD include maternal use of certain substances during pregnancy, such as valproic acid, ethanol, thalidomide or misoprostol; low birth weight (or intrauterine growth retardation), congenital rubella and other infections, as well as cerebral palsy [32-38]. Environmental insults may increase the risk to ASD in genetically sensitive individuals, possibly by promoting cellular oxidative stress, and adaptive responses that could include reduced methylation activity, which is the most common epigenetic mechanism. Interestingly, the 15q11-q13 chromosomal region is subject to methylation-dependent genomic imprinting [39]; in addition, GABAergic genes in the same region, GABRB3, GABRA5, and GABRG3, were found to be epigenetically dysregulated in a subset of ASD patients [40].

2. Problem statement

Despite important advances in molecular genetics, the complete spectrum of the genetic component of ASD is still largely unresolved. There are many possible reasons for this partial lack of success. Among them, the complexity of the Central Nervous System, the relatively unique set of risk factors in each patient, which includes the combined effect of genetic (long/short, common, rare, and/or de novo sequences), and the interaction with environmental and epigenetic components. Furthermore, the possibility of genetic loci affecting two or more distinct traits or phenotypes (pleiotropy), and an incomplete penetrance (lack of clinical symptoms in individuals who carry risk alleles) also complicate the genetic studies of ASD.

The core symptoms of ASD, differences in intellectual and language abilities, and comorbidity, among other characteristics help highlight the presence of clinical heterogeneity in ASD. Knowledge about variability of genetic, environmental, and epigenetic factors in these disorders, as well as the presence of clinical heterogeneity, has propelled the search for more homogenous groups of patients through the study of potential endophenotypes. They may contribute to facilitate the identification of genetic risk factors and basic molecular mechanisms involved in ASD.

3. Application area

The concept of phenotype refers to the traits and features that are characteristic of a person. Thus, the phenotype includes body structures, physiological processes, but also conducts that result from the expression of the genotype in a given environment, and a specific epigenetic profile. Each individual has a unique phenotype.

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Neuropsychiatric disorders tend to be classified as discrete diagnostic entities. This classification is limited to clinical symptoms and functioning. However, it has been suggested that these phenotypes may be arbitrary and they may encompass a heterogeneous group of subjects [41].

The concept of endophenotype was adopted in Genetics in 1966 for the study of insects, specifically grasshoppers, to indicate an internal phenotype, a behavior or conduct that did not affect the external features of the animal. In 1967 this term was used in the field of human behavior; the goal was to measure situations that were not perceptible without instruments.

In general, endophenotypes are not considered the diagnosis of the disorder per se, or the clinical characteristics observed by the physician when interviewing the patient. They could be defined by internal attributes associated with the disorder or hidden to the naked eye; they could potentially be associated with more basic phenomena and be defined by inherited quantitative traits associated with a genetic risk to a familiar disorder [42, 43].

An endophenotype would ideally have a precise biological meaning, and a more direct relationship with the action of specific genes. Therefore, its study may facilitate the identification of complex behaviors that are associated with genetics in the population or in an important fraction of it. At the end, this is a strategy to try to understand the pathological role of certain genetic variants and to facilitate the identification of the mechanisms involved in disorders. Endophenotypes may be related with neurophysiological activities, neuroanatomy, neuropsychology, cognitive development (such as language and memory), or brain volume [44, 45].

Any biomarker should contribute to identify the presence of a given disorder, but it may be influenced by the health status of the person or by the effects of environmental factors. In order to be considered as an endophenotype, the biomarker is expected to be heritable, to cosegregate with the disorder, and as such, to be influenced by the genetic component of the disorder [46]. Endophentoypes have sometimes been referred to as intermediate phenotypes, but some authors do not agree on the indistinctive use of these two terms. An intermediate phenotype could be considered as a subclinical picture of psychopathology [47].

Different endophenotypes may be associated with ASD. Ideally, each one should:

a. Cosegregate with the disorder.

b. Be involved in the etiology rather than the effects of the disorder.

c. Be, at least partially, heritable.

d. Be stable even if the symptoms of the disorder are not manifested.

e. Be found in unaffected relatives of patients more frequently than in the general population.

f. Be associated with alleles that contribute to quantitatively distinguish patients and unaffected relatives from people with no ASD.

g. Vary in a continuous way in the general population.

h. Be objective and confirmed by different levels of analysis.

i. Be identified for genetically related disorders [48-51].

Thus far, the identification of endophenotypes has been successful in several fields of Medicine. Endophenotypes were useful in the identification of genes for QT syndrome, idiopatic hemochromatosis, juvenile myoclonic epilepsy, and familial adenomatous intestinal polyposis. Biochemical assays, physiological measures and challenges contribute as primary evidence of pathology in the detection of increased risk to diabetes, hypercholesterolemia, obesity, hypertension, and osteoporosis [48, 52, 53]. Furthermore, different endophenotypes have been proposed for neuropsychiatric disorders.

4. Research course

First degree relatives of patients are key elements in the study of endophenotypes. They are considered at-risk individuals. Even so, only a relatively small percentage of siblings of an individual with ASD will develop such disorders, but a larger proportion is expected to exhibit phenotypes that may fulfill the requirements of endophenotypes.

It has been shown that siblings of patients with ASD as well as other first degree relatives sometimes exhibit social, communication, and/or learning deficits, and ASD are more frequent in them than in the general population. Several possible endophentoypes for ASD have been proposed so far and are related with language and communication and/or with cognition, anatomy, or neurophysiology.

5. Methods

Medline database was searched for articles related with autism and autism spectrum disorder endophenotypes (query terms: autism spectrum disorders and endophenotypes, neuroanatomy, neurophysiology, endocrinology, cognition, social communication, and language. OMIM compendium was searched for disease and gene names. We will discuss potential endophenotypes based on studies in which one or more of their characteristics were fulfilled.

6. Status

Potential endophenotypes related with language and social communication

A continuous distribution of social deficits has been described in the general population, being more frequent in boys than in girls and more prevalent in brothers and fathers than in sisters and mothers of patients with ASD [54]. The estimated frequency of such disorders in siblings ranges from 2.6% to 61.7% [55-59].

It has been suggested that siblings later diagnosed with ASD may be distinguished from other siblings and low-risk infants by unusual eye contact, visual tracking, disengagement of visual

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attention, orienting to name, imitation, and delayed social expressive and receptive language [60].

Moreover, there are reports of poor social and communicative performance in parents without a diagnosis of ASD and siblings of children with such disorders [61]. Families with multiple affected individuals were compared with single-incidence autism families, and Down syndrome families as controls. In most cases with multiple affected relatives, both parents had autism-related characteristics. This was not observed in single-incidence families [62].

Furthermore, children with ASD and their parents have been shown to have an impaired performance in rapid automatized naming. Siblings of patients had intermediate performances when compared with controls [62, 63].

Poor verbal imitation and reduced response to vocal approaches have also been described in children with ASD or children who later developed ASD [64, 65]. In a study, 100% of the 12-month-old infants with no risk for ASD responded on the first or second name call, but 14% of at risk infants responded later. At two years of age developmental problems were identified in many of the children who failed to respond [66].

Impairment in joint attention abilities at age 20 months was also associated with later social and language symptoms [67]. At that same age, children with ASD failed to orient towards biological motion [68]. In addition, affected children who were three to four years old performed worse not only in social orienting and joint attention, but also in attention to the distress of someone else when compared with children without ASD [69].

There are genes that have been associated with language and social impairment in children with ASD and their siblings. This may be illustrated by a familial mutation of the MET gene. The mutation consists of a deletion of 4 exons that cause a frameshift and a premature stop codon. On the homologous chromosome 7 the patient carried an allele that was associated with a decrease in MET expression.

A sibling who was also a carrier of the deletion had language and social impairment [70]. MECP2 gene has been associated with difficulty in recognizing emotional expressions and less time spent looking at facial features [71]; it has also been described as a regulator of the expression of genes involved in social behavior [72]. In animal models, social deficits are observed when the activity of specific genes is lacking, such as FMR1 and Mu-opiod recepetor gene (OPRM1) [73].

Cognitive, anatomical and neurophysiological candidate endophenotypes

Atypical patterns of brain activation, for example, in the fusiform gyrus and the amygdala have been identified in individuals with ASD during face processing [74, 75]. In adults, parents and siblings of individuals with ASD were less able to discriminate subtle differences between faces than control individuals, but performed better than adults with ASD. Relatives were significantly worse at identifying expressions of fear and disgust than controls and did not show the typical sensitivity to direct eye gaze direction as opposed to averted eye-gaze, a characteristic observed in adults with ASD [76]. In a prospective study, 6 to 10 month-old

infants were asked to view faces with eye gaze directed toward or away from the infant. Characteristic components of event-related potentials were associated with ASD diagnosed later, at 36 months [77]. In one study, functional magnetic resonance imaging and eye tracking in unaffected siblings of individuals with ASD were performed. There were important differences in gaze fixation and brain activity in response to images of human faces when unaffected siblings were compared with typically developing controls. Siblings performed in a similar way than the ASD patients. When amygdala volume was compared, individuals with ASD and their siblings had similar volumes, which were significantly reduced when compared with volumes in the control group [78]. Small differences were independently found in the left amygdala when subjects with ASD or siblings were compared with controls [79]. Moreover, boys with ASD and unaffected brothers of individuals with ASD showed deficits in a visual attention task. Atypical fronto-cerebellar activation was identified in patients and unaffected brothers when they were compared with controls [80, 81].

Differences in gray matter in the cerebellum, parietal lobe, and left occipital lobe have been described between patients with ASD and controls. In some cases, differences between siblings without ASD and controls have also been reported [79, 82]. Furthermore, deficits in frontal, temporal, and occipital lobes have been identified in discordant monozygotic twins. Eight out of nine of the unaffected twins showed a social or language delay [83]. The functional magnetic resonance imaging response to happy facial expression was different between unaffected siblings and healthy controls without a family history of ASD. Here there were no statistically differences in response between unaffected siblings and patients with ASD [84].

The CNTNAP-2 gene (at 7q35 region) is mutated in individuals with intellectual disability, seizures, autistic features, and language impairment. Connectivity in the frontal lobe has been associated with CNTNAP-2 genetic variants [85].

White matter structure was analyzed in a voxel-based diffusion tensor imaging study. Children with ASD and their unaffected siblings had significantly reduced white matter fractional anisotropy values in the frontal parietal and temporal lobes when compared with controls. There were no significant differences in white matter structure between the ASD and sibling groups [86].

In other studies, children with ASD and their parents showed eye movement abnormalities that suggested a poorer spatial accuracy with respect to controls. The authors proposed that the spatial working memory may be affected in parents [87].

It has been suggested that ASD is characterized by a tendency towards local rather than global information processing. This has been called weak central coherence, which has also been reported in fathers of boys with ASD, as indicated by piecemeal processing in four tests [88]. In addition, some parents preferred nonsocial activities and ability in detail-focused processing, as is expected in subjects with ASD. A questionnaire completed by parents discriminated between ASD individuals and controls, but did not differentiate siblings [89]. In addition, atypical activation of temporal and frontal regions during the Embedded Figures Task was found in subjects with ASD and in unaffected siblings. The reduced activation on the ASD

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group when compared with controls was correlated with the severity of reciprocal social interaction deficits [90].

Regarding body measurements, although there is a high degree of variability in head circumference of children with ASD, the rate of macrocephaly is increased in these patients, if compared with the general population. Mean standardized head circumference and frequency of macrocephaly were similar in patients with ASD and their parents. Increased head circumference was associated with ASD severity and with a late onset of language [91]. Macrocephaly appearing in the first year of life has been described in subgroups of patients with ASD, mental retardation, and/or language delay who carry mutations on the Phosphatase and tensin homolog (PTEN) gene. Numerous relatives of individuals with a PTEN mutation also had macrocephaly and mental retardation [92-94]. Mutations in the hepatocyte cell adhesion molecule gene (HEPACAM) have also been associated with macrocephaly and ASD [95].

Other researchers have documented impairment in cortical sensory processing in ASD cases. For example, it has been suggested that early auditory responses as well as transient memory are impaired in some children with ASD; auditory stimuli produce messages that are sent from the brainstem to the thalamus and into the auditory cortex. Event related potentials were found to be delayed in affected children, and indicated a deficiency to achieve typical maturational development of the auditory system in individuals with ASD [96, 97]. In addition, children who were at risk for ASD showed atypical neural lateralization to speech in their first year of life [98].

Impairment in cortical sensory processing has been found in patients with Rett syndrome. In addition, auditory and visual evoked potentials in mice that were heterozygous for a loss of function variant of the MeCP2 gene demonstrated impairments in sensory processing. For example, increased N1 amplitude, latency of auditory P2 component, and suppression of beta-band activity were identified. There was a decreased suppression of induced gamma-band activity [99]. Gamma-band activity differences have been identified between parents of children with ASD and control adults [100].

Another area of potential endophenotypes is related with movement. There have been reports that suggest that specific motor developmental clues may be identified early in infants who will develop ASD. These signs tend to be persistent, and may be associated with abnormalities at the cerebellar, vestibular, cortical or fronto-striatal level [101]. Moreover, infants who were 18-month old and who had an older sibling with ASD were at higher risk for a delay in postural change and stability, language production and comprehension if compared with infants with no risk for ASD [56]. An association of motor anomalies and specific genes has been proposed. MeCP2, SHANK3, 22q13.3, Neurexin 1 (NRXN1) deletion, 15q11.1-q13.3, and KIAA0442 gene (known as Autism Susceptibility Candidate 2 or AUTS2) have been associated with hypotonia, stereotypes and/or motor delay; RNA-binding protein FOX1 (RBFOX1) has been associated with motor assymetry [102].

7. Results

According to the studies so far discussed, different techniques have proven to be useful in the identification of endophenotypes or potentially promising biomarkers. Social deficits, as well as cognitive, anatomical, and/or neurophysiological findings are encouraging and in some cases are associated with candidate genes. Endophenotypes may help detect children who are at higher risk for ASD. This could promote better and earlier diagnosis and treatment, as well as the establishment of prevention strategies. It is also probable that new drug targets can be identified and that personalized treatments can be available.

The precise genetic, environmental, and epigenetic factors that increase susceptibility to ASD may vary in several ways from one affected child to another. For this reason, it is very important to continue the search for means that allow us to form less heterogenous groups of patients. Endophenotypes, at least in some cases, could contribute to achieve this goal. They could help recognize risk factors that participate or affect common pathways or processes, such as chromatin remodeling and transcription that may affect neurodevelopment.

In some instances, de novo mutations associated with ASD may be highly penetrant, and in absence of a family history of ASD, endophenotypes may not be observed in relatives, but could still contribute to an earlier identification of symptoms in the carrier of the mutation; the next generations could also benefit from early assessments and prevention strategies. On the other hand, there will be families in which relatives will probably share enough risk factors with the patient, as to exhibit one or more endophenotypes or ASD.

8. Future research

Further studies in patients and relatives, preferably of first and second degree, will help determine if biomarkers fulfill the criteria of heritability and cosegregation.

Knowledge about the neuroetiology of ASD will be enriched by research in areas such as neuroanatomy, physiology, and social behavior. Multiple investigations are underway, and risk factors for ASD will continue to be identified, possibly in more homogenous groups of patients.

Future research should ideally involve longitudinal research in large samples that include twin pairs, nuclear families and/or extended pedigrees. These conditions may facilitate the identification or confirmation of endophenotypes, in which the criteria of heritability and cosegregation are fulfilled. Whenever possible, it will be useful to obtain detailed information about clinical and demographic aspects, not only regarding the individual with ASD, but about first and second degree relatives. While the grouping of individuals in a dichotomous way, as affected or unaffected will continue to be evaluated, and offers advantages, this approach can be complemented with the evaluation of endophenotypes [46].

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9. Conclusion

Several social, cognitive, anatomical, and neurophysiological biomarkers are under investigation and may be associated with candidate genes. Given that certain deficits have been identified in first degree relatives, mainly in siblings and parents of individuals with ASD, it is highly probable that at least some of them are indeed true endophenotypes. Longitudinal studies with large samples of cases and controls, but also of nuclear and extended families are needed in order to determine if all the requirement for endophenotypes are fulfilled. Once this phenotypes are confirmed, they may help detect infants and first degree relatives with an increased risk for ASD. This represents an excellent opportunity to initiate preventive measures and/or an early treatment when necessary. An early identification of risk may facilitate a better prognosis.

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This book starts with a new sub category of Autism Criminal Autistic Psychopathy and school shootings. It focuses on a number of interventions, including speech and language pathology, speech and language assessment instruments, occupational therapy, improving functional language development in autism with natural gestures, communication boards etc as well as helping people with autism using the pictorial support, training of concepts of significant others, theory of mind, social concepts and a conceptual model for empowering families of children with autism cross culturally. It also examines the issue of hyperandrogenism and evidence-based treatments of autism. In terms of assessment, it focuses on psychological and biological assessment including neurotransmitters systems, structural and functional brain imaging, coping strategies of parents, examines the intertwining of language impairment, specific language impairment and ASD, as well as implicit and spontaneous Theory of Mind reading in ASD. In terms of aetiology, it focuses on genetic factors, epigenetics, synaptic vesicles, toxicity during neurodevelopment, immune system and sex differences. It also examines the link between social cognitive anatomical and neurophysiologic biomarkers and candidate genes. This book will be relevant to all mental health professionals because autism occurs in all the different areas of psychiatry and professionals who will find it helpful will be psychiatrists, psychologists, social workers, nurses, teachers and all those working with persons with Autism including parents who nowadays are interested in knowing more and more, at a detailed level about their children or adults with autism.

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