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Transcranial Magnetic Stimulation in Neuropsychiatry

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TRANSCRANIAL MAGNETIC STIMULATION IN NEUROPSYCHIATRY

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http://dx.doi.org/10.5772/intechopen.69368
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First published in London, United Kingdom, 2018 by IntechOpen
eBook (PDF) Published by IntechOpen, 2019
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, The Shard, 25th floor, 32 London Bridge Street
London, SE19SG – United Kingdom
Printed in Croatia

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Additional hard and PDF copies can be obtained from orders@intechopen.com

Transcranial Magnetic Stimulation in Neuropsychiatry
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p. cm.

Print ISBN 978-1-78923-650-7

Online ISBN 978-1-78923-651-4

eBook (PDF) ISBN 978-1-83881-385-7

Meet the editor

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Contents

Preface

This book describes several aspects of transcranial magnetic stimulation (TMS) in neuropsychiatry. The first chapter opens the book with some basic information. The second chapter is focused on the research of inhibitory and excitatory mechanisms of the human brain and the use of TMS in the research and treatment of cognitive disorders. The third chapter explores the possibilities of research and therapeutic application of TMS aimed at the cerebellum. The fourth chapter discusses the effect of TMS on impulsivity in attention deficit hyperactivity disorder and borderline personality disorder. The fifth chapter describes the use of repetitive TMS (rTMS) in the treatment of tinnitus, and the sixth chapter looks at the current knowledge of its efficacy in the treatment of obsessive–compulsive disorder. The seventh chapter is focused on the role of non-invasive brain stimulation methods (including rTMS) in the treatment of pain, and the eighth chapter discusses the treatment of chronic headache. Last but not least, the ninth chapter discusses the safety of rTMS for staff.

I would like to thank all the authors and Miss Kristina Kardum from IntechOpen for their cooperation in the preparation of this book. We hope that it will help to expand the knowledge of TMS.

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Chapter 1

Introductory Chapter: Introduction to Transcranial Magnetic Stimulation in Neuropsychiatry

Libor Ustohal

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.78689

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive neurostimulation (or neuromodulation) method. The principle of TMS is based on the Faraday's principle of electromagnetic induction. Around the primary coil, through which a time-varying current is flowing, a changing magnetic field is created, which is able to induce a secondary current in conductors (including human brain) within its reach. It was not until 1985 when Barker and his collaborators developed a device that could generate a magnetic field of sufficient intensity to depolarize cortical neurons. The generated magnetic field lasts approximately 100–300 ms, and its intensity usually ranges from 1.0 to 2.5 T. Secondary current induces depolarization or hyperpolarization of cortical neurons—only neurons up to 1.5–2.0 cm from the stimulation coil can be influenced directly, but deeper parts of the brain can be influenced via transsynaptic connections. TMS causes activation of neurons, metabolic, hemodynamic, and behavioral changes [1].

TMS pulses can be administered individually—single-pulse TMS, in pairs few milliseconds apart—paired-pulse TMS, or repeatedly in a sequence (called usually train) lasting from seconds to minutes—repetitive TMS (rTMS). The first two types are usually used for research or diagnostic purposes (e.g., to assess the physiology of the human motor system, including cortical excitability), rTMS is used in the treatment because it can modulate cortical excitability and connectivity by inducing long-term potentiation-like or long-term depression-like plastic changes outlasting the stimulation period [2, 3].

The main indication of rTMS is the treatment of major depressive disorder. This method was approved in this indication by the Food and Drug Administration (FDA) in 2008; the approval was obtained in the European Union, too. Meta-analyses confirm the efficacy of

high-frequency (usually 5–25 Hz) rTMS of the left dorsolateral prefrontal cortex (DLPFC), low-frequency (≤1 Hz) of the right DLPFC, or bilateral stimulation (combination of high-frequency and low-frequency stimulation) [4, 5]. Other indications of rTMS are more or less experimental. They include the treatment of schizophrenia—either auditory hallucinations (low-frequency rTMS of the temporoparietal cortex) or negative symptoms (high-frequency rTMS of the left DLPFC) [3]. Another promising indication is the treatment of substance addiction, especially nicotine addiction by the decrease of craving (high-frequency rTMS of the left DLPFC). Tinnitus is another experimental indication with some promising results as well as the treatment of the obsessive compulsive disorder (OCD). Some positive results were published in the treatment of posttraumatic stress disorder (high-frequency or low-frequency rTMS of the DLPFC). TMS seems to be effective also in algesiology—especially in the treatment of neuropathic pain (high-frequency rTMS of the contralateral M1 area) or maybe of complex regional pain syndrome type I. The list of possible indications of rTMS includes Parkinson's disease (high-frequency rTMS of the M1 area), epilepsy (low-frequency focal stimulation), postictal rehabilitation, cognitive disorders (mild cognitive impairment and Alzheimer's disease), attention deficit hyperactivity disorder (ADHD), borderline personality disorder, eating disorders (especially bulimia nervosa), and some others [1, 4].

The advantage of rTMS is its good tolerability and safety. An only absolute contraindication is a metallic object in close contact with the stimulation coil. Relative contraindications include personal history of epilepsy (high-frequency rTMS); various (vascular, traumatic, tumoral, infectious, or metabolic) lesion of the brain; administration of drugs that can lower seizure threshold (without anticonvulsant medication); sleep deprivation, alcohol addiction; implanted brain electrodes; pregnancy (but several case studies and case series of the safe administration of rTMS in pregnant women were published), and severe or recent heart disease [6, 7]. The most serious side effect is the induction of seizure. However, this risk is very low. Other side effects include pain at the stimulation site and headaches. They are more frequent than seizures but usually mild. As for mental side effects, several cases of shift into mania in patients with bipolar disorder were reported, and several times positive symptoms of schizophrenia occurred after the stimulation for negative symptoms [1].

This book describes several aspects of TMS in neuropsychiatry. Hopefully, it will help to enhance the knowledge of TMS and its role in this developing discipline.

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References

[1] Ustohal L, Valková B. Biological treatment methods in psychiatry—Other methods. In: Hosák L, Hrdlička M, editors. Psychiatry and Pedopsychiatry. 1st ed. Prague: Karolinum; 2016. pp. 392-400

[2] Camprodon JA, Pascual-Leone A. Multimodal applications of transcranial magnetic stimulation for circuit-based psychiatry. JAMA Psychiatry. 2016;**73**(4):407-408

[3] Ustohal L, Sverak T, Albrechtova L, Hojgrova M, Hublova V, Kasparek T. Transcranial magnetic stimulation in schizophrenia. In: Shen Y-C, editor. Schizophrenia Treatment—The New Facets. 1st ed. Rijeka: InTech; 2016. pp. 135-150

[4] Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clinical Neurophysiology. 2014;**125**(11):2150-2206

[5] Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ, Carvalho AF. Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes. A systematic review with network meta-analysis. JAMA Psychiatry. 2017;**74**(2):143-153

[6] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clinical Neurophysiology. 2009;**120**(12): 2008-2039

[7] Felipe RM, Ferrao YA. Transcranial magnetic stimulation for treatment of major depression during pregnancy: A review. Trends in Psychiatry and Psychotherapy. 2016;**38**(4):190-197

Chapter 2

Transcranial Magnetic Stimulation and Cognitive Impairment

Stefan Martin Golaszewski and Raffaele Nardone

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.75841

Abstract

With transcranial magnetic stimulation (TMS), the motor system in neuropsychiatric disorders has extensively been investigated, and effects of certain pharmacological agents have been monitored. The most consistent finding in neuropsychiatric disorders is a significant reduction of short-latency afferent inhibition (SAI). SAI provides a reliable biomarker of cortical cholinergic dysfunction in neuropsychiatric disorders. Cortical hyperexcitability and asymptomatic motor cortex functional reorganization in the early stages of neuropsychiatric disorders have been demonstrated by TMS. Together with high-density EEG TMS and paired-associative stimulation, TMS showed impaired cortical plasticity and functional connectivity across different neural networks in neuropsychiatric disorders. Neuromodulatory techniques, especially as repetitive TMS (rTMS), hold promise as a therapeutic tool for cognitive rehabilitation because rTMS can enhance cognitive functions in neuropsychiatric disorders.

Keywords: repetitive transcranial magnetic stimulation, cognitive impairment, cortical plasticity, neuromodulation, neurorehabilitation

1. Introduction

Transcranial magnetic stimulation (TMS) allows non-invasive investigation and modulation of brain cortical excitability and brain function [1]. Alternating magnetic fields induce cortically electric currents in specific brain regions. Cortical excitability may be increased or decreased by different stimulation parameters, and the induced changes may be transient or long lasting. Different changes in behavior can be induced with regard to the stimulated region, the stimulation parameters, and the physiology of the stimulated cortical tissue. These effects can be enhancement or can interfer with cognitive functions [2, 3].

The chapter reviews studies reporting about applications of TMS in neuropsychiatric disorders. Most reports have applied TMS to characterize important neurophysiologic and pathophysiologic aspects of neurodegenerative diseases. Several studies using TMS have demonstrated abnormalities in cortical excitability, plasticity and functional connectivity between the motor cortex and other cortical regions. Other studies aimed to evaluate and monitor the effects of certain pharmacological agents.

Long-term neuromodulatory effects applying repetitive TMS (rTMS) can be induced with promising therapeutic potential in neuropsychiatric disorders. These applications can improve our understanding of brain plasticity mechanisms, the basis for the development of new therapeutic strategies in neuropsychiatric disorders.

2. TMS parameters in clinical application

2.1. Central motor conduction time

The so-called central motor conduction time (CMCT) can be calculated by subtraction of the peripheral conduction time from spinal cord to muscles from the conduction time of responses evoked by cortical stimulation. Demyelination of motor pathways increases CMCT, while low amplitude MEPs with little delay or absence of responses are rather suggestive of neuronal or axonal loss [4, 5].

The amplitude of the MEP reflects the integrity of the corticospinal tract and the excitability of motor cortex and spinal level, as well as the conduction along the peripheral motor pathway to the muscles [4, 5].

TMS also allows cortical mapping procedures, with single TMS pulses applied on several scalp positions overlying the motor cortex, exploring the site of maximal excitability (hotspot) and the "center of gravity" of motor cortical output [6].

2.2. Motor threshold

The resting motor threshold (RMT) is by definition the minimum stimulus intensity that produces a motor evoked potential (MEP) greater than 50 μV in 50% out of 10 trials at the completely relaxed tested muscle. RMT provides information about a central core of neurons in the muscle representation in the motor cortex, and reflects both neuronal membrane excitability [7–9] and non-N-methyl-D-aspartate (NMDA) receptors' [8, 9] glutamatergic neurotransmission. The minimum stimulus intensity that produces a MEP (about 200 μV in 50% of 10 trials) during isometric contraction of the tested muscle at about 10% maximum defines the active motor threshold (AMT). AMT provides a measure of corticospinal excitability with greater dependence on the spinal segmental level excitability [4, 5].

2.3. Short-latency afferent inhibition

Short-latency afferent inhibition (SAI) refers to the suppression of the amplitude of a MEP produced by a conditioning afferent electrical stimulus applied to the median nerve at the wrist approximately 20 ms prior to the TMS pulse to the hand area of the contralateral motor cortex [10]

SAI reflects the integrity of central cholinergic neural circuits. It is reduced or absent by the muscarinic antagonist scopolamine in healthy subjects [11]. SAI may also be dependent on the integrity of circuits linking sensory input and motor output [12]. Cholinergic transmission underlies also the neuromodulation of other neurotransmitters.

2.4. Cortical silent period, paired pulse intracortical inhibition and facilitation

Single-pulse TMS delivered during voluntary muscle contraction produces a period of EMG suppression known as the cortical silent period (cSP). TMS can also investigate the intracortical facilitatory and inhibitory mechanisms that influence motor cortical output. Paired pulse TMS techniques involve paired-stimuli based on a conditioning-test paradigm [13]. Stimulation parameters such as the intensity of the conditioning stimulus (CS) and test stimulus (TS) together with the time between the two stimuli (interstimulus interval, ISI) determine interactions between stimuli. When the conditioning stimulus is below and the test stimulus is above the MT, the conditioning stimulus decreases the MEP to the test stimulus at interstimulus intervals from 1 to 5 ms (short-latency intracortical inhibition, SICI), while the conditioning stimulus induces a facilitation of the response to the test stimulus at interstimulus intervals from 6 to 20 ms (intracortical facilitation, ICF).

Short latency intracortical inhibition reflects to a large extent $GABA_A$-mediated intracortical inhibitory synaptic activity [14]. The early part of the silent period originates from spinal inhibition, while the later part is caused by a long-lasting cortical inhibition mediated by $GABA_B$ primarily in the motor cortex [15]. The intracortical facilitation with interstimulus intervals from 6 to 20 ms reflects motorcortical excitatory neurotransmission primarily mediated by NMDA receptors [15].

2.5. Cortical connectivity and plasticity measures

Combined measures of EEG and TMS (EEG) [16–18] can provide real-time information on cortical connectivity and distributed network dynamics.

Several other TMS techniques are currently used to modulate noninvasively the excitability of the cerebral cortex. Cortical responses to rTMS and paired-associative stimulation (PAS) provide information about different aspects of cortical plasticity [4, 15, 19]. TMS can influence brain function if delivered repetitively. RTMS is a technique that delivers single TMS pulses in trains with a constant frequency and intensity for a given time. Depending on the stimulation parameters, particularly the frequency of stimulation, cortical excitability can be modulated and rendered facilitated or suppresses. The modulation induced by rTMS can induce significant and long-lasting changes in focal and non-focal neural plasticity. Generally, low-frequency rTMS (stimulus rates of 1 Hz or less) induces inhibitory effects on motor cortical excitability allowing creation of a reversible 'virtual lesion' [20], while high-frequency rTMS (5–20 Hz) usually promotes an increase in cortical excitability [21, 22].

PAS involves repeated pairs of electrical stimulation of a peripheral nerve (usually the median nerve) followed by TMS applied over the contralateral hand area of the motor cortex [23]. PAS induces a lasting increase in corticospinal excitability, which can be considered a marker of motor cortical plasticity, with long-term plasticity-like mechanisms thought to play a major role [23].

3. Cortical excitability, connectivity and plasticity

3.1. Motor threshold

Most of the studies found significantly reduced RMT in neuropsychiatric disorders as compared with healthy subjects [24–36], while other reports have found a tendency toward a reduced RMT without statistical significance [37–44]. One study noted no difference in RMT between patients with Alzheimer disease (AD) and controls [45], while [46] found increased RMT in AD patients. It can be hypothesized that, in the early stages, mechanisms related to RMT are preserved [45], or that RMT changes reflect functional damage of cortical motor neurons. As the disease progresses, the decrease in RMT might be compensatory to the loss of motor cortex neurons [36, 39]. In a combined TMS-MRI study [47], it was reported recently that motor cortex excitability did not correlate with the cortical thickness in AD subjects. It can be hypothesized that a protective mechanism of hyperexcitability on the sensorimotor cortex may counteract the loss of cortical volume. This protective mechanism was not found in the patients with mild cognitive impairment (MCI). Lahr et al. [48] could show in MCI patients with the TMS technique of paired-associative stimulation (PAS) that there is no difference in synaptic long-term potentiation (LTP)-like plasticity between MCI patients and healthy controls [48]. Another study with transcranial magnetic stimulation addressed mild cognitive impairment in the elderly [49]. About 10 Hz rTMS everyday enhanced memory in the elderly MCI patients after 10 sessions. Thus, rTMS might be effective in cognitive therapy for MCI patients. In a recent study, Nardone et al. [50] found a normal short-latency afferent inhibition (SAI) in 20 subjects with subjective memory impairment [50]. An abnormal SAI was reported in amnestic multiple domain mild cognitive impairment patients. Therefore, SAI holds promise to be a useful biomarker for differentiating individuals with subjective memory complaints those in whom cholinergic degeneration has occurred.

There are a few studies that have assessed AMT in AD patients; only two found significant decreases in AMT when compared with healthy subjects [31, 36]. Therefore, the excitability of spinal projections seems to be relatively preserved during early course AD.

The increased excitability to TMS in AD patients may be the functional correlate of an abnormal glutamatergic system. This hypothesis has been supported by a study demonstrating an altered response to rTMS in AD patients [32].

In contrast with AD patients, patients with dementia with Lewy bodies (DLB) present a normal excitability to single-pulse TMS [29, 51]. This finding suggests that the glutamatergic system is not involved in DLB patients. However, cortical excitability to visual stimuli of lower visual areas (V1–3) as measured by TMS appears to be normal in DLB. TMS-determined phosphene threshold and fMRI-related visual activation shows a positive relationship in controls but a negative one in DLB that suggests a loss of inhibition in the visual system in DLB, which may predispose individuals to visual dysfunction and visual hallucinations [52].

Patients with vascular dementia (VD) have decreased RMT [29, 53]. This increased excitability could represent a functional consequence of the vascular lesions. RMT was recently found to be significantly lower in patients with subcortical ischemic VD, but not in patients with

subcortical ischemic disease without dementia [54]. In a study of Guerra et al. [55], there is evidence for common compensatory mechanisms in subcortical ischemic vascular dementia as it is known from Alzheimer's disease [55] supporting the idea that cortical hyperexcitability can promote cortical plasticity. These results indicate that motor cortex hyperexcitability is a common finding in different dementing illnesses, subcortical or cortical in origin.

3.2. Motor evoked potential amplitude and central motor conduction time

Most studies found no significant differences in MEP amplitude between patients with AD and healthy subjects [25, 27, 31–33, 38, 45, 46], while significant increases in MEP amplitude in AD patients were detected in fewer studies [24, 26, 36]. Interestingly, the center of gravity of motor cortical output shows a frontal and medial shift in patients with AD, without changes in the hot-spot location [39]. This finding may indicate functional reorganization, likely including the dysregulation of the inhibitory frontal centers [39].

MEP amplitude was found to be larger in patients with subcortical ischemic VD with dementia than in patients with subcortical ischemic disease without dementia [54].

None of the studies that examined CMCT in AD [24, 26, 27, 40–42, 46] found statistically significant differences between patients and healthy age-matched subjects. These results confirm that the integrity of the corticospinal tract is not compromised at least in mild to moderate stages of AD.

In contrast, Di Lazzaro et al. [30] found that cortical excitability to single-pulse TMS was impaired in 5 out 20 patients with frontotemporal dementia (FTD). In three patients, MEPs were absent, and a very small MEP was obtained only at maximum stimulator output in two patients. In agreement with these results, patients with FDT are more likely than patients with AD to have motor abnormalities. This finding suggests that TMS may reveal subclinical central motor pathways involvement in patients with FTD. Paired pulse TMS applying the parameters SICI, ICF and SAI can also distinguish AD from FTD with a sensitivity of 91.8% and specificity of 88.6% [56]. AD patients show an impairment of SAI, while FTD shows a remarkable dysfunction of SICI and ICF parameter.

3.3. Cortical silent period, intracortical inhibition and facilitation

A significant reduction of SICI was found by some authors [35, 40, 42, 45], but most studies did not find differences in SICI between AD patients and control subjects [27–29, 31, 36, 37, 41]. In a study, the amount of disinhibition was found to correlate with the severity of AD [40]. Most studies by [25, 27, 32, 40], but not all [24, 46] studies failed to find any significant differences in the cSP duration between AD patients and healthy controls. Taken together, these findings do not support impairments in GABAergic inhibitory circuits in AD. On the other hand, dysfunction of GABAergic circuits has not been demonstrated, and the GABA system seems to be relatively spared in AD [57].

Di Lazzaro et al. found an impairment of SICI in 16% of patients with VD [29]. One study showed a decrease in cortical benzodiazepine receptors in patients with VD due to leukoaraiosis [58],

thus the abnormality of SICI in some VD patients might be related to the disruption of inhibitory GABAergic circuits. However, a study provides evidence of functional changes also in excitatory cortical circuits in patients with subcortical ischemic vascular disease and cognitive impairment (but no dementia) [59].

Alberici et al. [37] found that patients with FTD were comparable with healthy subjects and AD patients for SICI and ICF. In contrast, patients with corticobasal degeneration (CBD) presented significantly reduced SICI at ISI 3 ms, the selective impairment of intracortical inhibition in CBD may help in distinguishing among the FTD clinical spectrum.

None of the previous studies has found significant changes in ICF in patients with AD as compared to healthy controls [27, 35–37, 40–42, 45]. These findings seem to point to a normal NMDA receptor-dependent glutamate excitatory activity in AD, as tested by this cortical excitability measure. However, other studies suggest that abnormalities of glutamatergic neurotransmission might play an important role in AD. The glutamatergic hypothesis of AD has been proposed as an auxiliary mechanism to the cholinergic hypothesis [39] and this may be due to an imbalance between the non-NMDA and NMDA neurotransmission [39, 60–63].

3.4. Short-latency afferent inhibition

The most consistent finding of abnormal cortical excitability in AD patients regards SAI. In fact, all studies reported significant reductions of SAI in patients with AD as compared to healthy individuals [27, 29–31, 34, 41, 42, 44, 60, 64, 65]. SAI was also found to be negatively correlated with performance in abstract thinking [29, 31] and long-term memory [29]. SAI testing may be a useful marker of central cholinergic dysfunction even in early stages of AD [66], while it was found to be not significantly reduced in subjects with MCI [44]. However, in this study the diagnosis of MCI was based on criteria proposed by Petersen in 1999 instead of the revised ones [67] and the relationships to the different MCI subtypes was not defined. In a more recent study, a reduced SAI was found in amnestic MCI-multiple domain patients, while SAI was not significantly different in amnestic MCI-single domain patients and in non-amnestic MCI patients [68].

SAI is significantly reduced also in adults with Down Syndrome (DS) and Alzheimer-type dementia [51] the values correlated with the patient's age and the score on Dementia Scale for DS. This technique may thus represent an additional tool for the diagnosis of Alzheimer-type dementia in subjects with DS.

Nardone et al. [51] described this putative marker of cholinergic activity in patients with DLB and showed a clear tendency toward a reduced SAI. These authors performed SAI testing without randomization of different conditions and the diagnosis of DLB was based on criteria proposed in 1996 instead of the revised ones [69]. Di Lazzaro et al. [29] examined 10 patients with a clinical diagnosis of DLB according to the NINCDS-ADRDA criteria [69] and found a significantly reduced SAI in these patients. Interestingly, SAI correlates with hallucinations in DLB patients and with euphoric manic state and disinhibition in AD patients [70]. SAI investigation may also be useful in the distinction between DLB and Parkinson's disease (PD), because SAI is normal or even enhanced in PD [12, 71].

SAI was evaluated in 20 patients with FTD and compared data with those from 20 patients with AD and 20 control subjects [30]. SAI was normal in FTD, whereas it has been reduced in AD. SAI may thus represent an additional tool to discriminate FTD from AD. These findings are consistent with post-mortem studies showing central cholinergic deficits in AD [72–74] but not in FTD [75].

A reduced SAI has been found in patients with VD, but not to the same extent as AD. Nardone et al. [66] reported that SAI responses in patients with subcortical ischemic VD varied widely, ranging from normal to markedly reduced values. In another TMS study, significant SAI abnormalities were disclosed in 3 out of 12 patients with VD [29]; SAI was strongly correlated with neuropsychological measures of long-term memory and other cognitive functions. In patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), the amount of SAI was found to be significantly smaller than in normal subjects [76]. This finding supports the hypothesis of a central cholinergic system impairment in CADASIL. Interestingly, Mesulam [77] demonstrated that pure white matter infarcts, similar to those seen in subcortical VD, can cause cortical cholinergic denervation.

It should be considered that AD and VD are not mutually exclusive conditions; VD patients with SAI abnormalities could have concomitant neuropathological changes of AD and thus represent the percentage of patients with a mixed form of dementia.

In contrast to AD where the major features of the cholinergic neuropathology show few interindividual variations, VD may show considerable interindividual variation in the location of subcortical infarcts and, therefore, in the distribution and magnitude of the resultant cortical cholinergic deficits. In contrast to AD, where there are a few interindividual variations in the pattern and extent of the cholinergic neuropathology, VD may show considerable interindividual variation in the location of subcortical infarcts and, therefore, in the distribution and magnitude of the resultant cortical cholinergic deficit.

3.5. Cortical plasticity and functional connectivity

Some studies have examined non-invasively motor cortical plasticity and functional connectivity in AD. Inghilleri et al. [32] investigated the effects of modulation of cortical motor areas induced by suprathreshold high-frequency (5 Hz) rTMS. Whereas in control subjects 5 Hz-rTMS elicited normal MEPs that progressively increased in size, in AD patients the amplitude of MEPs progressively decreased during the training. These results suggest an altered cortical plasticity in excitatory motor cortical circuits in AD. Conversely, 5 Hz rTMS induced an increase in cSP in both groups, thus indicating a normal plasticity of the cortical inhibitory circuits. Battaglia et al. [38] studied LTP-like plasticity of the motor cortex in AD patients and healthy subjects by employing PAS with interval between peripheral nerve stimulation and TMS set at 25 ms (PAS25); they also performed biochemical analyses in brain slices of amyloid precursor protein (APP)/presenilin-1 (PS1) mice, an AD animal model. PAS-induced plasticity has been significantly reduced in AD patients; moreover, 4–4.5-month-old APP/PS1 mice exhibited deficits of NMDA receptor-dependent neocortical and hippocampal long-term potentiation (LTP), and a marked alteration of NMDA receptor activity.

Julkunen and co-workers [33] have investigated functional connectivity between the motor cortex and other cortical regions. Fifty single TMS pulses 3 s apart were delivered to the motor cortex to evaluate spreading of navigated TMS-evoked EEG responses throughout the brain. Significant motor cortical differences from averaged left and right hemispheres in AD patients were observed. Using real-time integration of TMS and EEG, the authors also demonstrated prominent changes in cortical connectivity. The TMS-evoked response at 30–50 ms decreased significantly over multiple brain regions in patients with AD compared to both healthy elders and subjects with MCI. In particular, a significant reduction has been seen in the ipsilateral parietal cortex and contralateral fronto-central areas. In addition, a significant decrease in the N100 amplitude in the MCI subjects when compared with the control subjects has been found. In a subsequent study, Julkunen et al. [78] found that the TMS-EEG response P30 amplitude correlated with cognitive dysfunction and showed high specificity and sensitivity in identifying healthy individuals from MCI or AD patients.

4. Therapeutic interventions

4.1. Neuromodulatory techniques

RTMS is capable of modulating cortical excitability and inducing lasting effects [79, 80]; both have been shown to have potential therapeutic efficacy in cognitive neuroscience [81]. RTMS has been proven to influence cortical excitability and the metabolic activity of neurons. TDCS is another simple and powerful tool to modulate brain activity, which delivers constant low-intensity current (below the perceptual threshold, 1–2 mA) over the scalp via two large electrodes. The resulting constant electrical field penetrates the skull and influences neuronal function.

rTMS can be applied as continuous trains of low-frequency (1 Hz) or bursts of higher frequency (≥ 5 Hz) rTMS [81]. In general, low-frequency rTMS reduces, and high-frequency rTMS enhance excitability in the targeted cortical region.

The physiologic impact of both neuromodulatory techniques involves synaptic plasticity, specifically LTP and LTD.

4.2. Repetitive transcranial magnetic stimulation

Three studies have dealt with rTMS effects on naming and language performance in AD patients. In two crossover, sham-controlled, single-session studies [82, 83], rTMS was applied to the dorsolateral prefrontal cortex (DLPFC) during the execution of naming tasks. In the first study, a significantly improved accuracy in action naming, but not in object naming, was observed after high-frequency rTMS of both the left or right DLPFC [82]. In the second study [83], the results of the previous study were obtained only in patients with mild AD (Mini-Mental-State-Examination (MMSE) ≥ 17/30), while in patients with moderate to severe AD (MMSE <17/30) both action and object naming were facilitated after rTMS over both left and right DLPFC. In a later study, Cotelli et al. [84] investigated whether the application of high-frequency rTMS to the left DLPFC may lead to a facilitation of language production and/or comprehension in patients with moderate AD. Ten patients were assigned to one of two

groups in which they received either 4-week real rTMS or 2 weeks of sham rTMS followed by 2 weeks of real rTMS stimulation. No significant effects were found on naming performance, while a significant effect was detected on auditory sentence comprehension after 2 weeks of real rTMS sessions. Two additional weeks of daily rTMS sessions resulted in no further improvements, while a significant beneficial effect on auditory sentence comprehension was still observed 8 weeks after the end of the rTMS intervention. An important finding was the absence of any effects on memory and executive functions.

Rektorova et al. [85] examined whether one session of high-frequency rTMS applied over the left DLPFC or over the left motor cortex (MC) would induce any evaluable cognitive changes in seven patients with cerebrovascular disease and MCI. Patients improved in the Stroop interference results after stimulation of the DLPFC but not MC, and in the digit symbols subtest of the Wechsler adult intelligence scale-revised regardless of the stimulation site.

Recently, Cotelli et al. [84] found that rTMS of the left parietal cortex increased accuracy in an association memory task in a patient with amnestic MCI, and the improvement was maintained for 24 weeks.

In another study, Ahmed et al. [86] aimed to compare the long-term effects of high- versus low-frequency rTMS, applied over the DLPFC of both hemispheres, on cortical excitability and cognitive function of AD patients. All patients received one session daily for five consecutive days. The high-frequency rTMS group improved significantly more than the low-frequency and sham groups in all assessed rating scales (MMSE, Instrumental Daily Living Activity Scale and the Geriatric Depression Scale). The improvement was still significant 24 weeks after stimulation began.

Since cognitive training (COG) is known to improve cognitive functions in AD, Bentwich et al. [87] aimed to obtain a synergistic effect of rTMS interlaced with COG (rTMS-COG). Eight patients with mild or moderate probable AD were subjected to daily rTMS-COG sessions (5/week) for 6 weeks, followed by a maintenance phase (2/week) for additional 3 months. Broca's and Wernicke's areas, right and left DLPFC, right and left parietal somatosensory association cortex were stimulated, and COG tasks were developed to fit these brain regions. Alzheimer Disease Assessment Scale (ADAS)-Cognitive and Clinical Global Impression of Change improved significantly after both 6 weeks and 4.5 months of treatment. MMSE, the ADAS-Activities of Daily Living, and the Hamilton Depression Scale improved, but without statistically significant differences. In a recent single case study [88], a patient with initial AD was treated by rTMS over the left DLPFC for 10 stimulation sessions over 2 weeks. Cognitive improvements occurred especially in tests of episodic memory and speed processing, and were still evident 1 month after the last stimulation. In a recent study, Rabey and Dobronevsky could prove that rTMS combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease [89].

5. Discussion

This chapter intended to review the most relevant studies using non-invasive brain stimulation in dementias. A number of studies showed that several TMS techniques might represent a useful additional tool for the functional evaluation of patients with dementia. Among the

studies focusing on motor cortical excitability measures, a particularly consistent and important finding is the significant reduction of SAI in AD patients. Abnormal SAI has also been reported in DLB [29] a form of dementia that responds to cholinergic medications [90]. In contrast, SAI was found to be normal in FTD [30], a non-cholinergic form of dementia. Therefore, SAI testing can be used as a non-invasive test for the assessment of cholinergic pathways in patients with dementia and may represent a useful additional tool in the differential diagnosis between the cholinergic and the non-cholinergic forms of dementia. Furthermore, TMS can thus be used to monitor AD progression and response to treatment [64]. It remains relatively unclear, how early in the course of the disease neurochemical and neuropathological alterations occur. However, neurobiological changes should be examined earlier in the disease process, when presumably they are more relevant for the pathogenesis of AD. Therefore, the findings that SAI abnormalities can be observed in patients with early diagnosis of AD [41] and even in patients with amnestic MCI-multiple domain may have potential diagnostic and therapeutic implications. Identification of SAI abnormalities that occur early in the course of the disease will allow earlier treatment with cholinergic drugs, and may be useful in identifying MCI individuals at increased risk of conversion to AD.

The second most frequent cause of dementia following AD is VD. It was suggested that cholinergic mechanisms play a role also in the pathogenesis of VD; however, the role of the cholinergic system in the development of cognitive impairment is still under discussion in VD, also because previous studies failed to found significant SAI abnormalities in most VD patients.

Interestingly, the cumulative effect of micro bleeds (MBs) on cognition appears to be independent of coexisting ischemic cerebrovascular disease, in particular of the severity of ischemic subcortical VD as assessed by magnetic resonance imaging (MRI) white matter changes [68]. $T2^*$-weighted gradient echo-MRI may thus be a helpful adjunct to standard MRI in clarifying the mechanism of cognitive impairment in patients with cerebrovascular risk factors. Anyway, TMS studies in patients with VD and other dementias have some limitations. First, only post-mortem histology allows confirmation of the precise nature of dementia. Moreover, a simple visual evaluation of MRI was employed and not more advanced neuroimaging techniques, such as voxel-based morphometry, that could contribute to the identification of different forms of dementia.

The combination of TMS and EEG also enables the exploration of neural plasticity and connectivity across different neural networks. Encouraging findings, showing impaired cortical plasticity and functional connectivity between motor and non-motor brain regions in AD, have been obtained. This method may provide a novel tool for examining the degree and progression of dementia.

Overall, several issues should be more carefully addressed in future studies. The impact of TMS depends on the distance between targeted cortex and scalp, as the magnetic field decreases with distance [91]. Since regional cortical thinning has been observed in AD [92], brain atrophy can substantially alter the effect of TMS [81]. Volumetric studies of white matter volume and cortical thinning should thus be included in future studies in order to ameliorate the interpretation of TMS results in patients with cerebral atrophy and dementing illnesses.

On the other hand, the motor cortex does not seem the best cortical area to assess in AD patients, especially in the earlier stages of the disease. In fact, neuropathologic and neuroimaging

studies suggest that non-motor cortical regions, for example, temporo-parietal and frontal association cortices, are profoundly and early affected in AD.

It should be noted that most of the TMS findings show considerable variability between studies. In addition to TMS methodological issues, age at disease onset and duration of disease, genetic factors may also represent a possible cause for such variability. It has been demonstrated that the Val66Met nucleotide polymorphism of the brain derivate neurotrophic factor (BDNF) gene differentially modulates brain plasticity and the response to transcranial stimulation [93]. In addition, the presence of Apolipoprotein E (*APOE*) and its ε4 allele is known to distinctively modulate the clinical phenotype of AD, as revealed by functional neuroimaging [94]. Therefore, the presence of BDNF-Val66Met polymorphism and of the *APOE*-ε4 may influence cortical excitability and plasticity as assessed by TMS. Moreover, it has been reported [95] that levels of total tau (t-Tau) detected in CSF of AD patients mediates abnormal excitatory activity, as measured with 1 Hz rTMS; CSF t-Tau may thus impact mechanisms of cortical plasticity.

The novel techniques of non-invasive neurostimulation have begun to be used to improve cognitive performances in AD. rTMS appears to be safe in patients with AD, even if long-term risks have not always been thoroughly evaluated. For all future studies a careful experimental design is needed and patient selection aspects, stimulation parameters, as well as clinical, cognitive and behavioral assessment tools should be considered. In fact, cognitive decline is not homogeneous across patients with AD and pathological features might affect neural networks differently. Of great importance would also be a careful choice of uniform and validate outcome measures, also to enable comparison across studies. Therefore, appropriately powered studies with more comprehensive outcome measures and sound blinding procedures are needed to confirm the effectiveness of rTMS in patients with dementia. On the other hand, the assumption that cortical plasticity enhancement is needed for the improvement of the cognitive status of patients with AD may be incorrect [96]. Even if TMS studies point to cortical hyperexcitability in AD, the employed techniques aimed at increasing cortical excitability. For this reason, the cortical physiology should be appropriately tested before and after therapeutic brain stimulation. In addition, high-frequency rTMS may not lead to an enhanced cortical excitability in AD. Indeed, rTMS effects are dependent on the baseline cortical activation state at the time of stimulation [97].

Finally, multiple-target stimulation protocols are necessary in order to overcome the widespread cognitive impairment in AD, especially in the more advanced stages of the disease [96].

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References

[1] Lisanby SH et al. Transcranial magnetic stimulation: Applications in basic neurosci ence and neuropsychopharmacology. The International Journal of Neuropsychophar macology. 2000;**3**(3):259-273

[2] Boroojerdi B et al. Enhancing analogic reasoning with rTMS over the left prefrontal cortex. Neurology. 2001;**56**(4):526-528

[3] Grafman J et al. Induction of a recall deficit by rapid-rate transcranial magnetic stimulation. Neuroreport. 1994;**5**(9):1157-1160

[4] Hallett M. Transcranial magnetic stimulation and the human brain. Nature. 2000; **406**(6792):147-150

[5] Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. Lancet Neurology. 2003;**2**(3):145-156

[6] Rossini PM et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: Basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalography and Clinical Neurophysiology. 1994;**91**(2):79-92

[7] Bliem B et al. Homeostatic metaplasticity in the human somatosensory cortex. Journal of Cognitive Neuroscience. 2008;**20**(8):1517-1528

[8] Ziemann U et al. The effect of lorazepam on the motor cortical excitability in man. Experimental Brain Research. 1996;**109**(1):127-135

[9] Ziemann U et al. Effects of antiepileptic drugs on motor cortex excitability in humans: A transcranial magnetic stimulation study. Annals of Neurology. 1996;**40**(3):367-378

[10] Tokimura H et al. Short latency inhibition of human hand motor cortex by somatosensory input from the hand. Journal of Physiology. 2000;**523**(Pt 2):503-513

[11] Di Lazzaro V et al. Muscarinic receptor blockade has differential effects on the excitability of intracortical circuits in the human motor cortex. Experimental Brain Research. 2000;**135**(4):455-461

[12] Sailer A et al. Short and long latency afferent inhibition in Parkinson's disease. Brain. 2003;**126**(Pt 8):1883-1894

[13] Kujirai T et al. Corticocortical inhibition in human motor cortex. The Journal of Physiology. 1993;**471**:501-519

[14] Paulus W et al. State of the art: Pharmacologic effects on cortical excitability measures tested by transcranial magnetic stimulation. Brain Stimulation. 2008;**1**(3):151-163

[15] Ziemann U et al. Consensus: Motor cortex plasticity protocols. Brain Stimulation. 2008;**1**(3):164-182

[16] Ives JR et al. Electroencephalographic recording during transcranial magnetic stimulation in humans and animals. Clinical Neurophysiology. 2006;**117**(8):1870-1875

[17] Thut G et al. A new device and protocol for combining TMS and online recordings of EEG and evoked potentials. Journal of Neuroscience Methods. 2005;**141**(2):207-217

[18] Thut G, Pascual-Leone A. A review of combined TMS-EEG studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience. Brain Topography. 2010;**22**(4):219-232

[19] Chen R, Udupa K. Measurement and modulation of plasticity of the motor system in humans using transcranial magnetic stimulation. Motor Control. 2009;**13**(4):442-453

[20] Chen R et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. Neurology. 1997;**48**(5):1398-1403

[21] Berardelli A et al. Facilitation of muscle evoked responses after repetitive cortical stimulation in man. Experimental Brain Research. 1998;**122**(1):79-84

[22] Pascual-Leone A et al. Akinesia in Parkinson's disease. II. Effects of subthreshold repetitive transcranial motor cortex stimulation. Neurology. 1994;**44**(5):892-898

[23] Stefan K et al. Mechanisms of enhancement of human motor cortex excitability induced by interventional paired associative stimulation. The Journal of Physiology. 2002;**543**(Pt 2):699-708

[24] Alagona G et al. Transcranial magnetic stimulation in Alzheimer disease: Motor cortex excitability and cognitive severity. Neuroscience Letters. 2001;**314**(1-2):57-60

[25] Alagona G et al. Motor cortex excitability in Alzheimer's disease and in subcortical ischemic vascular dementia. Neuroscience Letters. 2004;**362**(2):95-98

[26] de Carvalho M et al. Magnetic stimulation in Alzheimer's disease. Journal of Neurology. 1997;**244**(5):304-307

[27] Di Lazzaro V et al. Direct demonstration of the effects of repetitive transcranial magnetic stimulation on the excitability of the human motor cortex. Experimental Brain Research. 2002;**144**(4):549-553

[28] Di Lazzaro V et al. Motor cortex hyperexcitability to transcranial magnetic stimulation in Alzheimer's disease. Journal of Neurology, Neurosurgery, and Psychiatry. 2004;**75**(4):555-559

[29] Di Lazzaro V et al. In vivo functional evaluation of central cholinergic circuits in vascular dementia. Clinical Neurophysiology. 2008;**119**(11):2494-2500

[30] Di Lazzaro V et al. In vivo cholinergic circuit evaluation in frontotemporal and Alzheimer dementias. Neurology. 2006;**66**(7):1111-1113

[31] Di Lazzaro V et al. Functional evaluation of cerebral cortex in dementia with Lewy bodies. NeuroImage. 2007;**37**(2):422-429

[32] Inghilleri M et al. Altered response to rTMS in patients with Alzheimer's disease. Clinical Neurophysiology. 2006;**117**(1):103-109

[33] Julkunen P et al. Navigated TMS combined with EEG in mild cognitive impairment and Alzheimer's disease: A pilot study. Journal of Neuroscience Methods. 2008;**172**(2):270-276

[34] Martorana A et al. Dopamine modulates cholinergic cortical excitability in Alzheimer's disease patients. Neuropsychopharmacology. 2009;**34**(10):2323-2328

[35] Martorana A et al. L-dopa modulates motor cortex excitability in Alzheimer's disease patients. Journal of Neural Transmission (Vienna). 2008;**115**(9):1313-1319

[36] Pepin JL et al. Motor cortex inhibition is not impaired in patients with Alzheimer's disease: Evidence from paired transcranial magnetic stimulation. Journal of the Neurological Sciences. 1999;**170**(2):119-123

[37] Alberici A et al. The contribution of TMS to frontotemporal dementia variants. Acta Neurologica Scandinavica. 2008;**118**(4):275-280

[38] Battaglia F et al. Cortical plasticity in Alzheimer's disease in humans and rodents. Biological Psychiatry. 2007;**62**(12):1405-1412

[39] Ferreri F et al. Motor cortex excitability in Alzheimer's disease: A transcranial magnetic stimulation study. Annals of Neurology. 2003;**53**(1):102-108

[40] Liepert J et al. Motor cortex disinhibition in Alzheimer's disease. Clinical Neurophys iology. 2001;**112**(8):1436-1441

[41] Nardone R et al. Abnormal short latency afferent inhibition in early Alzheimer's disease: A transcranial magnetic demonstration. Journal of Neural Transmission (Vienna). 2008;**115**(11):1557-1562

[42] Nardone R, Bratti A, Tezzon F. Motor cortex inhibitory circuits in dementia with Lewy bodies and in Alzheimer's disease. Journal of Neural Transmission (Vienna). 2006;**113**(11):1679-1684

[43] Olazaran J et al. Cortical excitability in very mild Alzheimer's disease: A long-term follow-up study. Journal of Neurology. 2010;**257**(12):2078-2085

[44] Sakuma K, Murakami T, Nakashima K. Short latency afferent inhibition is not impaired in mild cognitive impairment. Clinical Neurophysiology. 2007;**118**(7):1460-1463

[45] Pierantozzi M et al. Different TMS patterns of intracortical inhibition in early onset Alzheimer dementia and frontotemporal dementia. Clinical Neurophysiology. 2004;**115**(10): 2410-2418

[46] Perretti A et al. Evaluation of the motor cortex by magnetic stimulation in patients with Alzheimer disease. Journal of the Neurological Sciences. 1996;**135**(1):31-37

[47] Niskanen E et al. New insights into Alzheimer's disease progression: A combined TMS and structural MRI study. PLoS One. 2011;**6**(10):e26113

[48] Lahr J et al. No difference in paired associative stimulation induced cortical neuroplasticity between patients with mild cognitive impairment and elderly controls. Clinical Neurophysiology. 2016;**127**(2):1254-1260

[49] Drumond Marra HL et al. Transcranial magnetic stimulation to address mild cognitive impairment in the elderly: A randomized controlled study. Behavioural Neurology. 2015;**2015**:287843

[50] Nardone R et al. Subjective memory impairment and cholinergic transmission: A TMS study. Journal of Neural Transmission (Vienna). 2015;**122**(6):873-876

[51] Nardone R et al. Reduced short latency afferent inhibition in patients with down syndrome and Alzheimer-type dementia. Clinical Neurophysiology. 2006;**117**(10):2204-2210

[52] Taylor JP, Firbank M, O'Brien JT. Visual cortical excitability in dementia with Lewy bodies. The British Journal of Psychiatry. 2016;**208**(5):497-498

[53] Pennisi G et al. Motor cortex excitability in Alzheimer disease: One year follow-up study. Neuroscience Letters. 2002;**329**(3):293-296

[54] Pennisi G et al. Motor cortex hyperexcitability in subcortical ischemic vascular dementia. Archives of Gerontology and Geriatrics. 2011;**53**(2):e111-e113

[55] Guerra A et al. Neurophysiological features of motor cortex excitability and plasticity in subcortical ischemic vascular dementia: A TMS mapping study. Clinical Neurophysiology. 2015;**126**(5):906-913

[56] Benussi A et al. Transcranial magnetic stimulation distinguishes Alzheimer disease from frontotemporal dementia. Neurology. 2017;**89**(7):665-672

[57] Rossor MN et al. A post-mortem study of the cholinergic and GABA systems in senile dementia. Brain. 1982;**105**(Pt 2):313-330

[58] Ihara M et al. Decrease in cortical benzodiazepine receptors in symptomatic patients with leukoaraiosis: A positron emission tomography study. Stroke. 2004;**35**(4):942-947

[59] Bella R et al. Enhanced motor cortex facilitation in patients with vascular cognitive impairment-no dementia. Neuroscience Letters. 2011;**503**(3):171-175

[60] Di Lazzaro V et al. Motor cortex hyperexcitability to transcranial magnetic stimulation in Alzheimer's disease: Evidence of impaired glutamatergic neurotransmission? Annals of Neurology. 2003;**53**(6):824 (author reply 824-25)

[61] Di Lazzaro V et al. Ketamine increases human motor cortex excitability to transcranial magnetic stimulation. The Journal of Physiology. 2003;**547**(Pt 2):485-496

[62] Farlow MR. NMDA receptor antagonists. A new therapeutic approach for Alzheimer's disease. Geriatrics. 2004;**59**(6):22-27

[63] Hynd MR, Scott HL, Dodd PR. Glutamate-mediated excitotoxicity and neurodegeneration in Alzheimer's disease. Neurochemistry International. 2004;**45**(5):583-595

[64] Di Lazzaro V et al. Neurophysiological predictors of long term response to AChE inhibitors in AD patients. Journal of Neurology, Neurosurgery, and Psychiatry. 2005;**76**(8):1064-1069

[65] Di Lazzaro V et al. Changes in motor cortex excitability in facioscapulohumeral muscular dystrophy. Neuromuscular Disorders. 2004;**14**(1):39-45

[66] Nardone R et al. Cholinergic dysfunction in subcortical ischaemic vascular dementia: A transcranial magnetic stimulation study. Journal of Neural Transmission (Vienna). 2008;**115**(5):737-743

[67] Petersen RC et al. Current concepts in mild cognitive impairment. Archives of Neurology. 2001;**58**(12):1985-1992

[68] Nardone R et al. Cognitive function and cholinergic transmission in patients with subcortical vascular dementia and microbleeds: A TMS study. Journal of Neural Transmission (Vienna). 2011;**118**(9):1349-1358

[69] McKeith IG et al. Diagnosis and management of dementia with Lewy bodies: Third report of the DLB consortium. Neurology. 2005;**65**(12):1863-1872

[70] Marra C et al. Central cholinergic dysfunction measured "in vivo" correlates with different behavioral disorders in Alzheimer's disease and dementia with Lewy body. Brain Stimulation. 2012;**5**(4):533-538

[71] Di Lazzaro V et al. Normal or enhanced short-latency afferent inhibition in Parkinson's disease? Brain. 2004;**127**(Pt 4):E8 (author reply E9)

[72] Coyle JT, Price DL, DeLong MR. Alzheimer's disease: A disorder of cortical cholinergic innervation. Science. 1983;**219**(4589):1184-1190

[73] Davies P, Maloney AJ. Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet. 1976;**2**(8000):1403

[74] Whitehouse PJ et al. Alzheimer's disease and senile dementia: Loss of neurons in the basal forebrain. Science. 1982;**215**(4537):1237-1239

[75] Procter AW, Qurne M, Francis PT. Neurochemical features of frontotemporal dementia. Dementia and Geriatric Cognitive Disorders. 1999;**10**(Suppl 1):80-84

[76] Manganelli F et al. Motor cortex cholinergic dysfunction in CADASIL: A transcranial magnetic demonstration. Clinical Neurophysiology. 2008;**119**(2):351-355

[77] Mesulam M, Siddique T, Cohen B. Cholinergic denervation in a pure multi-infarct state: Observations on CADASIL. Neurology. 2003;**60**(7):1183-1185

[78] Julkunen P et al. Combining transcranial magnetic stimulation and electroencephalography may contribute to assess the severity of Alzheimer's disease. International Journal of Alzheimer's Disease. 2011;**2011**:654794

[79] Freitas C, Fregni F, Pascual-Leone A. Meta-analysis of the effects of repetitive transcranial magnetic stimulation (rTMS) on negative and positive symptoms in schizophrenia. Schizophrenia Research. 2009;**108**(1-3):11-24

[80] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. The Journal of Physiology. 2000;**527**(Pt 3):633-639

[81] Wagner T, Valero-Cabre A, Pascual-Leone A. Noninvasive human brain stimulation. Annual Review of Biomedical Engineering. 2007;**9**:527-565

[82] Cotelli M et al. Effect of transcranial magnetic stimulation on action naming in patients with Alzheimer disease. Archives of Neurology. 2006;**63**(11):1602-1604

[83] Cotelli M et al. Transcranial magnetic stimulation improves naming in Alzheimer disease patients at different stages of cognitive decline. European Journal of Neurology. 2008;**15**(12):1286-1292

[84] Cotelli M et al. Improved language performance in Alzheimer disease following brain stimulation. Journal of Neurology, Neurosurgery, and Psychiatry. 2011;**82**(7):794-797

[85] Rektorova I et al. Cognitive functioning after repetitive transcranial magnetic stimulation in patients with cerebrovascular disease without dementia: A pilot study of seven patients. Journal of the Neurological Sciences. 2005;**229-230**:157-161

[86] Ahmed MA et al. Effects of low versus high frequencies of repetitive transcranial magnetic stimulation on cognitive function and cortical excitability in Alzheimer's dementia. Journal of Neurology. 2012;**259**(1):83-92

[87] Bentwich J et al. Beneficial effect of repetitive transcranial magnetic stimulation combined with cognitive training for the treatment of Alzheimer's disease: A proof of concept study. Journal of Neural Transmission (Vienna). 2011;**118**(3):463-471

[88] Haffen E et al. A case report of daily left prefrontal repetitive transcranial magnetic stimulation (rTMS) as an adjunctive treatment for Alzheimer disease. Brain Stimulation. 2012;**5**(3):264-266

[89] Rabey JM, Dobronevsky E. Repetitive transcranial magnetic stimulation (rTMS) combined with cognitive training is a safe and effective modality for the treatment of Alzheimer's disease: Clinical experience. Journal of Neural Transmission (Vienna). 2016;**123**(12):1449-1455

[90] Emre M et al. Rivastigmine for dementia associated with Parkinson's disease. The New England Journal of Medicine. 2004;**351**(24):2509-2518

[91] Wagner T et al. Transcranial magnetic stimulation and brain atrophy: A computer-based human brain model study. Experimental Brain Research. 2008;**186**(4):539-550

[92] Dickerson BC et al. The cortical signature of Alzheimer's disease: Regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. Cerebral Cortex. 2009;**19**(3):497-510

[93] Cheeran B et al. A common polymorphism in the brain-derived neurotrophic factor gene (BDNF) modulates human cortical plasticity and the response to rTMS. The Journal of Physiology. 2008;**586**(23):5717-5725

[94] Wolk DA, Dickerson BC, Neuroimaging I A's D. Apolipoprotein E (APOE) genotype has dissociable effects on memory and attentional-executive network function in Alzheimer's disease. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**(22):10256-10261

[95] Koch G et al. CSF tau levels influence cortical plasticity in Alzheimer's disease patients. Journal of Alzheimer's Disease. 2011;**26**(1):181-186

[96] Freitas C, Mondragon-Llorca H, Pascual-Leone A. Noninvasive brain stimulation in Alzheimer's disease: Systematic review and perspectives for the future. Experimental Gerontology. 2011;**46**(8):611-627

[97] Silvanto J, Pascual-Leone A. State-dependency of transcranial magnetic stimulation. Brain Topography. 2008;**21**(1):1-10

Chapter 3

Non-invasive Stimulation of the Cerebellum in Health and Disease

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73218

Abstract

The cerebellum is linked to motor, cognitive and affective functions. Anatomically, the cerebellum is part of an interconnected network including a wide range of other brain structures. This chapter reviews ways in which non-invasive stimulation has been used to activate or inhibit these circuits and how this has contributed to our understanding of cerebellar function in both motor and non-motor domains. The utility of non-invasive stimulation of the cerebellum in the treatment of neurological and psychiatric diseases (Parkinson's disease, cerebellar ataxia, stroke, depression and schizophrenia) is discussed. The chapter concludes with consideration of the challenges that must be overcome if non-invasive cerebellar stimulation is to be adopted in a wider clinical setting.

Keywords: cerebellum, tDCS, tACS, TMS, motor learning, emotion and cognition

1. Introduction

The mammalian cerebellum is a highly folded structure at the back of the brain, which contains the majority of all neurones within the central nervous system (approximately 80% in humans and other species [1]). It has long been known to play a key role in movement control, regulating a range of motor functions (both reflexive and voluntary) [2, 3].

There is now also growing evidence that cerebellar contributions to behaviour are not restricted to motor control but also extend to the cognitive domain (for a review, see [4]). There is a high degree of interconnectivity between the cerebellum and almost all other brain regions, with connections from cerebrum to the cerebellum primarily through the pontocerebellar tract, and reciprocal connections to the cerebral hemispheres primarily from the lateral

cerebellum via the dentato-thalamo-cortical tract [5]. Other cerebellar output pathways originate from its paravermal and vermal compartments and these are known to play significant roles in motor and non-motor functions [6, 7].

Given the interconnectivity between the cerebellum and other structures such as hippocampus [8, 9], and prefrontal cortex [10–12], a role in higher order information processing is perhaps unsurprising. Indeed, there is now a substantial literature based on functional imaging and reports of cerebellar patients linking the cerebellum with cognitive functions such as verbal working memory, attention and emotion [13–18].

However, a comprehensive understanding of the way the cerebellum makes its contribution to behaviour (motor and non-motor) remains unresolved. Two major classes of theory dominate current thinking. On the one hand are those that suggest that the cerebellum acts to learn associations between stimuli (learning hypotheses), and on the other, those that suggest the cerebellum acts as a timing device (timing hypotheses).

Learning hypotheses stem from Marr's original theoretical proposal [19] and typically centre on the plasticity of synaptic inputs to the principal neurones of the cerebellar cortex—the Purkinje cells (for a review of cerebellar anatomy, see [3]). The numerous synaptic inputs to each Purkinje cell, via the mossy fibre-granule cell pathway, are thought to transmit sensorimotor information during movement. When a behavioural error occurs (thought to be a mismatch in the sensory consequences of the predicted movement) this is signalled to the Purkinje cells, via their powerful synaptic input from climbing fibres (originating from the inferior olive). This teaching signal induces plasticity mechanisms in the mossy fibre-granule cell synaptic connections to the same Purkinje cells, modifying synaptic weights and thereby adjusting the pattern of sensorimotor integration performed by Purkinje cells [20].

By contrast, timing hypotheses generally propose that the olivocerebellar circuit (made up of a feedback loop between inferior olive neurones, cerebellar cortical Purkinje cells and the output of the cerebellum, the cerebellar nuclei) is able to generate rhythmic and synchronised activity, to drive timing and spatial organisation of motor sequences [21], and other functions [22].

While studies of the cerebellum have generally considered its function in the context of either learning or timing hypotheses, they have been discussed together with the view that the two hypotheses are not mutually exclusive [23].

In order to further our understanding of cerebellar function, non-invasive methods of neurostimulation have been used to manipulate cerebellar function in humans. This chapter will focus on studies of non-invasive techniques to alter cerebellar activity in both health and disease—however it is by no means an exhaustive account of current literature. We will begin by outlining basic research involving direct (invasive) stimulation of the cerebellum, and highlight how manipulation of cerebellar activity can lead to changes in a wide variety of behaviours. Research using the two major forms of non-invasive stimulation (transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS)) will then be discussed, including possible mechanisms of action. We will then discuss the use of these techniques as potential therapeutic methods to treat neurological and psychiatric conditions, including both motor and affective disorders. The chapter will conclude with a consideration of the challenges facing the use of non-invasive stimulation of the cerebellum.

2. Basic research

2.1. Direct cerebellar stimulation

Neurophysiological investigations of the cerebellum have long utilised manipulation of neuronal activity to explore its function. Of interest to this review is the use of direct cerebellar stimulation to alter behaviour.

Direct electrical stimulation of fastigial nucleus afferents and cerebellar nuclei have been shown to activate groups of muscles leading to multi-joint movements [24–26], suggesting that the cerebellum is able to directly shape complex movements. Stimulation of the cerebellar nuclei has also been shown to affect autonomic physiology such as cardiovascular and respiratory control and gut motility, but also integrated responses related to emotional behaviour (reviewed in [6, 27]).

Clinically, chronic stimulation of cerebellar cortex in epileptic patients was observed to improve not only motor symptoms, but cognitive and affective symptoms (increased alertness, attention, and suppression of rage reactions) [28]. However, whether the latter effects were due to the direct cerebellar stimulation or were a secondary effect of relief from the epileptic seizures and debilitating motor symptoms remains unclear.

Recent findings in mice have also shown that electrical stimulation of the cerebellar cortex and dentate nucleus are able to moderate dopamine release in the prefrontal cortex, consistent with a cerebellar role in cognition [29]. In addition, optogenetic stimulation of cerebellothalamic projections in a mouse model of frontal schizophrenia has been shown to rescue timing performance deficits in an interval timing task [30]. In relation to epilepsy, optogenetic stimulation of a subtype of Purkinje cells in a mouse model of temporal lobe epilepsy led to the suppression of either seizure duration, or seizure occurrence, depending on specific cerebellar target [31]. Overall, a growing body of evidence therefore points toward the cerebellum playing an important role in a myriad of physiological and pathophysiological processes, with direct stimulation of the cerebellum capable of manipulating these processes.

In contrast to animal studies, direct stimulation of neural tissue in humans is restricted by the availability of patients with implanted electrodes, especially in the cerebellum. The advent of non-invasive methods has therefore provided a valuable alternative approach to manipulate cerebellar activity in humans, in both healthy and disease states.

2.2. Non-invasive stimulation of the cerebellum

Typically, transcranial electrical stimulation (direct or alternating current) of the cerebellum is achieved with an active electrode, usually a 20–35 cm^2 saline soaked sponge, placed over the back of the skull approximately 2–3 cm left or right of inion for activating the cerebellar hemisphere of interest. Note that the cerebellum exhibits mainly ipsilateral control for motor related tasks. The opposing polarity electrode (often referred to as the 'return' electrode) is usually placed over a deltoid/buccinator muscle or at a frontal-supraorbital location. Such an arrangement is thought to help draw current flow primarily through the cerebellar cortex and away from other structures so that any observed effects are due mainly to manipulations of cerebellar

activity. Magnetic stimulation methods do not have the same issue, however careful consideration of coil geometry is needed as this affects the targetability of the induced fields [32].

Modelling studies for both electric and magnetic stimulation show that it is possible to target predominantly cerebellar tissue, albeit with some spread of stimulation into occipital areas [33–36]. However, selective sub-cerebellar structure targeting (vermis versus hemispheres) has so far not been clearly demonstrated. As such, although some reports in the literature suggest the targeting of certain cerebellar areas, without further validation of electrical currents via either direct measurement or modelling techniques, this should be taken with caution. It is likely that future advances in our understanding of stimulation parameters and electrode montages/geometries, will lead to further specificity of stimulation. However, it is generally accepted that it may be possible to selectively target the cerebellum with non-invasive stimulation techniques when careful attention is given to stimulation parameters and electrode placement.

2.2.1. Motor-learning

Since the original demonstrations that transcranial direct stimulation (tDCS) over the motor cortex was able to elicit motor evoked potentials, investigations of motor learning in humans have relied extensively on non-invasive stimulation methods [37, 38].

Typically, TMS and tDCS have been used in combination to show a dissociation in temporal involvement of the cerebellum and primary motor cortex during motor learning. Such studies infer an effect of non-invasive stimulation on cerebellar activity of functional connectivity by measuring changes to the amplitude of motor evoked potentials elicited by a TMS pulse delivered to the motor cortex after TMS stimulation of the cerebellum (cerebellar brain inhibition, CBI). It has recently been shown that CBI is reduced during early phases of motor skill acquisition, whereas motor cortex plasticity may be restricted to later learning phases [39]. A significant reduction of CBI was restricted to early learning (returning to baseline levels during later test sessions), and the magnitude of these changes were proportional to the level of individual skill acquisition. Conversely, measurements of plasticity states in the primary motor cortex revealed that plasticity in the primary motor cortex was occurring in later, but not early learning phases, and was proportional to skill retention on subsequent days, suggesting a role in consolidation of a newly learned motor memory. In a separate study, reduction in CBI was also shown during sensorimotor adaptation in early stages of an abruptly imposed perturbation, but not in either later stages, or when the perturbation was introduced gradually [40], further suggesting that the cerebellum is involved in the early stages of in motor learning.

tDCS has also been used to show a similar dissociation between the cerebellum and motor cortex [41]. Anodal stimulation over the cerebellum increased the rate of reduction of behavioural errors when a rotation transformation was imposed onto a computer based reaching task (visuomotor adaptation—see [42]), whereas motor cortical stimulation led to improved retention of the previously learned rotation on repeated exposure, with no effect on the learning rate.

In summary, studies using non-invasive stimulation methods provide evidence that the cerebellum is involved in the initial phases of motor learning (when behavioural errors are large).

This involvement declines when this initial adaptive period is complete. Further research is needed to investigate whether the temporal dissociation of the cerebellum and motor cortex in motor adaptation represents either different learning mechanisms, or a transfer of information from the cerebellum to the motor cortex about the new relationship between motor programs and sensory consequences for long term storage and use. The picture is, however, by no means clear cut. As will be discussed in the final section of this chapter, there are conflicting reports of effectiveness of non-invasive stimulation of the cerebellum to affect motor behaviours.

2.2.2. Cognition and emotion

Non-invasive stimulation methods have also contributed to our understanding of cerebellar involvement in higher order functions. For example, cathodal tDCS stimulation to the right cerebellum in healthy participants improved performance during two cognitive tasks of varying difficulty (Paced Auditory Serial Addition Task and Paced Auditory Serial Subtraction Task) [43]. Improvements in attention and working memory performance following cerebellar stimulation were proposed to result from task dependent dis-inhibition of prefrontal circuitry, with greater disinhibition during the more difficult task.

EEG based studies determined that theta-burst cerebellar TMS modulates oscillatory activity in both M1 and posterior parietal cortex (PPC), further demonstrating the widespread effect of cerebellar stimulation [44]. Modulatory effects in both time and frequency domains were dependent on the stimulation protocol. Specifically, continuous theta burst TMS (three 50 Hz pulse bursts repeated every 200 ms, for 600 total pulses) over the cerebellum increased the magnitude of TMS induced evoked potentials (~100–200 ms post stimulation) over both M1 and PPC at 10 minutes after the TMS protocol. Conversely, intermittent theta-burst TMS (2 s trains of pulses, repeated 20 times, every 10 s for a total of 600 pulses) decreased the magnitude of TMS evoked potentials in these frontal areas.

EEG recordings over the prefrontal cortex of healthy participants, with TMS over the cerebellar vermis, revealed increased theta band oscillations compared to a sham stimulation protocol [45]. Frontal theta oscillations (specifically septo-hippocampal circuits) have been related to cognitive processes such as working memory maintenance and also anxiety states [46, 47], suggesting a cerebellar role in regulation of cognitive and emotional processes. Other studies have suggested that cerebellar influence on frontal theta oscillations are fundamental to temporal processing (interval timing) and synchronisation of multiple brain regions [48], which may subserve a role in working memory. Indeed, a cerebellar role in verbal working memory has been demonstrated via deficits in a task based on the Sternberg Task induced by a TMS 'virtual lesion' [49] and in a digit span task using cathodal tDCS [50].

In agreement with the wider literature on a cerebellar role in timing, TMS studies have directly tested its role in timing perception. In a series of experiments requiring subjects to discriminate whether test tones resemble a long or short template tone, repetitive TMS of the right lateral and medial cerebellum disrupted tone perception of sub-second durations, but not durations longer than one second [51]. Similar results were observed using a task requiring participants to reproduce specified stimulus durations [52]. Specifically, repetitive TMS to

the left lateral cerebellum resulted in participants overestimating the duration of short (up to 600 ms) tone durations, but had no effect on tone durations longer than 1600 ms [52]. Together these experiments provide evidence that the cerebellum plays an important role in maintaining the perception of rhythmic time intervals when such intervals are short (sub-second), but not necessarily at longer intervals. In support of this view, Purkinje cell simple spike discharge have been shown to be consistent with a predictive timing role, in relation to operation of an internal model of a target's motion, with operating ranges of at least 200–300 ms [53].

In summary, these studies demonstrate how non-invasive stimulation of the cerebellum has been utilised to investigate functional connectivity between the cerebellum and other brain structures associated with cognition, complementing anatomical and neuroimaging based studies [10, 54]. Such an approach also has the potential to be used to influence higher cognitive processing in both health and disease.

3. Clinical studies

Notwithstanding the challenges that will be discussed later, non-invasive stimulation methods promise a useful avenue for clinical therapy of many neurological and psychiatric conditions. Such an approach is attractive because of the ease of use, suitability for high-risk populations (elderly, overweight, and those who elect against surgical interventions), low cost (especially in the case of tDCS), and good safety record, with only mild, transient side effects [55, 56]. The cerebellum is well placed to be a target for treatment of a number of clinical impairments [57].

3.1. Parkinson's disease and essential tremor

A number of TMS protocols have indicated that targeting the motor cortex with non-invasive stimulation can lead to short term improvements in Parkinsonian symptoms, most commonly motor aspects, but also depression [58]. Parkinson's has classically been associated with the degeneration of the dopaminergic pathways of the basal ganglia, leading to both motor and affective symptoms. Recent studies propose however that the disease mechanism(s) may be better understood as a dysfunction of a basal ganglia-cortical-cerebellar network [59], and evidence for a role of the cerebellum has been building [60]. Indeed there are Parkinsonian symptoms (particularly resting tremor) in populations with spinocerebellar ataxia type 3 [61], which support a cerebellar link in such symptoms.

Compared to a sham protocol, low frequency repetitive TMS over the cerebellum in early stage Parkinson's patients has been shown to improve gross upper limb motor function (around a 10% improvement), but a non-significant decrease in fine finger control [62]. Significant decreases in fine motor control have also been noted in healthy participants [63]. The beneficial effect on gross motor function is thought to be mediated by a reduction in the tonic inhibitory influence of the cerebellum on the motor cortex, however the opposing effects on fine motor control remain unexplained. Since it may be undesirable to modestly improve gross motor functions at the detriment of fine motor control, further studies are needed to

resolve the mixed results of this TMS protocol before it can be considered a reliable clinical intervention for early stage Parkinson's.

Cerebellar targeted theta burst repetitive TMS over a 2-week period in Parkinson's patients who had developed levodopa-induced dyskinesia, resulted in improvements in dyskinesia symptoms up to 4-weeks after the stimulation period [64]. By contrast, a 15 minute, 1 Hz repetitive TMS stimulation over the supplementary motor cortex has been reported to have no long term effect [65]. A recent report revealed that cerebellar (as well as motor cortical) tDCS may also provide positive therapeutic outcomes in levodopa-induced dyskinesia [66]. The mechanisms of action remain poorly defined, but one possibility is the overall increase in CBI (see above). Overall, the cerebellum may therefore provide a promising target for manipulating network activity underlying motor symptoms of Parkinson's disease.

3.2. Cerebellar ataxia

Studies utilising TMS over motor cortex have shown abnormal motor cortex excitability in cerebellar ataxic patients, attributed both to direct cerebellar influence [67], and compensatory motor cortical mechanisms [68]. The heterogeneous origins of individual ataxias (with degeneration possible in both cortical, and peduncle locations) likely means that this is not strictly the case for all patients [69]. Indeed, cerebellar ataxia may not be explained solely by disruption to motor cortical excitability, but disruption of the cerebellum's role in co-ordinating multiple muscle groups to produce smooth, accurate movements [70].

Despite the limited literature on the use of therapeutic non-invasive cerebellar stimulation in patients [71], cerebellar TMS has shown the potential for therapeutic use, successfully alleviating ataxic symptoms [72, 73] through facilitation of motor cortex excitability [74]. Conversely, a study testing the effects of anodal cerebellar tDCS on grip force in both ataxic patients and healthy controls did not reveal any effects in either group [75]. Regardless of the unresolved, and probably heterogeneous causes of motor disability in ataxic patients, cerebellar TMS stimulation may be well placed to rescue cerebellar function in cases of partial cerebellar degeneration, but is unlikely to benefit those with substantial dysfunction of cerebellar structures.

3.3. Cerebral stroke

Cerebral stroke can affect motor, cognitive, and/or emotional abilities depending on the size and location of the insult. Non-invasive stimulation procedures over the motor cortex have been investigated, however the effectiveness of targeting the motor cortex has been questioned [76]. As detailed above, cerebellar stimulation can modulate a wide range of behaviours in healthy subjects, and so has the potential to influence symptoms suffered by stroke patients. Certainly, a few small scale studies have shown success in improving post-stroke symptoms, such as greater recovery of language and spelling abilities with multiple sessions of cerebellar tDCS combined with spelling therapy compared to therapy alone [77].

A prevalent outcome of stroke is the development of depression [78]. Repetitive TMS of frontal sites has been shown to have some beneficial effect, although questions still remain over the longer term success [79]. Direct stimulation of the cerebellar fastigial nucleus alleviates

some depression-like symptoms in rat, including weight loss, reduced sucrose preference, and reduced locomotor activities [80]. However, translating these results to non-invasive human stimulation will be challenging; particularly as non-invasive techniques have so far been limited to modulating cerebellar cortex.

Another common consequence of cerebellar stroke is the inability to swallow effectively (post-stroke dysphagia) [81]. Although the precise mechanisms leading to dysphagia are unresolved, non-invasive brain stimulation techniques have been explored as potential tools for the management of dysphagia [81]. The cerebellum has been implicated in effective swallowing [6], and repetitive TMS of the cerebellum has been shown to improve swallowing mechanisms (reviewed in [82]), as measured by an increase in pharyngeal motor evoked potential following stimulation.

Taken together these findings therefore suggest that non-invasive stimulation of the cerebellum may be a useful method for the treatment of a range of post stroke symptoms.

3.4. Major depression and schizophrenia

The majority of interest in using non-invasive brain stimulation methods to treat psychiatric disorders has focussed on cerebral targets [83]. However, in a rodent model of schizophrenic deficits in interval timing tasks, optogenetic stimulation of cerebellar projections at 2 Hz resulted in a return of control level performance in an interval timing task, which correlated with a return of medial-frontal delta (1–4 Hz) oscillations, not observed in unstimulated animals [30]. In addition, a study in schizophrenic patients has shown the potential utility of non-invasive cerebellar stimulation to alleviate some of the symptoms of the disorder; such as reduced depression (measured on the Calgary Depression Scale), and fewer omissions in working memory tasks [84]. Given the growing understanding of the brain-wide networks involved in these types of disorder, the cerebellum is clearly a potential target for further investigation [57].

4. Challenges and the future of non-invasive cerebellar stimulation

Since the revival of interest in non-invasive stimulation techniques about 2–3 decades ago, there have been clear advances made in both their use as research tools—advancing our knowledge about neurophysiological processes—and as therapeutic interventions. However, the literature is still awash with many uncertainties about the efficacy of the techniques, and there is typically a high degree of variability in the results. For example, a recent attempt to replicate an experiment dissociating the roles of the cerebellum and M1 in motor adaptation [41] was unsuccessful in a like-for-like experiment [85]. The study went further and pooled data across several experiments (varying some parameters of the design). The pooled data re-captured the effects of the original experiment, however the effect size was reduced. The authors concluded that some publications may be overestimating the effects of tDCS, possibly because of underpowered experiments.

Although changing, many studies assume that the electrical fields induced in the underlying brain tissue are uniform—or at least quasi-uniform—and so the stimulation delivered to the

local circuitry of the target area can be considered homogenous. However, it is now recognised that this is almost certainly an oversimplification. Even in the localised space of a single cerebral cortical gyrus or cerebellar folium, neurones can be hyperpolarised or depolarised by the same field because of differences in the orientation of the cellular compartments (see **Figure 1**), and differences in the geometry of current flow [86–88]. Consequently, small inter-individual variations in brain morphology, or inaccurate electrode/coil placements could lead to significant differences in the polarisation of the target tissue. Given the much greater level of cortical folding in cerebellar folia compared to cerebral areas, this is likely of greater influence on cerebellar circuitry than cerebral circuitry. Certainly, data collected from cerebral tissue may not accurately reflect patterns of polarisation in cerebellar tissue.

Such issues can be investigated directly in animal models which allow investigation of neurophysiological mechanisms at the cellular level. Different compartments of individual neurones (dendritic vs. somatic) have been shown to exhibit opposing polarities in an electric field in *ex vivo* preparations of rodent cerebral tissue [89–91], and turtle cerebellar tissue [92]. How such effects translate to the whole living brain remains an open question, and further *in vivo* studies are needed in animals [93–96].

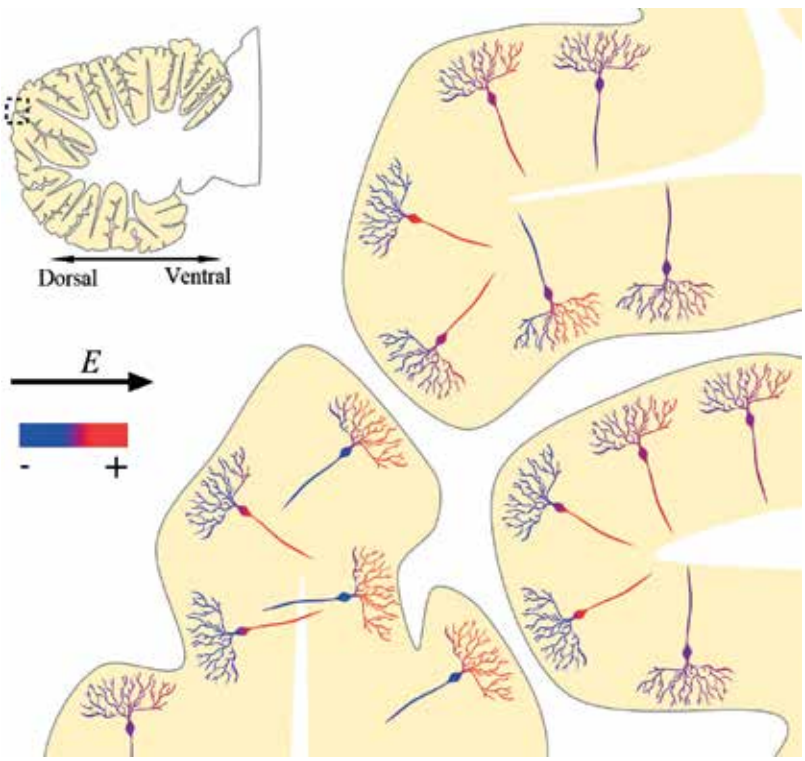

Figure 1. Representation of non-uniform Purkinje cell polarisation in a uniform electric field. Schematic showing cerebellar folia with Purkinje cells polarised in a uniform electric field. Inset shows cerebellum in sagittal plane, with location of expanded region shown in dotted box. Direction of the electric field *E* shown by arrow. This field orientation will generate hyperpolarisation (−) in dorsal cell compartments and depolarisation (+) in ventral cell compartments. Note how the orientation of Purkinje cells in different locations affects the relative polarisation of the soma and dendrites.

An additional consideration not commonly controlled for in non-invasive stimulation (particularly electrical stimulation) studies are factors such as individual skull thickness [87], gender [97], time of day [98], and brain network state [99]. With electrical stimulation, variability can also result from the specific arrangement (montage) of electrodes used—influencing the intensity, and focality of stimulation [56, 87, 100]—while for magnetic stimulation, coil geometry has been shown to alter the effectiveness of TMS [32], and positioning of the coils will clearly affect the focus of stimulation.

Stimulation intensity is also an important variable. In the case of electrical stimulation, a current of between 1 and 2 mA is typically used. The consensus is that these levels of current are well below any thresholds that will lead to neuronal damage [101, 102]. Large scale systematic studies testing the effects of increasing stimulation intensities (remaining within safety limits) would establish if there is a relationship between stimulus intensity and effect size/consistency. Advances in the use of modelling induced electric fields and the availability of individualised computational models to predict these fields would help electrode/coil placement for optimal targeting in individual subjects [86]. Furthermore, a large proportion of TMS research utilises MRI based registration methods to aid targeting. Perhaps more widespread adoption of MRI registration techniques in tDCS research to aid electrode placement might further benefit standardised targeting of tDCS. Careful choice of stimulation montages, and clear reporting of stimulus parameters would also be helpful.

In conclusion, a growing body of evidence suggests that the cerebellum is an important node in brain networks, associated with a wide range of motor and cognitive functions; and non-invasive stimulation of the cerebellum can manipulate these circuits. However, a greater understanding of the neurophysiological effects of such stimulation are needed in animal models. This could lead to more consistent approaches across human studies. As a result, the cerebellum may prove to be a useful and reliable target in altering brain activity in both health and disease.

Acknowledgements

Funding – BBSRC SWBio DTP studentship, MRC grant G1100626.

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References

[1] Herculano-Houzel. Coordinated scaling of cortical and cerebellar numbers of neurons. Frontiers in Neuroanatomy. 2010;**4**:12. DOI: 10.3389/fnana.2010.00012

[2] Proville RD, Spolidoro M, Guyon N, Dugué GP, Selimi F, Isope P, et al. Cerebellum involvement in cortical sensorimotor circuits for the control of voluntary movements. Nature Neuroscience. 2014;**17**(9):1233-1239. DOI: 10.1038/nn.3773

[3] Apps R, Garwicz M. Anatomical and physiological foundations of cerebellar information processing. Nature Reviews. Neuroscience. 2005;**6**(4):297-311. DOI: 10.1038/nrn1646

[4] Strick PL, Dum RP, Fiez JA. Cerebellum and nonmotor function. Annual Review of Neuroscience. 2009;**32**(1):413-434. DOI: 10.1146/annurev.neuro.31.060407.125606

[5] Buckner RL, Krienen FM, Castellanos A, Diaz JC, Yeo BTT. The organization of the human cerebellum estimated by intrinsic functional connectivity. Journal of Neurophysiology. 2011;**106**(5):2322-2345. DOI: 10.1152/jn.00339.2011

[6] Zhang X-Y, Wang J-J, Zhu J-N. Cerebellar fastigial nucleus: From anatomic construction to physiological functions. Cerebellum & Ataxias. 2016;**3**:9. DOI: 10.1186/s40673-016-0047-1

[7] Pakaprot N, Kim S, Thompson RF. The role of the cerebellar interpositus nucleus in short and long term memory for trace eyeblink conditioning. Behavioral Neuroscience. 2009;**123**(1):54-61. DOI: 10.1037/a0014263

[8] Yu W, Krook-Magnuson E. Cognitive collaborations: Bidirectional functional connectivity between the cerebellum and the hippocampus. Frontiers in Systems Neuroscience. 2015;**9**: 177. DOI: 10.3389/fnsys.2015.00177

[9] Onuki Y, Van Someren EJW, De Zeeuw CI, Van Der Werf YD. Hippocampal-cerebellar interaction during spatio-temporal prediction. Cerebral Cortex. 2015;**25**(2):313-321. DOI: 10.1093/cercor/bht221

[10] Middleton F, Strick PL. Cerebellar projections to the prefrontal corex of the primate. The Journal of Neuroscience. 2001 Jan 15;**21**(2):700-712 PMID: 11160449

[11] Watson TC, Jones MW, Apps R. Electrophysiological mapping of novel prefrontal - cerebellar pathways. Frontiers in Integrative Neuroscience. 2009;**3**:18. DOI: 10.3389/neuro.07.018.2009

[12] Watson TC, Becker N, Apps R, Jones MW. Back to front: Cerebellar connections and interactions with the prefrontal cortex. Frontiers in Systems Neuroscience. 2014;**8**(Feb):4. DOI: 10.3389/fnsys.2014.00004

[13] De Smet HJ, Paquier P, Verhoeven J, Mariën P. The cerebellum: Its role in language and related cognitive and affective functions. Brain and Language. 2013;**127**(3):334-342. DOI: 10.1016/j.bandl.2012.11.001

[14] Sullivan EV. Cognitive functions of the cerebellum. Neuropsychology Review. 2010;**20**(3): 227-228. DOI: 10.1007/s11065-010-9144-8

[15] Turner BM, Paradiso S, Marvel CL, Pierson R, Boles Ponto LL, Hichwa RD, et al. The cerebellum and emotional experience. Neuropsychologia. 2007;**45**(6):1331-1341. DOI: 10.1016/j.neuropsychologia.2006.09.023

[16] Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain. 1998; **121**(4):561-579. DOI: 10.1093/brain/121.4.561

[17] Koziol LF, Budding D, Andreasen N, D'Arrigo S, Bulgheroni S, Imamizu H, et al. Consensus paper: The cerebellum's role in movement and cognition. Cerebellum. 2014;**13**(1):151-177. DOI: 10.1007/s12311-013-0511-x

[18] Blatt GJ, Oblak AL, Schmahmann JD. Cerebellar connections with limbic circuits: Anatomy and functional implications. In: Manto M, Schmahmann JD, Rossi F, Gruol DL, Koibuchi N, editors. Handbook of the Cerebellum and Cerebellar Disorders. Dordrecht: Springer Netherlands; 2013. pp. 479-496. DOI: 10.1007/978-94-007-1333-8

[19] Marr D. A theory of cerebellar cortex. The Journal of Physiology. 1969;**202**:437-470. PMCID: PMC1351491

[20] Ito M. Mechanisms of motor learning in the cerebellum. Brain Research. 2000;**886**:237-245. DOI: 10.1016/S0006-8993(00)03142-5

[21] Llinás RR. Cerebellar motor learning versus cerebellar motor timing: The climbing fibre story. The Journal of Physiology. 2011;**589**(Pt 14):3423-3432. DOI: 10.1113/jphysiol.2011.207464

[22] Ivry RB, Spencer RM, Zelaznik HN, Diedrichsen J. The cerebellum and event timing. Annals of the New York Academy of Sciences. 2002;**978**(1):302-317. DOI: 10.1111/j.1749-6632.2002.tb07576.x

[23] Lang EJ, Apps R, Bengtsson F, Cerminara NL, De Zeeuw CI, Ebner TJ, et al. The roles of the Olivocerebellar pathway in motor learning and motor control. A consensus paper. Cerebellum. 2017;**16**(1):230-252. DOI: 10.1007/s12311-016-0787-8

[24] Mori S, Matsui T, Mori F, Nakajima K, Matsuyama K. Instigation and control of treadmill locomotion in high decerebrate cats by stimulation of the hook bundle of Russell in the cerebellum. Canadian Journal of Physiology and Pharmacology. 2000;**78**(11):945-957. DOI: 10.1139/y00-065

[25] Rispal-Padel L, Cicirata F, Pons C. Cerebellar nuclear topography of simple and synergistic movements in the alert baboon (*Papio papio*). Experimental Brain Research. 1982;**47**(3):365-380. DOI: 10.1007/BF00239355

[26] Ekerot CF, Jörntell H, Garwicz M. Functional relation between corticonuclear input and movements evoked on microstimulation in cerebellar nucleus interpositus anterior in the cat. Experimental Brain Research. 1995;**106**(3):365-376. DOI: 10.1007/BF00231060

[27] Watson TC, Koutsikou S, Cerminara NL, Flavell CR, Crook JJ, Lumb BM, et al. The olivo-cerebellar system and its relationship to survival circuits. Front Neural Circuits. 2013;**7**(Apr):72. DOI: 10.3389/fncir.2013.00072

[28] Cooper IS, Amin I, Riklan M, Waltz JM, Poon TP. Chronic cerebellar stimulation in epilepsy. Clinical and anatomical studies. Archives of Neurology. 1976;**33**(8):559-570. DOI: 10.1001/archneur.1976.00500080037006

[29] Mittleman G, Goldowitz D, Heck DH, Blaha CD. Cerebellar modulation of frontal cortex dopamine efflux in mice: Relevance to autism and schizophrenia. Synapse. 2008;**62**(7): 544-550. DOI: 10.1002/syn.20525

[30] Parker KL, Kim YC, Kelley RM, Nessler AJ, Chen K-H, Muller-Ewald VA, et al. Delta-frequency stimulation of cerebellar projections can compensate for schizophrenia-related medial frontal dysfunction. Molecular Psychiatry. 2017;**22**(5):647-655. DOI: 10.1038/mp.2017.50

[31] Krook-Magnuson E, Szabo GG, Armstrong C, Oijala M, Soltesz I. Cerebellar directed Optogenetic intervention inhibits spontaneous hippocampal seizures in a mouse model of temporal lobe epilepsy. eNeuro. 2014;**1**(1):1-27. DOI: 10.1523/eneuro.0005-14.2014

[32] Hardwick RM, Lesage E, Miall RC. Cerebellar transcranial magnetic stimulation: The role of coil geometry and tissue depth. Brain Stimulation. 2014;**7**(5):643-649. DOI: 10.1016/j.brs.2014.04.009

[33] Parazzini M, Rossi E, Ferrucci R, Liorni I, Priori A, Ravazzani P. Modelling the electric field and the current density generated by cerebellar transcranial DC stimulation in humans. Clinical Neurophysiology. 2014;**125**(3):577-584. DOI: 10.1016/j.clinph.2013.09.039

[34] Sekino M, Hirata M, Sakihara K, Yorifuji S, Ueno S. Intensity and localization of eddy currents in transcranial magnetic stimulation to the cerebellum. IEEE Transactions on Magnetics. 2006;**42**(10):3575-3577. DOI: 10.1109/TMAG.2006.879821

[35] Bijsterbosch JD, Barker AT, Lee KH, Woodruff PWR. Where does transcranial magnetic stimulation (TMS) stimulate? Modelling of induced field maps for some common cortical and cerebellar targets. Medical & Biological Engineering & Computing. 2012;**50**(7):671-681. DOI: 10.1007/s11517-012-0922-8

[36] Rampersad SM, Janssen AM, Lucka F, Aydin U, Lanfer B, Lew S, et al. Simulating Transcranial direct current stimulation with a detailed anisotropic human head model. IEEE Transactions on Neural Systems and Rehabilitation Engineering. 2014;**22**(3):441-452. DOI: 10.1109/TNSRE.2014.2308997

[37] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. The Journal of Physiology. 2000;**527**(3):633-639. DOI: 10.1111/j.1469-7793.2000.t01-1-00633.x

[38] Priori A, Berardelli A, Rona S, Accornero N, Manfredi M. Polarization of the human motor cortex through the scalp. Neuroreport. 1998;**9**(10):2257-2260. DOI: 10.1097/00001756-199807130-00020

[39] Spampinato D, Celnik P. Temporal dynamics of cerebellar and motor cortex physiological processes during motor skill learning. Scientific Reports. 2017;**7**:40715. DOI: 10.1038/srep40715

[40] Schlerf JE, Galea JM, Bastian AJ, Celnik P. Dynamic modulation of cerebellar excitability for abrupt, but not gradual, visuomotor adaptation. The Journal of Neuroscience. 2012;**32**(34): 11610-11617. DOI: 10.1523/jneurosci.1609-12.2012

[41] Galea JM, Vazquez A, Pasricha N, Orban De Xivry JJ, Celnik P. Dissociating the roles of the cerebellum and motor cortex during adaptive learning: The motor cortex retains what the cerebellum learns. Cerebral Cortex. 2011;**21**(8):1761-1770. DOI: 10.1093/cercor/bhq246

[42] Krakauer JW. Motor learning and consolidation: The case of visuomotor rotation. Advances in Experimental Medicine and Biology. 2009;**629**:405-421. DOI: 10.1007/978-0-387-77064-2_21

[43] Pope PA, Miall RC. Task-specific facilitation of cognition by cathodal transcranial direct current stimulation of the cerebellum. Brain Stimulation. 2012;**5**(2):84-94. DOI: 10.1016/j.brs.2012.03.006

[44] Casula EP, Pellicciari MC, Ponzo V, Stampanoni Bassi M, Veniero D, Caltagirone C, et al. Cerebellar theta burst stimulation modulates the neural activity of interconnected parietal and motor areas. Scientific Reports. 2016;**6**(May):36191. DOI: 10.1038/srep36191

[45] Schutter DJLG, Van Honk J. An electrophysiological link between the cerebellum, cognition and emotion: Frontal theta EEG activity to single-pulse cerebellar TMS. NeuroImage. 2006;**33**(4):1227-1231. DOI: 10.1016/j.neuroimage.2006.06.055

[46] Jensen O, Tesche CD. Frontal theta activity in humans increases with memory load in a working memory task. The European Journal of Neuroscience. 2002;**15**(8):1395-1399. DOI: 10.1046/j.1460-9568.2002.01975.x

[47] Messerotti Benvenuti S, Mennella R, Buodo G, Palomba D. Frontal theta activity as an EEG correlate of mood-related emotional processing in Dysphoria. Journal of Psychopathology and Behavioral Assessment. 2017;**39**(2):241-252. DOI: 10.1007/s10862-016-9572-8

[48] Parker KL. Timing tasks synchronize cerebellar and frontal ramping activity and theta oscillations: Implications for cerebellar stimulation in diseases of impaired cognition. Frontiers in Psychiatry. 2016;**6**(Jan):190. DOI: 10.3389/fpsyt.2015.00190

[49] Desmond JE, Chen SHA, Shieh PB. Cerebellar transcranial magnetic stimulation impairs verbal working memory. Annals of Neurology. 2005;**58**(4):553-560. DOI: 10.1002/ana.20604

[50] Boehringer A, Macher K, Dukart J, Villringer A, Pleger B. Cerebellar transcranial direct current stimulation modulates verbal working memory. Brain Stimulation. 2013;**6**(4):649-653. DOI: 10.1016/j.brs.2012.10.001

[51] Lee KH, Egleston PN, Brown WH, Gregory AN, Barker AT, Woodruff PW. The role of the cerebellum in subsecond time perception: Evidence from repetitive transcranial magnetic stimulation. Journal of Cognitive Neuroscience. 2007;**19**(1):147-157. DOI: 10.1162/jocn.2007.19.1.147

[52] Koch G, Oliveri M, Torriero S, Salerno S, Lo GE, Caltagirone C. Repetitive TMS of cerebellum interferes with millisecond time processing. Experimental Brain Research. 2007;**179**(2):291-299. DOI: 10.1007/s00221-006-0791-1

[53] Cerminara NL, Apps R, Marple-Horvat DE. An internal model of a moving visual target in the lateral cerebellum. The Journal of Physiology. 2009;**587**:429-442. DOI: 10.1113/jphysiol.2008.163337

[54] Stoodley C. The cerebellum and cognition: Evidence from functional imaging studies. Cerebellum. 2012;**11**(2):352-365. DOI: 10.1007/s12311-011-0260-7

[55] Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, et al. Clinical research with transcranial direct current stimulation (tDCS): Challenges and future directions. Brain Stimulation. 2012;**5**(3):175-195. DOI: 10.1016/j.brs.2011.03.002

[56] Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clinical Neurophysiology. 2016;**127**(2):1031-1048. DOI: 10.1016/j.clinph.2015.11.012

[57] Miquel M, Toledo R, Garcia L, Coria-Avila G, Manzo J. Why should we keep the cerebellum in mind when thinking about addiction? Current Drug Abuse Reviews. 2009;**2**(1):26-40. DOI: 10.2174/1874473710902010026

[58] Lefaucheur JP. Repetitive transcranial magnetic stimulation (rTMS): Insights into the treatment of Parkinson's disease by cortical stimulation. Neurophysiologie clinique = Clinical Neurophysiology. 2006;**36**(3):125-133. DOI: 10.1016/j.neucli.2006.08.003

[59] Caligiore D, Helmich RC, Hallett M, Moustafa AA, Timmermann L, Toni I, et al. Parkinson's disease as a system-level disorder. npj Parkinson Disesases. 2016;**2**(1):16025. DOI: 10.1038/npjparkd.2016.25

[60] Mirdamadi JL. Cerebellar role in Parkinson's disease. Journal of Neurophysiology. 2016;**116**:917-919. DOI: 10.1152/jn.01132.2015

[61] Pedroso JL, Braga-Neto P, de Souza PVS, Barsottini OGP. The cerebellum in Parkinson's disease and parkinsonism in cerebellar disorders. Brain. 2013;**136**(9):e248-e248. DOI: 10.1093/brain/awt089

[62] Minks E, Mareček R, Pavlík T, Ovesná P, Bareš MI. The cerebellum a potential target for stimulation in parkinson's disease? Results of 1-Hz rTMS on upper limb motor tasks. Cerebellum. 2011;**10**(4):804-811. DOI: 10.1007/s12311-011-0290-1

[63] Miall RC, Christensen LOD. The effect of rTMS over the cerebellum in normal human volunteers on peg-board movement performance. Neuroscience Letters. 2004;**371**(2-3):185-189. DOI: 10.1016/j.neulet.2004.08.067

[64] Koch G, Brusa L, Carrillo F, Lo Gerfo E, Torriero S, Oliveri M, et al. Cerebellar magnetic stimulation decreases levodopa-induced dyskinesias in Parkinson disease. Neurology. 2009;**73**(2):113-119. DOI: 10.1212/WNL.0b013e3181ad5387

[65] Brusa L, Versace V, Koch G, Iani C, Stanzione P, Bernardi G, et al. Low frequency rTMS of the SMA transiently ameliorates peak-dose LID in Parkinson's disease. Clinical Neurophysiology. 2006;**117**(9):1917-1921. DOI: 10.1016/j.clinph.2006.03.033

[66] Ferrucci R, Cortese F, Bianchi M, Pittera D, Turrone R, Bocci T, et al. Cerebellar and motor cortical Transcranial stimulation decrease levodopa-induced Dyskinesias in Parkinson's disease. Cerebellum. 2016;**15**(1):43-47. DOI: 10.1007/s12311-015-0737-x

[67] Wessel K, Tegenthoff M, Vorgerd M, Otto V, Nitschke MF, Malin J-P. Enhancement of inhibitory mechanisms in the motor cortex of patients with cerebellar degeneration: A study with transcranial magnetic brain stimulation. Electroencephalography and Clinical Neurophysiology/Electromyography and Motor Control. 1996;**101**(4):273-280. DOI: 10.1016/0924-980X(96)95531-9

[68] Liepert J, Hallett M, Samii A, Oddo D, Celnik P, Cohen LG, et al. Motor cortex excitability in patients with cerebellar degeneration. Clinical Neurophysiology. 2000;**111**(7):1157-1164. DOI: 10.1016/S1388-2457(00)00308-4

[69] Ugawa Y, Genba-Shimizu K, Rothwell JC, Iwata M, Kanazawa I. Suppression of motor cortical excitability by electrical stimulation over the cerebellum in ataxia. Annals of Neurology. 1994;**36**(1):90-96. DOI: 10.1002/ana.410360117

[70] Bastian AJ, Martin TA, Keating JG, Thach WT. Cerebellar ataxia: Abnormal control of interaction torques across multiple joints. Journal of Neurophysiology. 1996;**76**(1):492-509. PMID: 8836239

[71] Minks E, Kopickova M, Marecek R, Streitova H, Bares M. Transcranial magnetic stimulation of the cerebellum. Biomedical Papers. 2010;**154**(2):133-139. DOI: 10.5507/bp.2010.020

[72] Shiga Y, Tsuda T, Itoyama Y, Shimizu H, Miyazawa K, Jin K, et al. Transcranial magnetic stimulation alleviates truncal ataxia in spinocerebellar degeneration. Journal of Neurology, Neurosurgery, and Psychiatry. 2002;**72**(1):124-126. DOI: 10.1136/jnnp.72.1.124

[73] Farzan F, Wu Y, Manor B, Anastasio EM, Lough M, Novak V, et al. Cerebellar TMS in treatment of a patient with cerebellar ataxia: Evidence from clinical, biomechanics and neurophysiological assessments. Cerebellum. 2013;**12**(5):707-712. DOI: 10.1007/s12311-013-0485-8

[74] Nakamura Y, Sakamoto H, Ueno S, Hirano M. Neuroplasticity and high frequency rTMS in hereditary pure cerebellar degeneration. In: 2012 ICME International Conference on Complex Medical Engineering (CME). IEEE; 2012. pp. 142-6. DOI: 10.1109/ICCME.2012.6275679

[75] John L, Küper M, Hulst T, Timmann D, Hermsdörfer J. Effects of transcranial direct current stimulation on grip force control in patients with cerebellar degeneration. Cerebellum & Ataxias. 2017;**4**(1):15. DOI: 10.1186/s40673-017-0072-8

[76] Plow EB, Cunningham DA, Varnerin N, Machad A. Rethinking stimulation of the brain in stroke rehabilitation: Why higher motor areas might be better alternatives for patients with greater impairments. Neuroscience. 2011;**21**(3):225-240. DOI: 10.1177/1073858414537381

[77] Sebastian R, Saxena S, Tsapkini K, Faria AV, Long C, Wright A, et al. Cerebellar tDCS: A novel approach to augment language treatment post-stroke. Frontiers in Human Neuroscience. 2017;**10**:695. DOI: 10.3389/fnhum.2016.00695

[78] Barra M, Evensen GSH, Valeberg BT. Cues and clues predicting presence of symptoms of depression in stroke survivors. Journal of Clinical Nursing. 2017;**26**(3-4):546-556. DOI: 10.1111/jocn.13482

[79] Shen X, Liu M, Cheng Y, Jia C, Pan X, Gou Q, et al. Repetitive transcranial magnetic stimulation for the treatment of post-stroke depression: A systematic review and meta-analysis of randomized controlled clinical trials. Journal of Affective Disorders. 2017;**211**:65-74. DOI: 10.1016/j.jad.2016.12.058

[80] Zhang L, Zhao M, Sui RB. Cerebellar fastigial nucleus electrical stimulation alleviates depressive-like behaviors in post-stroke depression rat model and potential mechanisms. Cellular Physiology and Biochemistry. 2017;**41**(4):1403-1412. DOI: 10.1159/000467940

[81] Simons A, Hamdy S. The use of brain stimulation in dysphagia management. Dysphagia. 2017;**32**(2):209-215. DOI: 10.1007/s00455-017-9789-z

[82] Michou E, Raginis-Zborowska A, Watanabe M, Lodhi T, Hamdy S. Repetitive Transcranial magnetic stimulation: A novel approach for treating Oropharyngeal dysphagia. Current Gastroenterology Reports. 2016;**18**(2):10. DOI: 10.1007/s11894-015-0483-8

[83] Dunlop K, Hanlon CA, Downar J. Noninvasive brain stimulation treatments for addiction and major depression. Annals of the New York Academy of Sciences. 2017;**1394**(1):31-54. DOI: 10.1111/nyas.12985

[84] Demirtas-Tatlidede A, Freitas C, Cromer JR, Safar L, Ongur D, Stone WS, et al. Safety and proof of principle study of cerebellar vermal theta burst stimulation in refractory schizophrenia. Schizophrenia Research. 2010;**124**(1-3):91-100. DOI: 10.1016/j.schres.2010.08.015

[85] Jalali R, Miall RC, Galea JM. No consistent effect of cerebellar transcranial direct current stimulation on visuomotor adaptation. Journal of Neurophysiology. 2017;**118**(2):655-665. DOI: 10.1152/jn.00896.2016

[86] Datta A, Baker JM, Bikson M, Fridriksson J. Individualized model predicts brain current flow during transcranial direct-current stimulation treatment in responsive stroke patient. Brain Stimulation. 2011;**4**(3):169-174. DOI: 10.1016/j.brs.2010.11.001

[87] Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri-precise head model of transcranial direct current stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimulation. 2009;**2**(4):201-207. DOI: 10.1016/j.brs.2009.03.005

[88] Rahman A, Toshev PK, Bikson M. Polarizing cerebellar neurons with transcranial direct current stimulation. Clinical Neurophysiology. 2014;**125**(3):435-438. DOI: 10.1016/j.clinph.2013.10.003

[89] Rohan JG, Carhuatanta KA, McInturf SM, Miklasevich MK, Jankord R. Modulating hippocampal plasticity with in vivo brain stimulation. The Journal of Neuroscience. 2015;**35**(37):12824-12832. DOI: 10.1523/jneurosci.2376-15.2015

[90] Bikson M, Inoue M, Akiyama H, Deans JK, Fox JE, Miyakawa H, et al. Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. The Journal of Physiology. 2004;**557**(1):175-190. DOI: 10.1113/jphysiol.2003.055772

[91] Rahman A, Reato D, Arlotti M, Gasca F, Datta A, Parra LC, et al. Cellular effects of acute direct current stimulation: Somatic and synaptic terminal effects. The Journal of Physiology. 2013;**591**(10):2563-2578. DOI: 10.1113/jphysiol.2012.247171

[92] Chan CY, Hounsgaard J, Nicholson C. Effects of electric fields on transmembrane potential and excitability of turtle cerebellar Purkinje cells in vitro. The Journal of Physiology. 1988;**402**(1):751-771. DOI: 10.1113/jphysiol.1988.sp017232

[93] Darch HT, Cerminara NL, Apps R. P308 the effects of cerebellar trans-cranial direct current stimulation on neural network dynamics in supraspinal motor circuits during motor adaptation in cats. Clinical Neurophysiology. 2017;**128**(3):e161. DOI: 10.1016/j.clinph.2016.10.415

[94] Oulad Ben Taib N, Manto M. Trains of epidural DC stimulation of the cerebellum tune corticomotor excitability. Neural Plasticity. 2013;**2013**:613197. DOI: 10.1155/2013/613197

[95] Podda MV, Cocco S, Mastrodonato A, Fusco S, Leone L, Barbati SA, et al. Anodal transcranial direct current stimulation boosts synaptic plasticity and memory in mice via epigenetic regulation of Bdnf expression. Scientific Reports. 2016;**6**(1):22180. DOI: 10.1038/srep22180

[96] Bolzoni F, Pettersson L-G, Jankowska E. Evidence for long-lasting subcortical facilitation by transcranial direct current stimulation in the cat. The Journal of Physiology. 2013;**591**(13):3381-3399. DOI: 10.1113/jphysiol.2012.244764

[97] Russell M, Goodman T, Wang Q, Groshong B, Lyeth BG. Gender differences in current received during transcranial electrical stimulation. Frontiers in Psychiatry. 2014;**5**(Aug):104. DOI: 10.3389/fpsyt.2014.00104

[98] Nuzum ND, Hendy AM, Russell AP, Teo W-P. Measures to predict the individual variability of Corticospinal responses following Transcranial direct current stimulation. Frontiers in Human Neuroscience. 2016;**10**(October):1-12. DOI: 10.3389/fnhum.2016.00487

[99] Silvanto J, Muggleton NG. New light through old windows: Moving beyond the "virtual lesion" approach to transcranial magnetic stimulation. NeuroImage. 2008;**39**(2):549-552. DOI: 10.1016/j.neuroimage.2007.09.008

[100] Nitsche MA, Doemkes S, Karaköse T, Antal A, Liebetanz D, Lang N, et al. Shaping the effects of transcranial direct current stimulation of the human motor cortex. Journal of Neurophysiology. 2007;**97**(4):3109-3117. DOI: 10.1152/jn.01312.2006

[101] Nitsche M, Liebetanz D, Lang N, Antal A, Tergau F, Paulus W, et al. Safety criteria for transcranial direct current stimulation (tDCS) in humans. Clinical Neurophysiology. 2003;**114**(11):2220-2223. DOI: 10.1016/S1388-2457(03)00235-9

[102] van Dun K, Bodranghien FCAA, Mariën P, Manto MU. tDCS of the cerebellum: Where do we stand in 2016? Technical issues and critical review of the literature. Frontiers in Human Neuroscience. 2016;**10**(May):199. DOI: 10.3389/fnhum.2016.00199

Chapter 4

Repetitive Transcranial Magnetic Stimulation Treating Impulsivity in Borderline Personality Disorder and Attention Deficit/Hyperactivity Disorder

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72787

Abstract

The need for novel treatment approaches that target impulsivity symptoms in neuropsychiatric disorders is clear. Repetitive transcranial magnetic stimulation (rTMS) allows selective neuromodulation of regions involved in the functional neuroanatomy of neuropsychiatric disorders. This chapter presents impulsivity in psychiatry, especially in borderline personality disorder (BPD) and attention-deficit hyperactivity disorder (ADHD), its neural underpinnings, and its possible treatment by rTMS. We reviewed available studies on rTMS in impulsivity in BPD and ADHD published before August 13, 2017, systematically searching in the PubMed, Web of Science, and Scopus databases. The results are discussed in the context of the latest neuropsychological models of impulsivity and their underlying functional neuroanatomy. rTMS treatment of impulsivity in BPD and ADHD seems to be a plausible approach. The functional neuroanatomy of processes related to impulsive behavior and decision making in these disorders is linked with abnormalities in the fronto-limbic structures that can be targeted and modulated by rTMS. Although limited evidence is available, rTMS seems to be a safe and potentially effective method of impulsivity treatment in patients with BPD and ADHD. However, more studies are needed to determine the most efficient cortical location and design for rTMS treatment of impulsivity.

Keywords: transcranial magnetic stimulation, rTMS, impulsivity, inhibition, decision making, reward processing, emotion regulation, borderline personality disorder, ADHD

1. Introduction

Impulsivity is a heterogeneous construct; problems with self-control can include impairment in different neural processes, such as behavioral inhibition, reward processing, and emotion regulation. This chapter shows that various frontal cortical regions have been found to underlie impulsivity. Therefore, repetitive transcranial magnetic stimulation (rTMS) is a potential treatment option since the key brain areas for impulsivity are easily accessed by TMS. So far, only a few studies have used rTMS for impulsivity reduction, or in other words for improving self-control, mainly in patients with BPD and ADHD. A proper theoretical justification based on impulsivity neuroimaging studies should precede the rTMS target selection and treatment design. However, the heterogeneous nature of impulsivity has led to find differences in the methodology of these studies. Several different tasks are used for measuring impulsivity and for neuroimaging, and these tasks also differ in their parameters across studies. We provide a review of impulsivity dimensions, measures, processes, and their neural substrates in the first part of this chapter. We then review the neural correlates of impulsivity and existing studies on rTMS of impulsivity in patients with BPD and ADHD. We conclude by suggesting future directions in rTMS treatment of impulsive behavior.

2. Impulsivity

Impulsivity can be broadly defined as a premature or unwanted behavior or act on the spur of the moment without considering consequences. Increased impulsivity can be frequently observed in patients with various neuropsychiatric diseases, especially borderline personality disorder (BPD) and attention-deficit/hyperactivity disorder (ADHD). Impulsivity is a diagnostic criterion for both BPD and ADHD according to DMS-V. Moreover, difficulties with self-control are commonly observed in a number of otherwise different neuropsychiatric disorders, including substance abuse disorders and addiction [1], eating disorders [2], bipolar disorder [3], antisocial personality disorder [4], schizophrenia [5], and Parkinson's disease [6]. Increased impulsivity significantly worsens the quality of everyday life, complicates treatment, and can have serious consequences. Impulsivity is manifested by a wide range of risky and (self) destructive behavior, such as drug abuse, dangerous sexual behavior, reckless driving, gambling, binge eating and buying, aggression, and self-harm, including suicidality. Both pharmacologic and psychotherapeutic approaches are used to treat impulsivity; however, psychiatry lacks effective impulsivity-focused treatment.

2.1. Dimensions of impulsivity

Theoretical conceptions of impulsivity are each closely related to different forms of measurement. In the personality approach, impulsivity is considered to be a personality trait, which is measured by self-report questionnaires. The most commonly used impulsivity questionnaires are the Barratt Impulsiveness Scale (BIS) [7] and the UPPS-P[1] Scale [8, 9]. Whereas the validity

[1]The name of the scale was derived from first letters of the scale dimensions: (Negative) **U**rgency, (Lack of) **P**remeditation, (Lack of) **P**erseverance, **S**ensation Seeking, **P**ositive Urgency.

of the BIS has been recently questioned [10–13], the UPPS-P Scale currently constitutes the most complex up-to-date self-report measure of impulsivity and can be recommended for impulsivity treatment evaluation. The behavioral approach to impulsivity is more relevant for rTMS treatment. Under this view, impulsive behavior follows from the impairment of a neurobiological function, namely behavioral inhibition, leading to Impulsive Action, with reward processing leading to Impulsive Choices. Different behavioral tasks are used for measuring and neuroimaging of these functions. In the current literature, authors use different labels for the same impulsivity dimensions, which can complicate understanding of the topic. Impulsivity facet specification should always stem from the task that has been used for its measurement.

2.1.1. Behavioral inhibition and Impulsive Action

Behavioral models of impulsivity can be divided into two areas. The first area is based on behavioral inhibition impairment, and the second is based on reward processing impairment. Behavioral inhibition can be defined as the ability to control one's behavior, namely to inhibit, postpone, or interrupt one's undesired or premature actions. Impairment in behavioral inhibition leads to Impulsive Action [14] (or Rapid-Response Impulsivity [15], etc.). Impulsive Action can be further distinguished into Waiting Impulsivity and Stopping Impulsivity [16]. Waiting Impulsivity is the ability to withhold one's own unwanted actions, whereas Stopping Impulsivity is the ability to interrupt one's own already ongoing actions. The most commonly used tasks for measuring behavioral inhibition are the Go/No-Go Task (GNG) [17] for Waiting Impulsivity and the Stop Signal Task (SST) for Stopping Impulsivity [18, 19].

2.1.2. Reward processing and Impulsive Choice

Reward processing is crucial for decision making, and its impairment leads to a decreased ability to postpone immediate rewards or gains even at the expense of negative future consequences. Immediate rewards preference can be associated with hypersensitivity to hedonic stimuli [20] or, on the other hand, general hyposensitivity to both positive and negative feedbacks [21, 22]. Impairment in reward processing leads to so-called Impulsive Choice [14] (or Choice Impulsivity [15], etc.). Manifestations of Impulsive Choice include decreased tolerance for waiting for a reward, preference of immediate rewards without considering future consequences, and even decreased ability to learn from negative consequences.

The most commonly used task for measuring Impulsive Choice is the Delay Discounting (DD) [23]. In DD, subjects make a series of choices between a higher, but delayed, reward (usually monetary), and a lower and immediate, reward, resulting in a discounting parameter that expresses how quickly the present value of a reward to the subject declines with a delay of its delivery. Other tasks related to Impulsive Choice focus on decision making using rewards and punishments (Iowa Gambling Task) or risk-taking (e.g. Balloon Analog Risk Task).

2.1.3. Emotion regulation and emotional impulsivity

The influence of emotions on impulsivity was neglected in impulsivity models for a long time. However, some patients have a significant tendency to act impulsively under the influence of both negative and positive emotions, known as Negative and Positive Urgency [8, 9]. Other authors refer to cold and hot (i.e. emotional) impulsivity [24]. For example, patients with BPD

show more pronounced behavioral inhibition impairment under the influence of stress [25], while in emotionally neutral situations, they might not show any difference in behavioral inhibition from healthy people [26, 27]. Moreover, emotional impulsivity in patients with BPD is often manifested by (self) destructive behaviors such as self-harm, suicidal behavior, aggression, substance abuse, and other dangerous impulsive behavior [28]. We hypothesize that impulsive behavior can occur as an attempt to handle the emotional tension that the person is unable to regulate by more adaptive means. In other words, behavioral inhibition impairment and impulsive decision making can occur as a result of insufficient emotion-regulation abilities. Impulsive, most often self-destructive behavior (getting hurt, taking drugs, etc.) can lead to momentary relief but almost always has negative consequences, including remorse, (self-)harm, and social condemnation. Thus, emotional impulsivity is a very dangerous phenomenon to which we should pay attention and which we should try to prevent in patients. In the treatment of patients with high emotional impulsivity, it is necessary to address not only behavioral inhibition or decision making, but also emotion-regulation skills.

Regarding the measurement of emotional impulsivity, the UPPS-P questionnaire includes dimensions of Negative Urgency and Positive Urgency. Previously mentioned, behavioral tests can be used in emotional variants, e.g. after stress induction or using emotional stimuli instead of neutral stimuli.

2.2. Neural correlates of behavioral inhibition

In neuroimaging studies of behavioral inhibition, a neuroimaging method is used while subjects perform a behavioral inhibition task. Studies using functional magnetic resonance imaging (fMRI) of behavioral inhibition are the most important for rTMS target selection. Swick et al. [29] performed a large meta-analysis of fMRI studies using Go/No-Go Tasks (GNG; 48 papers) and Stop Signal Tasks (SST; 21 papers) in healthy people. The authors found that the No-Go condition in GNG is associated with increased activity in the fronto-parietal network including the superior, middle, and inferior frontal cortical areas, including the dorsolateral prefrontal cortex (DLPFC), insula, dorsal medial frontal cortex including the (pre-) supplementary motor area (SMA/pre-SMA), and the inferior parietal lobule (IPL). All the largest clusters were bilateral but predominantly right-sided. Other activations included the right precuneus, left putamen/claustrum, posterior cingulate cortex, superior temporal cortex, and right inferior occipital cortex. In SST, the Stop condition was associated with a similar activation pattern, but compared to GNG, the activation was more pronounced in the left insula extending to the thalamus and putamen and the thalamus and posterior cingulate cortex. GNG activation was generally more right-sided and the maximal overlap between activations from the two tasks was found in the right insula and the SMA/pre-SMA. The important finding of this meta-analysis is that GNG and SST apparently do not measure the same processes, and thus the results from the two tasks cannot be combined. The authors further discuss that the SMA/pre-SMA could be the critical area for behavioral inhibition specifically, whereas the DLPFC could reflect more generally attentional executive control or top-down cognitive control, even though the previous literature on behavioral inhibition was mainly focused on the right DLPFC or inferior frontal gyrus (IFG).

Another two meta-analyses [30, 31] explored the hypothesis that the DLPFC and IFG are more related to attentional cognitive control than to behavioral inhibition itself. Simmonds et al. [30] reviewed 11 studies and compared activations between GNG tasks with stable No-Go stimulus

and variable No-Go stimulus, with the variable stimulus putting higher demands on cognitive control components such as attention, stimulus recognition, and working memory. The authors found that the IFG and DLPFC, as well as the insula and IPL, were more activated in more cognitively demanding tasks. On the other hand, common activations in all tasks were found in the SMA and the left fusiform gyrus. A second meta-analysis [31] reviewed 30 studies and compared activations from simple and complex GNG tasks. Simple tasks should include only one invariable Go and No-Go stimulus and an even ratio of Go to No-Go stimuli; complex tasks are more complicated and cognitively demanding. Activations only in complex tasks were found in the right IFG, right DLPFC, right SMA/pre-SMA, insula, and right IPL. Common activations in both tasks were found in bilateral DLPFC, left IPL, and right superior temporal gyrus. The authors of the meta-analyses hypothesize that regions activated commonly in all tasks are related specifically to behavioral inhibition, but areas activated only in complex tasks are related to cognitive control. However, the results of the two meta-analyses differ substantially.

To summarize, the most commonly activated frontal regions during inhibition tasks are the right DLPFC and IFG and the SMA/pre-SMA. However, the specific role of the different regions remains unclear. Recent studies have importantly revealed that neural activity associated with behavioral inhibition is task related.

2.3. Neural correlates of reward processing

The most important network for performance in Delay Discounting according to the current literature is the cortico-striatal loop, including the prefrontal, cingulate, and posterior parietal cortex in the cortical part and the nucleus accumbens/ventral Striatum (NAcc/VS) and amygdala in the striatal part. Within this network, the NAcc/VS and amygdala are thought to be related to reward processing and reward learning; the prefrontal cortex (PFC) is associated with decision making and conflict resolution [32]. Amygdala activity was found to be associated with immediate (i.e. more impulsive) choices [33], while PFC region activity is associated with delayed (i.e. less impulsive) choices [34]. Another approach to studying the neural correlates of Delay Discounting distinguishes hard choices, in which two options have subjectively similar values for the subject, and easy choices, in which one option has a subjectively much higher value for the subject. The idea is that in hard choices, people should engage in decision making with greater effort because they should consider the pros and cons of each of the possibilities more precisely. Existing studies [35–39] show that regardless of population type, hard choices, in comparison to easy choices, are associated with higher activity in the fronto-parietal network, including the DLPFC and/or ventro-lateral prefrontal cortex (VLPFC), the anterior cingulate cortex (ACC), the IPL, and the intraparietal sulcus. Moreover, more impulsive individuals tend to show lower activity in these regions during DD, suggesting insufficient effort or decision-making ability engaged in more difficult choices.

2.4. Neural correlates of emotion regulation

Impaired emotion regulation can be found frequently among psychiatric patients with different diagnoses and is often associated with dangerous impulsive behavior. Studies on humans and animals have largely established the amygdala as a key region in emotion processing. The amygdala was found to be involved in emotional implicit learning, memory, social perception, emotion inhibition, and emotion regulation [40, 41]. The amygdala activity during emotion processing is

regulated by a prefrontal-limbic negative coupling which represents top-down cognitive emotion control. Specifically, the decrease in amygdala activity has been shown to be associated with increases in various lateral and medial PFC areas [42–45]. Patients with emotion-regulation deficits show exaggerated amygdala response to emotional stimuli and disrupted amygdala-prefrontal connectivity [46–49]. Further, real-time fMRI neurofeedback studies showed that successful regulation of amygdala activity increases connectivity between the amygdala and DLPFC or VLPFC [50, 51], representing an increase in cognitive emotion-regulation abilities.

2.5. Possible targets for rTMS treatment of impulsivity

According to existing literature on neural correlates of impulsivity, the most suitable targets for rTMS impulsivity treatment seem to be the right lateral PFC areas, mainly the DLPFC or VLPFC. High frequency (HF) rTMS is used over these regions with the aim of the treatment should be to promote activity in the prefrontal areas. Lateral PFC activity, especially in the right hemisphere, has been consistently shown to be associated with successful behavioral inhibition, less impulsive decision making, and better emotion regulation. All of the areas mentioned could be improved through the application of HF rTMS treatment over the (right) DLPFC or VLPFC. Another promising candidate for rTMS application is SMA/pre-SMA that appears to be a crucial area for behavioral inhibition.

3. Transcranial magnetic stimulation in borderline personality disorder

According to DSM-V, BPD is characterized by a pervasive pattern of instability in interpersonal relationships, self-image, and affects, and marked impulsivity that begins by early adulthood and is present in a variety of contexts. BPD patients also have a high risk of mortality due to suicidal behavior. Up to 10% of BPD patients commit suicide; this rate is almost 50 times higher than in the general population [52]. BPD symptoms severely reduce patients' quality of life and impair their psychosocial functioning [49, 53]. The median prevalence of BPD is estimated from 1.6% up to 5.9% in the general population, up to 10% in psychiatric outpatients, and up to 20% in psychiatric inpatients [28, 54, 55]. BPD is about five times more common among first-degree biological relatives of those with the disorder than in the general population and it is also diagnosed predominantly (about 75%) in women [55]. One of the core elements of BDP is impaired emotion processing and impulsivity. BPD patients have impaired emotion-regulation abilities combined with emotional vulnerability characterized by marked sensitivity to emotional stimuli (low threshold) and unusually strong reactions (high amplitude) that abnormally slowly return to baseline (long duration) [56]. As mentioned earlier, impulsivity in BPD patients often appears under the emotional influence and usually manifests in various dangerous and (self-) destructive behavior.

3.1. Neurobiology and neurophysiology of impulsivity in BPD

BPD patients show impairment across various frontal regions and fronto-limbic connections crucial for behavioral inhibition, decision making, and emotion regulation. Functionally, patients

with BPD show increased amygdala reactivity and altered PFC responses including in the DLPFC and ACC and sensorial processing areas, including the superior temporal gyrus in face processing and the visual cortex in response to emotional stimuli, as compared to healthy people [49, 56–58]. Anatomically, patients with BPD were found to have reduced gray matter volume in the amygdala, insula, DLPFC, and orbitofrontal cortex (OFC) compared with healthy controls [49, 59]. Positron Emission Tomography (PET) studies have revealed altered baseline metabolism in the prefrontal regions in BPD patients [60–62]. Disinhibited impulsive aggression in BPD patients has been associated with serotonergic neurotransmission, which is also affected by the PFC [62]. In conclusion, neuroimaging studies indicate that hyperactivity in the amygdala could be a consequence of weak inhibitory control of limbic emotion reactivity by PFC areas.

Some studies tried to use TMS for assessing cortical neurophysiology in BPD, including cortical excitability and inhibitory and excitatory mechanisms [63]. From this point of view, impulsivity could stem from increased or decreased excitability in some brain structures. BPD patients were found to have shorter cortical silent periods (CSP) in the right hemisphere than healthy controls [64, 65]. It is assumed that CSP measures $GABA_B$ inhibitory activity [66]. A similar reduction of CSP was also found in ADHD [67] and in patients with tic disorder [68]. Some authors hypothesized that the GABA neurotransmitter is the main inhibition neurotransmitter and the reduction of GABA activity could result in impulsive behavior and affective instability [64]. Another hypothesis is that intracortical inhibition is more linked with shifts in cortical glutamate and glutamine concentrations than with GABA neurotransmitter levels. But glutamate probably specifically interacts with $GABA_B$ receptors, so the higher glutamate and glutamine concentrations seem to be linked to the higher levels of receptor activity revealed by proton magnetic resonance spectroscopy [69]. Further studies to examine these neurophysiology markers in BPD and how they could be used for therapeutic rTMS would be appropriate.

3.2. Review of rTMS treatment studies in BPD

We searched for relevant studies through the PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Web of Science (https://apps.webofknowledge.com/), and Scopus (https://www.scopus.com/) databases published before August 13, 2017. The following terms were used to search for publication titles: (borderline OR BPD) AND (TMS OR rTMS OR "transcranial magnetic stimulation"). We found seven (PubMed), six (Web of Science), and seven (Scopus) publications. After excluding duplicates and nonrelevant contributions (e.g. theoretical articles), five studies were included in the review [70–74].

The first rTMS study in BPD [70] was a case report published in 2013. A 22-year-old female BPD patient received high frequency (HF) 10 Hz stimulation over her left DLPFC at 100% of her individual motor threshold (MT). The trains lasted 5 s and intertrain intervals were 55 s; the whole protocol had 10 sessions (1500 pulses per session, one session per day). The results revealed a decrease in depression levels (Beck Depression Inventory score from 20 to 7 to 2),[2] negative affect experiences (Positive and Negative Affect Schedule score from 38 to 36 to 22), impulsivity (Barratt Impulsiveness Scale score from 71 to 67 to 61), and BPD symptom score

[2]The effects are presented from before the stimulation, immediately after the stimulation, and 1 month after the stimulation.

(SCID-II score from 13 to 11 to 6) directly after the treatment and 1 month after the treatment, respectively. Reassessment after 3 months showed regression in the symptoms. According to the patient's reports, the rTMS therapy led to decreased sleep duration, increased emotional control and stability, behavioral self-awareness, increased motivation for change, sociability, self-esteem, happiness, attention to the behavior of others, and planning ability.

Cailhol et al. [71] performed a randomized controlled stimulation of 10 BPD patients by HF 10 Hz rTMS over the right DLPFC. Five patients received active stimulation, and five patients received sham stimulation. One patient was excluded. The right DLPFC was targeted as 6 cm anterior to M1, stimulation was done at 80% intensity of individual MT, trains lasted 5 s and intertrain intervals lasted 25 s (2000 per session, 10 sessions in total). The response rate was defined as a 30% reduction in the Borderline Personality Severity Index (BPDSI) after the stimulation; this was reached by two patients from the active group and one patient from the sham group. BPDSI scores were significantly lower for the active rTMS group than for the sham stimulation group after 3 months of affective instability and anger. Performance in the Tower of London test improved only in the rTMS active group. The stimulation was well tolerated without any adverse events. The authors hypothesized that PFC activity could be increased by rTMS neuromodulation and thereby downregulate the subcortical structures. The effect of rTMS on anger and affect instability in BPD patients could be explained by this hypothesis.

Another stimulation design was presented by De Vidovich et al. [72], who stimulated the left cerebellum in BPD patients. This cerebellar stimulation was used based on cerebellar projections to the PFC through the ventrolateral thalamic nucleus (VL), which was observed in animal studies [75, 76]. Further, one tractography study in humans found that about 40% of fiber tracts from the cerebellum through the superior cerebellar peduncle actually reach the PFC through the VL [77]. In the study itself, eight patients with BPD and eight healthy controls received 1 Hz stimulation on 80% of MT for 10 min over the left lateral cerebellum (1 cm inferior and 3 cm left to the union). The effect of the rTMS was measured by the Affective Go No-Go task (AGN), using two categories of words (positive/negative and fruits/insect). The first and second block of the task included only the first category; the third and fourth part included both categories. BPD patients generally scored worse than healthy controls in AGN, especially in the latter category before the stimulation. After rTMS, their performance became equivalent to the healthy control performance. The stimulation was well tolerated, with no adverse events. These data support previous findings that inhibition performance in BPD patients is impaired when cognitive demands are high, and the situation requires complex associative capacities [78, 79]. The results suggest that LF cerebellar rTMS could have a facilitating effect on the PFC.

Feffer et al. [73] stimulated three women (39, 32, and 42 years old) with BPD and depression comorbidity. The severity of depression symptoms was measured by Beck Depression Inventory II (BDI-II). Two patients received bilateral intermittent (iTBS) stimulation of the DMPFC targeted by neuronavigation; the stimulation had 20 sessions (1 session per day), 1200 pulses per session (600 pulses to each hemisphere). The BDI-II score of the first patient was reduced from 56 to 16 points; the score of the second patient was reduced from 20 to 12 points. The third patient received 20 sessions (1 session per day) of 20 Hz bilateral stimulation to the DMPFC localized by neuronavigation. The duration of the train was 2.5 s and the duration of the intertrain interval was 10 s. Stimulation of each hemisphere contained 1500

pulses in one session. The BDI-II score of the third patient was reduced from 29 to 10 points. The stimulation was well tolerated without any adverse events. Two of the patients described a mild headache at the point of stimulation. All three of them subjectively described better control of emotional and behavior impulses and better emotional regulation.

The last study is from Reyes-López et al. [74]. They stimulated 29 BPD patients divided into two groups with two stimulation designs. One stimulation group received 1 Hz stimulation to the right DLPFC (15 patients), 900 pulses per session. The second group received 5 Hz stimulation to the left DLPFC, trains lasted 10 s, intertrain intervals were also 10 s, 1500 pulses per session (14 patients). The whole stimulation had 15 sessions (1 session per day); the DLPFC was targeted as 5 cm above the maximum stimulation point in the motor area and patients were stimulated on 100% of their individual MT. There was a significant reduction in the Clinical Global Impression Scale for BPD (CGI-BPD) score from baseline after rTMS, with a 29.4% change for 1 Hz group and 28.7% for 5 Hz group. The Borderline Evaluation of Severity over Time (BEST) scores were also reduced for both groups (1 Hz group: 20.4% reduction from baseline; 5 Hz group: 36.9% reduction from baseline). Scores in BIS were also reduced significantly (1 Hz group: 18.96% reduction from baseline; 5 Hz group: 11.83% reduction from baseline). The reduction in BDI scores was 49% for 1 Hz group and 60% for 5 Hz group. Lastly, the Hamilton Anxiety Rating Scale (HAM-A) score was also reduced by 60.3% for 1 Hz group and by 58.7% for 5 Hz group. These results show that both stimulation protocols were effective in reducing BPD symptoms, such as fear of abandonment, impulsivity, emotional instability, and anger.

3.3. Conclusions and future directions of rTMS treatment paradigms in BPD

Most existing studies used rTMS targeted to the left or right DLPFC or DMPFC; one study targeted the cerebellum. Both high and low-frequency protocols were used. Many authors connected the BPD symptoms with hypometabolism in the prefrontal regions and hyperactivation of the amygdala. Current studies have reported various effects of rTMS treatment, mostly after HF treatment in BPD patients, including improved self-control, emotion regulation, mood, anxiety, and executive functions. Some studies also reported effects after sham stimulation. Consequently, it is difficult to make any recommendation regarding rTMS targeting and protocol parameters. We might also speculate that targeting any PFC region by rTMS could improve BPD symptoms thanks to the rich cortico-cortical and cortico-limbic projections from the prefrontal regions. The low-frequency stimulation of the cerebellum could be also used to reduce BPD symptoms based on the cerebellothalamocortical tracts. One question is the laterality of rTMS treatment in BPD patients. Neuroimaging studies of impulsivity usually find a greater association with action control with the right prefrontal regions. Differences in the CSP between patients with BPD and healthy controls were found, especially in the right hemisphere [64]. However, current studies show effects for both right and left prefrontal stimulation protocols.

Another question was raised by the study by Reyes-López et al. [74]. They used low-frequency rTMS in the right DLPFC and found similar effects as after high-frequency rTMS over the same area. These findings contradict previous findings and theoretical underpinnings about hypometabolism in PFC in BPD patients and about the effect of low-frequency rTMS. For example, low and high-frequency rTMS over the left DLPFC in depressed patients have been found to have opposite effects [80].

3.4. Summary of rTMS treatment in BPD

The existing studies suggest that rTMS is a well-tolerated treatment in patients with BPD and is a potentially highly useful tool for reducing BPD symptoms including impulsivity and emotion regulation. There is a lack of double-blind randomized controlled studies with sufficient sample sizes. Current studies differ substantially in both rTMS cortical targets and stimulation protocols. Most studies have found an effect of high-frequency rTMS over the right DLPFC, but there are also studies that found low-frequency DLPFC, left-sided DLPFC, and cerebellar rTMS effective. More double-blind placebo-controlled studies and studies directly comparing different stimulation protocols in BPD are needed, and the duration of the therapeutic effects should be assessed.

4. rTMS in attention-deficit/hyperactivity disorder treatment

ADHD, in the ICD-10 represented by hyperkinetic disorder, is one of the most common mental disorders among children, with a prevalence of 3–7% [81]. ADHD was long viewed as a childhood diagnosis; however, many studies in the last decades have demonstrated that symptoms persist to adulthood in up to 80% of patients [82]. The latest revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) reexamined the diagnostic criteria and allowed the classification of ADHD as a lifelong disorder with the condition of onset before the 12th year of life [55]. ADHD symptom heredity is considered to be as high as 75% [83]. Like many neuropsychiatric disorders, ADHD seems to be a result of the complex interplay of genetic and environmental factors and has been recently viewed as a neurodevelopmental disorder [81].

The three typical symptoms of childhood ADHD—attention deficit, hyperactivity, and impulsivity—are partially modified during the lifespan. In adulthood, feelings of internal restlessness, disorganization, and unrestrainability, and some behavioral difficulties, including impaired executive functions, prevail [84]. The treatment of ADHD in children as well as in adults is an ongoing topic in psychiatry. There are several possible treatment options in ADHD therapy. Treatment guidelines for both children and adult patients recommend using drugs such as methylphenidate and atomoxetine. However, about 20–50% of patients are considered nonresponders due to insufficient symptom reduction or severe side effects. Moreover, combining pharmacotherapy with psychotherapy (cognitive behavioral therapy, education, and focused complex programs) and other nonpharmacological methods is recommended in all cases [85].

4.1. Neurobiology and neurophysiology of impulsivity in ADHD

Neuroimaging studies indicate that ADHD might be a neurobiologically heterogeneous category of diseases. This would mean that there are several different disorder patterns which manifest by similar clinical symptoms or that dysfunctions in different functional systems could lead to similar symptoms. Data-mining techniques suggest three clusters of neuropsychological abnormities in ADHD: cognitive-behavioral management, time processing, and motivation. These clusters did not significantly overlap between individual subjects [86]. Similarly, a systematic review of the findings in executive function areas suggests that not all ADHD patients are impaired in the same region [87].

ADHD is characterized by a delay in cortical maturation, which is most substantial in the prefrontal regions [88]. Earlier neuroimaging studies described structural and functional abnormalities in patients with ADHD, suggesting a hypofunction of catecholamine projection from the basal ganglia into the PFC. This dysfunction manifests as a relative hypoactivity of the cortical dopamine system with a relative hyperactivity of striatal dopamine [89]. A meta-analysis of functional studies showed hypoactivity in the frontal regions (DLPFC, inferior PFC, OFC), anterior cingulum, superior parietal regions, caudate nucleus, and thalamus [90]. Duerden et al. [91] also observed that adolescents with ADHD had a significantly greater cortical thickness in the pre-supplementary motor area (SMA) than controls. Further, impaired functional connectivity between the frontal and parietal cortex and between the frontal and cerebellar cortex have been found in patients with ADHD during interference control tasks and time discrimination tasks [92] associated with interference control, activity timing, and time predictions. Striatal hypoactivation in ADHD can lead to the insufficient detection of behaviorally important stimuli, inability to orientate one's activities to long-term goals, and insufficient feedback effect from behavioral modification [93–95].

Several studies used TMS to investigate neurophysiological parameters in ADHD. A meta-analysis by Dutra et al. [96] identified no significant differences between ADHD and control groups in CSP, resting MT, and motor-evoked potential. However, there was a consistent finding in reduced short intracortical inhibition (SICI) in both children with ADHD [97–100] and adult ADHD patients [67]. SICI is a subthreshold conditioning stimulus followed by a suprathreshold test stimulus with an interstimulus interval of 1–6 ms. The motor-evoked potential which was evoked by the second suprathreshold stimulus should be reduced by 50–90% [101]. The SICI is described as probably measuring $GABA_A$-mediated cortical inhibition [66, 102]. A study by Hasan et al. [103] also reported increased intracortical facilitation (ICF) in adult ADHD patients compared to healthy controls when considering an interstimulus interval of 7 ms between paired pulses applied to the left hemisphere. ICF is measured by TMS when the magnetic evoked potential generated by the suprathreshold is usually facilitated at an interstimulus interval of 8–30 ms [101]. However, there are too few studies to make a more robust conclusion.

4.2. Review of rTMS treatment studies in ADHD

We searched for relevant studies through the PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Web of Science (https://apps.webofknowledge.com/), and Scopus (https://www.scopus.com/) databases published before August 13, 2017. The following terms were used to search in the publication titles: (ADHD OR "attention deficit hyperactivity disorder") AND (TMS OR rTMS OR "transcranial magnetic stimulation"). We found 20 (PubMed), 32 (Web of Science), and 25 (Scopus) articles. After excluding duplicates and nonrelevant contributions (e.g. theoretical articles), seven studies were included in the review.

Current studies examining the treatment of ADHD by rTMS use two main protocols. The first protocol is the low-frequency (LF) stimulation of the SMA, intended to suppress motor symptoms of hyperactivity. The other protocol uses HF rTMS over the DLPFC, intended to facilitate dopaminergic neurotransmission in the PFC and induce the release of endogenous dopamine in the nucleus caudate nucleus and NAcc [104]. This kind of stimulation could improve the symptoms of ADHD mostly in the cognitive domain (deficit of attention and impulsive cognitive style).

In his pilot study, Niederhofer [105] presented a case study of an adult ADHD patient. This study used LF 1 Hz rTMS protocol over the SMA in order to reduce the symptoms of hyperactivity. The results describe a significant improvement that lasted for at least 4 weeks. Three years later, Niederhofer repeated the same protocol with a 42-year-old female ADHD patient on a 20 mg daily dose of methylphenidate (MPH). After 21 days of 1 Hz rTMS (1200 pulses per session, each session lasting 1 h) over the SMA, the daily MPH dose was lowered to 10 mg; simultaneously, the 10 hyperactivity-associated items of the Conners scale improved from the initial 25 to 17 points (measured during the therapy and a week after the termination). The attention items did not show any difference [106].

The largest study was conducted by Bloch et al. [107]. They performed a randomized, crossover, double-blind pilot study in 13 adult ADHD patients. They applied a single session of HF stimulation (42 × 2 s, 20 Hz stimuli at 100% of individual MT intensity, with a 30 s interstimulus interval) over the right DLPFC (located by measuring 5 cm anterior to the motor threshold). One patient dropped out of the study because the stimulation was painful, the other 12 completed the treatment and reported no side effects. The result of the study was a significant improvement in self-reported attention with no effects on mood or anxiety [positive and negative affect schedule (PANAS), visual analogue scales (VAS), and Cambridge neuropsychological test automated battery (CANTAB) were used]. No difference was found in the attention score when comparing the pre- and post-sham rTMS results. The limitation of that study was the fact that the symptoms were evaluated only before the treatment and 10 min after; therefore, no claims can be made about the long-term effects of this therapy.

Ustohal et al. [108] used a similar design in their own pilot study. They treated a 36-year-old male subject who was diagnosed with ADHD in childhood and experienced three major depression episodes in adulthood. The authors used HF 10 Hz frequency in 120% intensity of individual MT (10 s train, 30 s inter train interval, 1500 pulses per session). The study was divided into three sections, each lasting 1 week. In the first week, sham stimulation was applied; in the second week, the left DLPFC was stimulated; and in the third week, the right DLPFC was stimulated. In the first week, there was already a significant improvement in the d2 test of attention (from the initial 86.4 percentile to 98.2 percentile) and a small reduction on the depression scale (from MADRS 14 to 12). In the second week, there was a further reduction on the depression scale (MADRS score decreased to 7) and improvement in the d2 test of attention (98.9 percentile). On the first session of the third week, the patient described serious side effects—dysphoria, hypobulia, and increased tension. The MADRS score increased significantly (21 points). Therefore, the authors changed the target to the left DLPFC, which led to improved symptoms, reduced depression scale score (MADRS = 9), and improvement in the d2 test of attention (99.2 percentile). The authors discussed that these side effects may be related to the fact that LF rTMS of the right DLPFC is used in the treatment of depression [109] and, on the contrary, HF rTMS of this area has been used in patients with mania [110].

In another study, Weaver et al. [111] stimulated nine adolescents and young adults diagnosed with ADHD. They targeted the right DLPFC (located by measuring 5 cm anterior to the motor threshold) and used HF stimulation (10 Hz, 4 s trains, 26 s inter train interval, 2000 pulses per session) with 100% intensity of individual MT. This study had a double-blind design and each

of the patients was stimulated for 2 weeks (10 sessions). Results showed an overall significant improvement in the clinical global impression-improvement (CGI-I) and the ADHD-IV scales in both groups combined ($P < 0.01$); no significant differences between active and sham stimulation were described. The study also described no negative side effects of the stimulation.

In another study [112], 25 children with ADHD underwent rTMS treatment. The primary motor cortex (M1) was stimulated using LF 1 Hz rTMS at low intensity—80% of the individual MT. This study did not evaluate the clinical effect of the stimulation, it only measured the effect of rTMS on electrophysiological parameters of the cortical excitability by EEG. The result of this study was a significant decrease of the N100 which was evoked by rTMS and lasted for at least 10 min after the stimulation. EEG source analysis indicated that the TMS-evoked N100 change reflected rTMS effects in the stimulated motor cortex and therefore the TMS-evoked N100 could represent a promising candidate marker to monitor rTMS effects on cortical excitability in children with ADHD. No serious side effects of the stimulation were described; three patients reported a mild headache.

Another study with child ADHD patients was conducted by Gómez et al. [113]. The aim of the study was to evaluate the tolerability and safety of LF rTMS in children with ADHD. The study group included 10 children aged from 7 to 12 years. These patients received 1 Hz stimulation (a total of 1500 stimuli in each session) over the left DLPFC (the site for stimulation was defined by the F3 electrode position (10/20 International System)) for 5 consecutive days, the intensity was set to 90% of the individual MT. The assumption was that 1 Hz stimulation over the left DLPFC could be as effective as 10 Hz stimulation to the homologous right area. Seventy percent of the patients reported a mild headache or a local discomfort lasting for few minutes as the most frequent side effect, 20% reported also a mild neck pain. Their parents and teachers were asked to fill out the symptoms checklist (SCL) for ADHD from DSM-IV, before and 1 week after completing the rTMS sessions. There was improvement in inattentiveness symptoms at school (score dropped from 16.7 to 8.6) and in hyperactivity/impulsivity at home (score dropped from 30.8 to 11.4).

None of these studies reported any severe side effects of rTMS; the only common side effect was a temporary and mild headache. Theoretically, there is a higher risk of paroxysmal reaction on rTMS in child patients due to their lower seizure threshold, but so far no study has reported such a side effect. If the personal history, entry EEG exam, and safety limits are performed properly, the risk of provoking a paroxysmal reaction is very low [114].

4.3. Conclusions and future directions of rTMS treatment paradigms in ADHD

Using rTMS in treating ADHD symptoms is still a relatively unexplored area. However, current studies suggest it might be a promising nonpharmacological approach or it could be used in combination with pharmacotherapy. The benefit of using rTMS in ADHD treatment is the minimal occurrence of side effects among current studies, none of which is a serious side effect. Studies have explored the effect of rTMS in only small numbers of patients using different methodology, including different stimulation parameters and application targets. Current studies focus mostly on reducing inattention and impulsivity by stimulating the DLPFC. The

most widely used stimulation is high frequency rTMS over the right DLPFC. However, a study by Ustohal et al. [108] showed that this protocol can have a negative effect on patient's depression symptoms and suggests another stimulation site, such as left DLPFC, at least for patients with a personal history of depression. However, this side effect has only been observed in a single patient. Another treatment protocol to consider is low frequency rTMS over the left DLPFC, which could possibly have a similar effect. Hyperactivity symptoms of ADHD could also be reduced by using low frequency rTMS over the SMA; however, only two patients have been stimulated by this protocol, and further research is needed. There is a lack of reliable data on the duration of the therapeutic effect. Further understanding of the neurophysiological mechanisms of the effect and assessment of adequate stimulation parameters are required.

4.4. Summary of rTMS treatment in ADHD

Studies suggest that rTMS is a well-tolerated treatment in patients with ADHD and potentially a highly useful tool for reducing ADHD symptoms including impulsivity, motor hyperactivity, and reduced attention. There are not yet double-blind randomized controlled studies with sufficient sample sizes. The current studies differ substantially in both rTMS cortical targets and stimulation protocols. Most studies suggest stimulation over the right DLPFC by high frequency rTMS; another potentially promising protocol in ADHD is low frequency rTMS over the SMA. More double-blind placebo-controlled studies and evidence about the therapeutic effect of rTMS in ADHD patients are needed.

5. Conclusion

The most important application of rTMS for impulsivity reduction in BDP and ADHD seems to be stimulation over the left or right DLPFC, the SMA, or the cerebellum. However, it should be stressed that the neural activity associated with impulsivity differs according to the task parameters used during neuroimaging. This applies for studies of behavioral inhibition, Delay Discounting, and emotion regulation. This problem might be overcome by navigating rTMS individually according to functional fMRI from a specific task administered to the patients before stimulation. rTMS seems to be well tolerated without any adverse events in BPD and ADHD patients. The results of rTMS impulsivity treatment studies are promising, but double-blind studies with larger active and sham group sizes are needed to optimize the treatment results.

Acknowledgements

This contribution was supported by the Ministry of Health of the Czech Republic, grant no. 15-30062A. The authors like to thank Ms. Anne Johnson for proof-reading.

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References

[1] Smith JL, Mattick RP, Jamadar SD, Iredale JM. Deficits in behavioural inhibition in substance abuse and addiction: A meta-analysis. Drug and Alcohol Dependence. 2014;**145**:1-33

[2] Schag K, Schönleber J, Teufel M, Zipfel S, Giel KE. Food-related impulsivity in obesity and binge eating disorder—A systematic review. Obesity Reviews: An Official Journal of the International Association for the Study of Obesity. 2013;**14**(6):477-495

[3] Najt P, Perez J, Sanches M, Peluso MAM, Glahn D, Soares JC. Impulsivity and bipolar disorder. European Neuropsychopharmacology. 2007;**17**(5):313-320

[4] Turner D, Sebastian A, Tüscher O. Impulsivity and cluster B personality disorders. Current Psychiatry Reports. 2017;**19**(3):15

[5] Ouzir M. Impulsivity in schizophrenia: A comprehensive update. Aggression and Violent Behavior. 2013;**18**(2):247-254

[6] Maloney EM, Djamshidian A, Sullivan SSO. Phenomenology and epidemiology of impulsive-compulsive behaviours in Parkinsons disease, atypical Parkinsonian disorders and non-Parkinsonian populations. Journal of the Neurological Sciences. 2017;**374**:47-52

[7] Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt Impulsiveness Scale. Journal of Clinical Psychology. 1995;**51**(6):768-774

[8] Whiteside SP, Lynam DR. The five factor model and impulsivity: Using a structural model of personality to understand impulsivity. Personality and Individual Differences. 2001;**30**(4):669-689

[9] Cyders MA, Smith GT. Mood-based rash action and its components: Positive and negative urgency. Personality and Individual Differences. 2007;**43**(4):839-850

[10] Haden SC, Shiva A. Trait impulsivity in a forensic inpatient sample: An evaluation of the Barratt impulsiveness scale. Behavioral Sciences & the Law. 2008;**26**:675-690

[11] Ireland JL, Archer J. Impulsivity among adult prisoners: A confirmatory factor analysis study of the Barratt Impulsivity Scale. Personality and Individual Differences. 2008; **45**(4):286-292

[12] Reise SP, Moore TM, Sabb FW, Brown AK, London ED. The Barratt Impulsiveness Scale—11: Reassessment of its structure in a community sample. Psychological Assessment. 2013; **25**(2):631-642

[13] Vasconcelos AG, Malloy-Diniz L, Correa H. Systematic review of psychometric proprieties of barrattimpulsiveness scale version 11 (BIS-11). Clinical Neuropsychiatry. 2012; **9**(2):61-74

[14] Winstanley CA, Eagle DM, Robbins TW. Behavioral models of impulsivity in relation to ADHD: Translation between clinical and preclinical studies. Clinical Psychology Review. 2006;**26**(4):379-395

[15] Hamilton KR, Littlefield AK, Anastasio NC, Cunningham KA, Fink LHL, Wing VC, et al. Rapid-response impulsivity: Definitions, measurement issues, and clinical implications. Personality Disorders: Theory, Research, and Treatment. 2015;**6**(2):168-181

[16] Robinson ESJ, Eagle DM, Economidou D, Theobald DEH, Mar AC, Murphy ER, et al. Behavioural characterisation of high impulsivity on the 5-choice serial reaction time task: Specific deficits in "waiting" versus "stopping". Behavioural Brain Research. 2009; **196**(2):310-316

[17] Wright L, Lipszyc J, Dupuis A, Thayapararajah SW, Schachar R. Response inhibition and psychopathology: A meta-analysis of go/no-go task performance. Journal of Abnormal Psychology. 2014;**123**(2):429-439

[18] Verbruggen F, Logan GD. Models of response inhibition in the stop-signal and stop-change paradigms. Neuroscience and Biobehavioral Reviews. 2009;**33**(5):647-661

[19] Logan GD. On the ability to inhibit thought and action: A users' guide to the stop signal paradigm. In: Dagenbach D, Carr TH, editors. Inhibitory Processes in Attention, Memory, and Laguage. San Diego: Academic; 1994

[20] Weafer J, Burkhardt A, de Wit H. Sweet taste liking is associated with impulsive behaviors in humans. Frontiers in Behavioral Neuroscience. 2014;**8**(June):228

[21] Lole L, Gonsalvez CJ, Barry RJ. Reward and punishment hyposensitivity in problem gamblers: A study of event-related potentials using a principal components analysis. Clinical Neurophysiology. 2015;**126**(7):1295-1309

[22] Völlm B, Richardson P, McKie S, Elliott R, Dolan M, Deakin B. Neuronal correlates of reward and loss in Cluster B personality disorders: A functional magnetic resonance imaging study. Psychiatry Research: Neuroimaging. 2007;**156**(2):151-167

[23] Ainslie G. Specious reward: A behavioral theory of impulsiveness and impulse control. Psychological Bulletin. 1975;**82**(4):463-496

[24] Sebastian A, Jacob G, Lieb K, Tüscher O. Impulsivity in borderline personality disorder: A matter of disturbed impulse control or a facet of emotional dysregulation? Current Psychiatry Reports. 2013;**15**(2):339

[25] Krause-Utz A, Cackowski S, Daffner S, Sobanski E, Plichta MM, Bohus M, et al. Delay discounting and response disinhibition under acute experimental stress in women with borderline personality disorder and adult attention deficit hyperactivity disorder. Psychological Medicine. 2016;**46**:3137-3149

[26] Cackowski S, Reitz AC, Ende G, Kleindienst N, Bohus M, Schmahl C, et al. Impact of stress on different components of impulsivity in borderline personality disorder. Psychological Medicine. 2014;**44**(August):3329-3340

[27] Barker V, Romaniuk L, Cardinal RN, Pope M, Nicol K, Hall J. Impulsivity in borderline personality disorder. Psychological Medicine. 2015;**45**:1955-1964

[28] Lieb K, Zanarini MC, Schmahl C, Linehan MM, Bohus M. Borderline personality disorder. Lancet. 2004;**364**(364):453-461

[29] Swick D, Ashley V, Turken U. Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. NeuroImage. 2011; **56**(3):1655-1665

[30] Simmonds DJ, Pekar JJ, Mostofsky SH. Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. Neuropsychologia. 2008;**46**(1):224-232

[31] Criaud M, Boulinguez P. Have we been asking the right questions when assessing response inhibition in go/no-go tasks with fMRI? A meta-analysis and critical review. Neuroscience and Biobehavioral Reviews. 2013;**37**(1):11-23

[32] Winstanley CA. The neural and neurochemical basis of delay discounting. In: Madden GJ, Bickel WK, editors. Impulsivity: The Behavioral and Neurological Science of Discounting. Washington: American Psychological Association. 2002. pp. 95-122

[33] Ludwig VU, Nüsser C, Goschke T, Wittfoth-Schardt D, Wiers CE, Erk S, et al. Delay discounting without decision-making: Medial prefrontal cortex and amygdala activations reflect immediacy processing and correlate with impulsivity and anxious-depressive traits. Frontiers in Behavioral Neuroscience. 2015;**9**(280):1-15

[34] McClure SM, York MK, Montague PR. The neural substrates of reward processing in humans: The modern role of fMRI. Neuroscience. 2004;**10**(3):260-268

[35] Kishinevsky FI, Cox JE, Murdaugh DL, Stoeckel LE, Cook EW, Weller REFMRI. Reactivity on a delay discounting task predicts weight gain in obese women. Appetite. 2012; **58**(2):582-592

[36] Stoeckel LE, Murdaugh DL, Cox JE, Cook EW, Weller RE. Greater impulsivity is associated with decreased brain activation in obese women during a delay discounting task. Brain Imaging and Behavior. 2013;**7**(2):116-128

[37] Monterosso JR, Ainslle G, Xu J, Cordova X, Domier CP, London ED. Frontoparietal cortical activity of methamphetamine-dependent and comparison subjects performing a delay discounting task. Human Brain Mapping. 2007;**28**(5):383-393

[38] Meade CS, Lowen SB, MacLean RR, Key MD, Lukas SE. fMRI brain activation during a delay discounting task in HIV-positive adults with and without cocaine dependence. Psychiatry Research. 2011;**192**(3):167-175

[39] Clewett D, Luo S, Hsu E, Ainslie G, Mather M, Monterosso J. Increased functional coupling between the left fronto-parietal network and anterior insula predicts steeper delay discounting in smokers. Human Brain Mapping. 2014;**35**(8):3774-3787

[40] Armony JL. Current emotion research in behavioral neuroscience: The role(s) of the amygdala. Emotion Review. 2013;**5**(1):104-115

[41] Phelps EA, LeDoux JE. Contributions of the amygdala to emotion processing: From animal models to human behavior. Neuron. 2005;**48**(2):175-187

[42] Nimrod J, Sarkheil P, Zilverstand A, Kilian-hütten N, Schneider F, Goebel R, et al. NeuroImage self-regulation of human brain activity using simultaneous real-time fMRI and EEG neurofeedback. NeuroImage. 2016;**125**(6):1-18

[43] Paret C, Ruf M, Fungisai M, Kluetsch R, Demirakca T, Jungkunz M, et al. NeuroImage fMRI neurofeedback of amygdala response to aversive stimuli enhances prefrontal—Limbic brain connectivity. NeuroImage. 2016;**125**:182-188

[44] Kober H, Barrett LF, Joseph J, Bliss-Moreau E, Lindquist K, Wager TD. Functional grouping and cortical-subcortical interactions in emotion: A meta-analysis of neuroimaging studies. NeuroImage. 2008;**42**(2):998-1031

[45] Zotev V, Phillips R, Young KD, Drevets WC, Bodurka J. Prefrontal control of the amygdala during real-time fMRI neurofeedback training of emotion regulation. PLoS One. 2013;**8**(11):e79184

[46] Wei S, Geng H, Jiang X, Zhou Q, Chang M. Amygdala-prefrontal cortex resting-state functional connectivity varies with first depressive or manic episode in bipolar disorder. Neuroscience Letters. 2017;**641**:51-55

[47] Cisler JM. Childhood trauma and functional connectivity between amygdala and medial prefrontal cortex: A dynamic functional connectivity and large-scale network. Perspective. 2017;**11**(May):1-11

[48] Vargas C, López-Jaramillo C, Vieta E. A systematic literature review of resting state network-functional MRI in bipolar disorder. Journal of Affective Disorders. 2013;**150**(3):727-735

[49] Schulze L, Schmahl C, Niedtfeld I. Neural correlates of disturbed emotion processing in borderline personality disorder: A multimodal meta-analysis. Biological Psychiatry. 2016;**79**(2):97-106

[50] Paret C, Kluetsch R, Zaehringer J, Ruf M, Demirakca T, Bohus M, et al. Alterations of amygdala-prefrontal connectivity with real-time fMRI neurofeedback in BPD patients. Social Cognitive and Affective Neuroscience. 2016;**11**(6):952-960

[51] Nicholson AA, Rabellino D, Densmore M, Frewen PA, Paret C, Kluetsch R, et al. The neurobiology of emotion regulation in posttraumatic stress disorder: Amygdala down-regulation via real-time fMRI neurofeedback. Human Brain Mapping. 2017;**38**(1):541-560

[52] Oldham JM, Gabbard GO, Soloff P, Spiegel D, Stone M, Phillips KA. Practice guideline for the treatment of patients with borderline personality disorder. American Psychiatric Association. 2001;**3**(October):1-82

[53] Ansell EB, Sanislow CA, McGlashan TH, Grilo CM. Psychosocial impairment and treatment utilization by patients with borderline personality disorder, other personality disorders, mood and anxiety disorders, and a healthy comparison group. Comprehensive Psychiatry. 2007;**48**(4):329-336

[54] Torgersen S, Kringlen E. The prevalence of personality disorders in a community sample. Archives of General Psychiatry. 2001;**58**(6):590-596

[55] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Arlington: American Psychiatric Association; 2013. 991 p

[56] Donegan NH, Sanislow CA, Blumberg HP, Fulbright RK, Lacadie C, Skudlarski P, et al. Amygdala hyperreactivity in borderline personality disorder: Implications for emotional dysregulation. Biological Psychiatry. 2003;**54**(11):1284-1293

[57] Koenigsberg HW, Siever LJ, Lee H, Pizzarello S, New AS, Goodman M, et al. Neural correlates of emotion processing in borderline personality disorder. Psychiatry Research: Neuroimaging. 2009;**172**(3):192-199

[58] Mitchell AE, Dickens GL, Picchioni MM. Facial emotion processing in borderline personality disorder: A systematic review and meta-analysis. Neuropsychology Review. 2014;**24**(2):166-184

[59] Brunner R, Henze R, Parzer P, Kramer J, Feigl N, Lutz K, et al. Reduced prefrontal and orbitofrontal gray matter in female adolescents with borderline personality disorder: Is it disorder specific? NeuroImage. 2010;**49**(1):114-120

[60] De La Fuente JM, Goldman S, Stanus E, Vizuete C, Morlán I, Bobes J, et al. Brain glucose metabolism in borderline personality disorder. Journal of Psychiatric Research. 1997; **31**(5):531-541

[61] Soloff PH, Meltzer CC, Becker C, Greer PJ, Kelly TM, Constantine D. Impulsivity and prefrontal hypometabolism in borderline personality disorder. Psychiatry Research: Neuroimaging. 2003;**123**(3):153-163

[62] Soloff PH, Meltzer CC, Greer PJ, Constantine D, Kelly TM. A fenfluramine-activated FDGPET study of borderline personality disorder. Biological Psychiatry. 2000 Mar;**47**(6): 540-547

[63] Camprodon JA, Pascual-Leone A. Multimodal applications of transcranial magnetic stimulation for circuit-based psychiatry. JAMA Psychiatry. 2016 Apr 1;**73**(4):407

[64] Barnow S, Völker KA, Möller B, Freyberger HJ, Spitzer C, Grabe HJ, et al. Neurophysiological correlates of borderline personality disorder: A transcranial magnetic stimulation study. Biological Psychiatry. 2009;**65**(4):313-318

[65] Lang S, Stopsack M, Kotchoubey B, Frick C, Grabe HJ, Spitzer C, et al. Cortical inhibition in alexithymic patients with borderline personality disorder. Biological Psychology. 2011;**88**(2-3):227-232

[66] Radhu N, de Jesus DR, Ravindran LN, Zanjani A, Fitzgerald PB, Daskalakis ZJ. A meta-analysis of cortical inhibition and excitability using transcranial magnetic stimulation in psychiatric disorders. Clinical Neurophysiology. 2013;**124**(7):1309-1320

[67] Richter MM, Ehlis A-C, Jacob CP, Fallgatter AJ. Cortical excitability in adult patients with attention-deficit/hyperactivity disorder (ADHD). Neuroscience Letters. 2007;**419**(2): 137-141

[68] Moll GH, Heinrich H, Gevensleben H, Rothenberger A. Tic distribution and inhibitory processes in the sensorimotor circuit during adolescence: A cross-sectional TMS study. Neuroscience Letters. 2006;**403**(1-2):96-99

[69] Tremblay S, Beaule V, Proulx S, de Beaumont L, Marjanska M, Doyon J, et al. Relationship between transcranial magnetic stimulation measures of intracortical inhibition and spectroscopy measures of GABA and glutamate+glutamine. Journal of Neurophysiology. 2013;**109**(5):1343-1349

[70] Arbabi M, Hafizi S, Ansari S, Oghabian MA, Hasani N. High frequency TMS for the management of borderline personality disorder: A case report. Asian Journal of Psychiatry. 2013;**6**(6):614-617

[71] Cailhol L, Roussignol B, Klein R, Bousquet B, Simonetta-Moreau M, Schmitt L, et al. Borderline personality disorder and rTMS: A pilot trial. Psychiatry Research. 2014;**216**(1): 155-157

[72] De Vidovich GZ, Muffatti R, Monaco J, Caramia N, Broglia D, Caverzasi E, et al. Repetitive TMS on left cerebellum affects impulsivity in borderline personality disorder: A pilot study. Frontiers in Human Neuroscience. 2016;**10**(December):1-11

[73] Feffer K, Peters SK, Bhui K, Giacobbe P, Downar J. Successful dorsomedial prefrontal rTMS for major depression in borderline personality disorder: Three cases. Brain Stimulation. 2017;(February):2-3

[74] Reyes-López J, Ricardo-Garcell J, Armas-Castañeda G, García-Anaya M, Arango-De Montis I, González-Olvera JJ, et al. Clinical improvement in patients with borderline personality disorder after treatment with repetitive transcranial magnetic stimulation: Preliminary results. Revista Brasileira de Psiquiatria. 2017

[75] Çavdar S, lýz Onat FY, Yananli HR, Şehirli ÜS, Tulay C, Saka E, et al. Cerebellar connections to the rostral reticular nucleus of the thalamus in the rat. Journal of Anatomy. 2002;**201**(6):485-491

[76] Yamamoto T, Yoshida K, Yoshikawa H, Kishimoto Y, Oka H. The medial dorsal nucleus is one of the thalamic relays of the cerebellocerebral responses to the frontal association cortex in the monkey: Horseradish peroxidase and fluorescent dye double staining study. Brain Research. 1992;**579**(2):315-320

[77] Palesi F, Tournier JD, Calamante F, Muhlert N, Castellazzi G, Chard D, et al. Contralateral cerebello-thalamo-cortical pathways with prominent involvement of associative areas in humans in vivo. Brain Structure & Function. 2015;**220**(6):3369-3384

[78] Finn PR, Justus A, Mazas C, Steinmetz JE. Working memory, executive processes and the effects of alcohol on Go/No-Go learning: Testing a model of behavioral regulation and impulsivity. Psychopharmacology. 1999;**146**(4):465-472

[79] Hinson JM, Jameson TL, Whitney P. Impulsive decision making and working memory. Journal of Experimental Psychology. Learning, Memory, and Cognition. 2003;**29**(2):298-306

[80] Speer AM, Benson BE, Kimbrell TK, Wassermann EM, Willis MW, Herscovitch P, et al. Opposite effects of high and low frequency rTMS on mood in depressed patients: Relationship to baseline cerebral activity on PET. Journal of Affective Disorders. 2009;**115**(3): 386-394

[81] Barkley RA. Attention-Deficit Hyperactivity Disorder. A Handbook for Diagnosis and Treatment. 3rd ed. New York, NY, US: Guilford Press; 2006

[82] Ramsay JR, Rostain A. Cognitive-Behavioral Therapy for Adult ADHD: An Integrative Psychosocial and Medical Approach. New York, NY, US: Routledge/Taylor & Francis Group; 2008 (Practical clinical guidebooks series)

[83] Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, et al. Molecular genetics of attention-deficit/hyperactivity disorder. Biological Psychiatry. 2005 Jun;**57**(11):1313-1323

[84] Barkley RA. Deficient emotional self-regulation: A core component of attention-deficit/hyperactivity disorder. Journal of ADHD & Related Disorders. 2010;**1**(2):5-37

[85] Torgersen T, Gjervan B, Rasmussen K. Treatment of adult ADHD: Is current knowledge useful to clinicians? Neuropsychiatric Disease and Treatment. 2008 Feb;**4**(1):177-186

[86] Sonuga-Barke EJS. Disambiguating inhibitory dysfunction in attention-deficit/hyperactivity disorder: Toward the decomposition of developmental brain phenotypes. Biological Psychiatry. 2010;**67**(7):599-601

[87] Nigg JT, Willcutt EG, Doyle AE, Sonuga-Barke EJS. Causal heterogeneity in attention-deficit/hyperactivity disorder: Do we need neuropsychologically impaired subtypes? Biological Psychiatry. 2005;**57**(11):1224-1230

[88] Shaw P, Eckstrand K, Sharp W, Blumenthal J, Lerch JP, Greenstein D, et al. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proceedings of the National Academy of Sciences. 2007;**104**(49):19649-19654

[89] Todd RD, Neuman RJ, Lobos EA, Jong Y-JI, Reich W, Heath AC. Lack of association of dopamine D4 receptor gene polymorphisms with ADHD subtypes in a population sample of twins. American Journal of Medical Genetics. 2001 Jul;**105**(5):432-438

[90] Dickstein SG, Bannon K, Xavier Castellanos F, Milham MP. The neural correlates of attention deficit hyperactivity disorder: An ALE meta-analysis. Journal of Child Psychology and Psychiatry and Allied Disciplines. 2006;**47**(10):1051-1062

[91] Duerden EG, Tannock R, Dockstader C. Altered cortical morphology in sensorimotor processing regions in adolescents and adults with attention-deficit/hyperactivity disorder. Brain Research. 2012;**1445**:82-91

[92] Vloet TD, Gilsbach S, Neufang S, Fink GR, Herpertz-Dahlmann B, Konrad K. Neural mechanisms of interference control and time discrimination in attention-deficit/hyperactivity disorder. Journal of the American Academy of Child and Adolescent Psychiatry. 2010;**49**(4):356-367

[93] Bush G. Cingulate, frontal, and parietal cortical dysfunction in attention-deficit/hyperactivity disorder. Biological Psychiatry. 2011;**69**(12):1160-1167

[94] Kašpárek T, Theiner P, Filová A. Neurobiologie hyperkinetické poruchy pohledem zobrazovacích metod. Česká a slovenská psychiatrie. 2013 Apr;**109**(2):73-80

[95] Scheres A, Milham MP, Knutson B, Castellanos FX. Ventral striatal hyporesponsiveness during reward anticipation in attention-deficit/hyperactivity disorder. Biological Psychiatry. 2007;**61**(5):720-724

[96] Dutra TG, Baltar A, Monte-Silva KK. Motor cortex excitability in attention-deficit hyperactivity disorder (ADHD): A systematic review and meta-analysis. Research in Developmental Disabilities. 2016;**56**:1-9

[97] Gilbert DL, Isaacs KM, Augusta M, Macneil LK, Mostofsky SH. Motor cortex inhibition A marker of ADHD behavior and motor development in children. Neurology. 2011;**76**(7):615-621

[98] Moll GH, Heinrich H, Trott G-E, Wirth S, Rothenberger A. Deficient intracortical inhibition in drug-naive children with attention-deficit hyperactivity disorder is enhanced by methylphenidate. Neuroscience Letters. 2000;**284**(1):121-125

[99] Moll GH, Heinrich H, Trott G-E, Wirth S, Bock N, Rothenberger A. Children with comorbid attention-deficit-hyperactivity disorder and tic disorder: Evidence for additive inhibitory deficits within the motor system. Annals of Neurology. 2001 Mar 1;**49**(3):393-396

[100] Wu SW, Gilbert DL, Shahana N, Huddleston DA, Mostofsky SH. Transcranial magnetic stimulation measures in attention-deficit/hyperactivity disorder. Pediatric Neurology. 2012;**47**(3):177-185

[101] Wagle-Shukla A, Ni Z, Gunraj CA, Bahl N, Chen R. Effects of short interval intracortical inhibition and intracortical facilitation on short interval intracortical facilitation in human primary motor cortex. The Journal of Physiology. 2009;**587**(23):5665-5678

[102] Kaster TS, de Jesus D, Radhu N, Farzan F, Blumberger DM, Rajji TK, et al. Clozapine potentiation of GABA mediated cortical inhibition in treatment resistant schizophrenia. Schizophrenia Research. 2015;**165**(2-3):157-162

[103] Hasan A, Schneider M, Schneider-Axmann T, Ruge D, Retz W, Rösler M, et al. A similar but distinctive pattern of impaired cortical excitability in first-episode schizophrenia and ADHD. Neuropsychobiology. 2013;**67**(2):74-83

[104] Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. Journal of Neuroscience. 2001;**21**(15):RC157

[105] Niederhofer H. Effectiveness of the repetitive transcranical magnetic stimulation (rTMS) of 1 Hz for attention-deficit hyperactivity disorder (ADHD). Psychiatria Danubina. 2008 Mar;**20**(1):91-92

[106] Niederhofer H. Additional biological therapies for attention-deficit hyperactivity disorder: Repetitive transcranical magnetic stimulation of 1 Hz helps to reduce methylphenidate. Clinical Practice. 2011 Dec;**2**(1):e8

[107] Bloch Y, Harel EV, Aviram S, Govezensky J, Ratzoni G, Levkovitz Y. Positive effects of repetitive transcranial magnetic stimulation on attention in ADHD Subjects: A randomized controlled pilot study. The World Journal of Biological Psychiatry. The official Journal of the World Federation of Societies of Biological Psychiatry. 2010 Aug;**11**(5):755-758

[108] Ustohal L, Prikryl R, Kucerova HP, Sisrova M, Stehnova I, Venclikova S, et al. Emotional side effects after high-frequency RTMS of the right dorsolateral prefrontal cortex in an adult patient with ADHD and comorbid depression. Psychiatria Danubina. 2012;**24**(1):102-103

[109] Lefaucheur J, André-obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clinical Neurophysiology. 2014;**125**(11):2150-2206

[110] Saba G, Rocamora JF, Kalalou K, Benadhira R, Plaze M, Lipski H, et al. Repetitive transcranial magnetic stimulation as an add-on therapy in the treatment of mania: A case series of eight patients. Psychiatry Research. 2004;**128**(2):199-202

[111] Weaver L, Rostain AL, Mace W, Akhtar U, Moss E, O'Reardon JP. Transcranial magnetic stimulation (TMS) in the treatment of attention-deficit/hyperactivity disorder in adolescents and young adults: A pilot study. The Journal of ECT. 2012 Jun;**28**(2):98-103

[112] Helfrich C, Pierau SS, Freitag CM, Roeper J, Ziemann U, Bender S. Monitoring cortical excitability during repetitive Transcranial magnetic stimulation in children with ADHD: A single-blind, sham-controlled TMS-EEG study. PLoS One. 2012;**7**(11):e50073

[113] Gómez L, Vidal B, Morales L, Báez M, Maragoto C, Galvizu R, et al. Low frequency repetitive transcranial magnetic stimulation in children with attention deficit/hyperactivity disorder. Preliminary results. Brain Stimulation. 2014;**7**(5):760-762

[114] D'Agati D, Bloch Y, Levkovitz Y, Reti I. rTMS for adolescents: Safety and efficacy considerations. Psychiatry Research. 2010 May;**177**(3):280-285

Chapter 5

Transcranial Magnetic Stimulation in the Treatment of Tinnitus

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73221

Abstract

Tinnitus is a disturbing noise that is heard without any hearing stimulus, affects the quality of life of the individual, and leads to psychosocial problems. Its prevalence characteristically increases with aging. It is seen in 33% of the general population. Pathophysiology of tinnitus known to accompany nearly all disorders in auditory system has not been fully understood; therefore, there are some difficulties in evaluation and treatment thereof. Despite the restrictive factors of tinnitus treatment, progress in auditory neuroscience provides a positive view of tinnitus treatment. Transcranial magnetic stimulation (TMS) is a method based on the stimulation of neuronal tissue without depending on the transfer of electrical current by means of electrodes or the skin. TMS is used in the treatment of various diseases with developing neuroscience. In the recent years, the number of studies on TMS application with repetitive low frequency for the treatment of tinnitus has increased, and most of these studies have given successful results. Repetitive use of TMS in tinnitus is very novel; however, it is commonly used in psychiatric disorders, especially in the treatment of drug-resistant depression. The chapter shows that low-frequency repetitive TMS (rTMS) is useful in the treatment of chronic tinnitus.

Keywords: tinnitus, transcranial magnetic stimulation, tinnitus handicap inventory, rTMS, THI

1. Introduction

1.1. Tinnitus

Along with the development of technology and urbanization, there are some additional burdens along with the convenience of our lives. Increasing traffic with urbanization, increasing

use of mobile phones from early ages, and listening to loud music with headphones cause our life to become more loud and tense.

Tinnitus is a symptom thought to be heard without a voice stimulus. The presence of tinnitus also affects the quality of life of individuals and causes psychosocial problems. It is characteristic that it becomes more common with aging. It is present in one third of the general population [1].

Forty-sixty million people in the United States have a tinnitus on one occasion, and according to most of them, this does not pose any problem for any treatment. Only 1–5% of individuals with tinnitus have severe and uncomfortable ear tinnitus [2, 3].

Tinnitus occurs with 30-dB hearing loss at the rate of 75%. As the hearing level decreases, its incidence increases. It was detected that exposure to high sound or noise increases tinnitus prevalence.

Pathophysiology of tinnitus known to accompany nearly all disorders in auditory system has not been fully understood; therefore, there are some difficulties in evaluation and treatment thereof. Tinnitus is still a subject of research on neurotology. However, the etiology and physiopathology are not well known. Therefore, tinnitus treatment has not yet been clarified.

Tinnitus can also have a large economic effect. The lack of standardization of tinnitus diagnosis and treatment management increases the cost of health care [4]. Tinnitus reduces the concentration of the person, restricts their participation in professional activities, thus reducing the work efficiency of the person [5–7].

Despite the restrictive factors of tinnitus treatment, progress in auditory neuroscience provides a positive view of tinnitus treatment.

Transcranial magnetic stimulation (TMS) is a method based on the stimulation of neuronal tissue without depending on the transfer of electrical current by means of electrodes or the skin. TMS is used in the treatment of various diseases with developing neuroscience. Good news is coming from recent studies on TMS application with repetitive low frequency in tinnitus treatment. TMS inhibits abnormal cortical activities in the affected area. Tinnitus treatment is applied to auditory cortex. Positive results have been revealed during the studies [8, 9].

This chapter is devoted to evaluate the effects of transcranial magnetic stimulation (TMS) on the treatment of subjective tinnitus.

1.1.1. Tinnitus pathophysiology

The auditory system is a complex system and contains a large number of central nuclei that provide the cortical organ peripheral fibers in the spiral laminates, multiple afferent and efferent delivery channels, and complex integration in the upper centers of the central nervous system [10–12]. The pathologies that occur anywhere in these regions cause an increase in the perception of sound through unknown mechanisms. Researchers have tried to explain the formation and perception of tinnitus with many different mechanisms.

- Damage to inner and outer hair cells
- Ion imbalance in the cochlea
- Dysfunction in the cochlear neurotransmitter system
- Heterogeneous activation in the cochlear efferent system
- Heterogeneous activation in type I and II cochlear afferents
- Cross links between the eight nerve fibrils [13]

Every nerve fiber has an electrical discharge even at rest. This is called the spontaneous activity of that nerve. There is an increase in spontaneous activity in patients with tinnitus. All of the assumptions put forward to explain the pathogenesis of tinnitus are based on this spontaneous activity increase [1, 14]. Recent studies suggest that tinnitus is an event based on hyperactivity of the auditory system, which is temporarily adjusted by TMS [15]. Theories about pathophysiology of tinnitus can be grouped as follows:

According to Moller, some of the adjacent nerve fibers are damaged for some reason, resulting in artificial synapse between the nerve fibers, and these synapses between the fibers cause pathological transmissions. This results in increased spontaneous activity and tinnitus [1, 14, 16].

Jastreboff and Hazell note that when the temporal cortex is reduced in hearing impulses, there is an increase in neuronal sensitivity in the subcortical centers. For this reason, a tinnitus patient with normal hearing is thought to be associated with subcortical centers, which we hear as weak voices in auditory cues (e.g., in quiet rooms) [13].

Tonndorf states that tinnitus can originate from all levels of the auditory system. If tinnitus is acoustically masked, it is originated from peripheral auditory system, whereas if tinnitus masking is not present, it is originated from central auditory system. There is a chemical imbalance between the tinnitus cell membrane and the stereocilia. This leads to hyperactive flickering hair or hyperactive nerve fibers. For this reason, even very low spontaneous activities are perceived by these shaky hair or nerve fibers. This condition could be likened to postamputation phenomenon [1, 14, 17, 18]. In 1965, Melzack and Wall proposed the door control theory for chronic pain. Tonndorf proposed this theory for tinnitus [19, 20]. The balance of the impulse that comes from the afferent inner hair cell and the outer hair cell to brainstem, respectively, seems to shift unilaterally when one or more of the hair cell's subsystem is damaged. Tonndorf suggests that this imbalance of warning may cause tinnitus.

Salvi and Ahroon reported that spontaneous neural activity in the area of the cochlea lesion leads to tinnitus, that acoustic trauma affects cochlea when exposed to noise, and that spontaneous discharges more frequently occur in the high-frequency region of cochlea than in other regions. This increase in spontaneous activity level is expressed as tinnitus [21, 22].

According to Kiang, there are abnormal stereocilia. In the transition between normal and abnormal stereocilia, the suppression of normal cells is lost. This leads to increased spontaneous activity. This leads to tinnitus [14]. Sellick et al. argued that the displacement of the

membrane towards to scala tympani causes hyperactivity. It is thought that tinnitus occurs in this way [14].

In 1984, Eggermont assumed that there was hypersensitivity in stereocilia. This may be due to a reduction in the inhibition applied by the central route. Thus, nerve fibers perceive sounds that would normally not be heard. That said, tinnitus may be the cause [1, 14, 23]. In addition, Eggermont suggested in 1990 that the balance between stereocilia activities and nerve fiber activities could have contributed to tinnitus [24].

Although inner ear damage occurs and the eighth cranial nerve is cut, the continuation of tinnitus in some patients supports the concept of 'central tinnitus.' Peripheral tinnitus may be localized in one or two ears, while central tinnitus is usually not localized at one point. The major causes of central tinnitus are occupied lesions, inflammations, and vascular anomalies, and often masking does not succeed. Auditory brainstem response (ABR) is helpful in the diagnosis of central tinnitus [25].

Tinnitus can be defined as objective or subjective. Objective tinnitus can be detected by another person or physician.

Objective tinnitus usually has a pulsatile or rhythmic quality. **Table 1** lists common causes of objective tinnitus.

Objective tinnitus can be caused by auditory and nonauditory disorders such as Ménière's disease, Eustachian tube disorders, intracranial hypertension, middle ear diseases etc [26].

Objective tinnitus treatment depends on the underlying disease. This subject will not be discussed in this chapter.

Pulsatile

- *Venous etiologies*
  - Venous hum
  - Hypertension
  - Pseudotumor cerebri
  - Sigmoid sinus and jugular bulb anomalies
- *Arterial etiologies*
  - Paraganglioma (glomus tympanicum or jugulare)
  - Persistent stapedial artery
  - Intratympanic carotid artery
  - Arteriovenous fistula or malformation
  - Increased cardiac output (pregnancy and thyrotoxicosis)
  - Carotid artery stenosis
  - Vascular compression of cranial nerve VII
  - Intraosseous (Paget disease and otosclerosis)
- *Tensor tympani or stapedial muscle myoclonus*
- *Palatal myoclonus*

Nonpulsatile

- *Patulous Eustachian tube*
- *Spontaneous otoacoustic emission*
- *Idiopathic stapedial muscle spasm*

Table 1. Objective tinnitus subtypes.

1.1.2. Subjective tinnitus

The most common form of tinnitus is subjective tinnitus. Unlike objective tinnitus, subjective tinnitus cannot be heard by anyone else. The prevalence of subjective tinnitus is estimated between 8% and 30% and tinnitus should be defined according to the population of the study, the severity of tinnitus, and the evaluation of the methodology [2, 27, 28].

The most important cause of tinnitus is exposure to sound. The main problem in most patients is unknown [29].

Subjective tinnitus most commonly occurs due to sensorineural hearing loss (SNHL), which is caused by the presbycusis and acoustic trauma, conductive hearing loss, endolymphatic hydrops, and cerebellopontine angle neoplasia, which are more rare causes of tinnitus. Subjective tinnitus is the most common form that affects adults, and it is the focus of this chapter. Tinnitus subtype classification schemes can be useful to identify forms of tinnitus that are responsive to specific targeted treatment programs. **Table 2** lists common causes of subjective tinnitus.

1.1.2.1. Hearing loss

Urbanization and industrialization are accompanied by increased hearing loss due to noise. Noise-induced hearing loss (NIHL) is a significant and increasing health problem. Unfortunately,

- **Otologic factors**
  - Presbycusis
  - Noise-induced hearing loss
  - High-frequency hearing loss
  - Outer hair cell dysfunction
  - Ménière's disease
- **Somatic tinnitus**
  - Temporomandibular joint syndrome
- **Typewriter tinnitus**
- **Psychological factors**
  - Anxiety
  - Depression
- **Pharmacological factors**
  - Aspirin compounds
  - Nonsteroidal anti-inflammatory drugs
  - Aminoglycosides
  - Heavy metals
- **Metabolic factors**
  - Hypothyroidism
  - Hyperthyroidism
  - Hyperlipidemia
  - Vitamin deficiency
- **Neurologic abnormalities**
  - Multiple sclerosis
  - Meningitic effects
  - Skull fracture or closed head trauma

Table 2. Subjective tinnitus subtypes.

many people do not care about industrial noise, fire alarms, listening to music loudly and other noises, or how unaware they are. According to a study conducted, 61% of people who went to the concert found hearing loss and temporary ringing of ears after the concert [30]. The prevalence of chronic tinnitus associated with NIHL is 50–70% [31].

Presbycusis is a sensorineural hearing loss that occurs with aging. Personal and environmental factors play a role in the development of presbycusis, but it mainly involves complex genetic factors. The best-known environmental factor is noise, and hearing is better protected in elderly people who are not exposed to high sound.

1.1.2.2. Somatic tinnitus

Somatic tinnitus can be modulated by maneuvers or stimulation of the head and neck region. Patients with temporomandibular joint (TMJ) disorder had higher incidence of tinnitus compared to control groups [32]. When tinnitus occurs in association with disorders of the head and neck such as TMJ dysfunction, unilateral facial pain, otalgia, and occipital or temporal headache, successful tinnitus alleviation may be possible using interventions that target the somatic dysfunction [17].

1.1.2.3. Typewriter tinnitus

This type of tinnitus may be confused with tinnitus that arises from a muscular source, such as spasm of the tensor tympani or stapedius muscles, or palatal myoclonus. Typewriter tinnitus is defined, as its name implies, by the characteristic sensation of a staccato quality to tinnitus, similar to a typewriter tapping, popcorn popping, or Morse code signaling. Typewriter tinnitus is distinct from these somatic sources, as illustrated by a patient with typewriter tinnitus that failed to respond to tensor tympani and stapedius resection [33].

1.1.2.4. Psychological factors

Emotional distress and disturbance of sleep are often associated with severe tinnitus. Stress often increases the perception of tinnitus severity, and depression frequently accentuates the complaint. In some cases, tinnitus itself may be the cause of the psychological disorder. Depression is common in patients with tinnitus, but it is not always clear whether depression is primary or secondary.

1.1.2.5. Pharmacological factors

The pharmaceutical industry has developed in the last 50 years. Despite the developing world, rational drug use is not yet fully established. Almost every medication can be considered as a possible cause for tinnitus. The main ones responsible are listed in **Table 3**.

The aim of tinnitus treatment is to reduce or, if it is possible, to eliminate the voice that disturbs the patients [22]. Symptomatic treatment options are important because etiologic causes are detected in 5% of the cases [34, 35].

Nonsteroidal anti-inflammatory drugs
- Ibuprofen
- Indomethacin
- Naproxen
- Phenylbutazone
- Sulindak

Amikacin

Aminoglycoside antibiotics
- Streptomycin
- Neomycin
- Gentamycin
- Tobramycin

Aspirin and aspirin-containing compounds
- Darvon
- Percodan
- Ecotrin
- Bufferin

Heterocyclic antidepressants
- Nortriptyline
- Amitriptyline
- Trazodone
- Amoxapine
- Doxepin
- Trimipramine

Table 3. Medications that cause tinnitus.

1.1.3. Examination and tests

In order to be able to treat patients with tinnitus or to improve the effectiveness of treatment, detailed evaluation of the patients and the investigation of the etiology are required. We have not created a successful standard protocol for evaluating tinnitus until now. Assessment of tinnitus is medically and audiologically interpreted and is used to make individual plans for tinnitus treatment [36]. The transactions to be made in the evaluation can be listed as follows:

1. History: the major importance in the evaluation of tinnitus patients is anamnesis [37, 38]. A detailed history of the patient should be taken. Age at which tinnitus began, audiovestibular symptoms (hearing loss and dizziness), the nature of tinnitus (intensity and frequency) and daytime changes, family history, history of exposure to noise, smoking, alcohol use, systemic diseases, head trauma, ototoxic drug use, epilepsy, otosclerosis, and past meningitis must be questioned.

2. Physical examination: after obtaining a complete history of the patient with tinnitus, clinical management should begin with a general medical evaluation followed by a complete head and neck examination. All tinnitus patients should undergo neurological examination including a detailed ENT examination, temporomandibular joint examination and diapason tests, general medical evaluation, and cranial nerve examination [10, 11].

3. Audiologic evaluation: pure audio audiometry, speech audiometry, percentage of speech discrimination, disturbing auditory height, impedance metric evaluation, otoacoustic emission (OAE), and auditory brainstem response (ABR) can be performed [39–42].

4. Laboratory tests: complete blood cell count and extensive biochemical examinations should be performed routinely. If the patient is suspected of any metabolic or medical condition, more detailed examination should be performed.
5. Radiological evaluation: temporomandibular joint disease should be excluded by radiological evaluation. In patients with unilateral hearing loss, radiological evaluation may be needed to exclude posterior fossa tumors. Computed tomography (CT) is sufficient in the evaluation of most tumors and anomalies. MRI should be performed to exclude vestibular schwannoma or other cerebellopontine angle sister neoplasms if there is a clinical suspicion for patients with nonpulsatile tinnitus [43].

1.1.4. Tinnitus and audiologic findings

1.1.4.1. Pure sound audiogram

It has been reported that 13% of tinnitus cases have transmission-type hearing loss and 39% have sensorineural-type hearing loss. Hearing loss was more frequent in the high-frequency range of the sensorineural hearing loss group [37].

1.1.4.2. Otoacoustic emissions (OAE)

It is thought that OAE is a special evaluation method for cochlear auditory dysfunction in the light of the studies performed and objectively confirms cochlear dysfunction in patients with normal audiogram and tinnitus complaints [44].

Tyler and his colleagues reported that only one of their 25 patients had spontaneous OAEs and found no connection between spontaneous OAEs and tinnitus curtain or severity [45]. Penner and Burns investigated whether the SOAE measurement would be of an objective value in terms of tinnitus correlation, but they could not find a relationship [46]. As a result of some studies on the relationship between SOAE and tinnitus, only a small group of patients has been identified [45, 47]. Studies are underway to investigate the relationship between distortion product otoacoustic emissions (DPOAE) and tinnitus. In these studies, it was revealed that there is a significant relationship between the frequency of tinnitus emergence and DPOAE responses [48].

1.1.4.3. Auditory brainstem response (ABR)

It is a diagnostic measure to help determine the type of tinnitus. There was no difference in the ABR test of the tinnitus patient group in the study of all normal hearing individuals [49].

1.1.5. Evaluation of findings

There are many questionnaires to evaluate the severity of tinnitus and its negative impact on the patient. A standard assessment is needed to document and report the results of clinical trials. Tinnitus, which is defined and graded on this scale, is standardized, and the common denominator in the treatment approach is unified.

Various methods can be used to evaluate the findings of the patients. Tinnitus handicap inventory (THI) is an easily applicable test that is not affected by age, sex, and hearing loss of the patient [50]. A confidence interval of 95% for THI is 20 points, which suggests that a difference in scores of 20 points or greater represents a statistically and clinically significant change.

1.1.6. Tinnitus treatment strategies

Tinnitus is a complex, multifactorial problem with many potential options that can help the patient cope with the condition. You cannot cure tinnitus without understanding tinnitus. We try to approach some treatment modalities for subjective tinnitus after excluding organic causes. Currently, there are some treatment options for patients with tinnitus. Based on the 2014 tinnitus guidelines, the treatment options are shown in **Table 4** [26].

1.1.6.1. Education and counseling

Patient education should instead emphasize that tinnitus itself is a symptom and not a dangerous disease, and a comprehensive assessment can exclude any associated medical conditions that require prompt treatment.

When counseling the patient, it is absolutely necessary to explain the importance of avoiding noise. The relationship between noise and tinnitus should be reminded.

1.1.6.2. Sound therapy

Acoustic stimulation has an important place in the treatment of tinnitus. Sound therapy can decrease the subjective loudness of tinnitus, which can significantly decrease the annoyance, but this may require weeks to months of daily application. Acoustic stimulation can be achieved in many ways. Masking of tinnitus is based on the principle of suppressing the inner voice from the outside. Masking can be applied with various methods such as hearing aids, tinnitus instruments, and maskers.

A hearing aid is a simple method that can be used in patients with hearing loss who have tinnitus. The hearing aid reduces tinnitus by masking the annoying sound the patient perceives by increasing the volume of the sound coming from the outside.

The tinnitus instrument is a device that includes both the properties of the hearing aid and the masking device. Hearing aid input and masking device input are independent of each other,

• Education and counseling
• Sound therapy
• Cognitive behavioral therapy
• Medical therapy
• Dietary supplements
• Acupuncture
• Transcranial magnetic stimulation

Table 4. Tinnitus treatment options.

which can only increase the masking volume at night or in quiet environments where tinnitus is intensified. Masking is only a substitute solution for tinnitus and not a cure.

1.1.6.3. Cognitive behavioral therapy (CBT)

Cognitive behavioral therapy has been shown to be effective in the treatment of tinnitus-related disorders. In many patients, stress or depression is a major factor in the intensity and severity of their complaints. Cognitive behavioral therapy (CBT) is a psychotherapy based on identification and modification of maladaptive behaviors using therapist-mediated cognitive restructuring techniques. Andersson and Lyttkens analyzed 18 studies of psychological treatments for tinnitus and concluded that CBT was more effective than behavioral treatments alone [51].

1.1.6.4. Medical therapy

With the development of the pharmaceutical industry, in the last 50 years, pharmacological treatment for tinnitus has come to the forefront. Drugs used in the treatment of tinnitus are used as useful medicines in terms of improving the emotional state of the patient, reducing anxiety, and improving sleep. Anesthetics (lidocaine, tocainide, and mexiletine), anticonvulsants (carbamazepine and gabapentin), and tranquilizers (diazepam, clonazepam, and oxazepam) have been investigated as tinnitus treatments.

At this time, there are no medications approved by the US Food and Drug Administration (FDA) for treatment of tinnitus.

1.1.6.5. Dietary supplements

Tinnitus appears to be a disease that is unlikely to be treated for most patients. This situation forces the physicians and patients to try other treatment methods. *Ginkgo biloba* and melatonin are the products of recent use that is increasing. *G. biloba* extract contains multiple compounds with vasotropic, potential neuroprotective, and antioxidant effects. Several other dietary supplements have been used for tinnitus, including lipoflavonoids, garlic, homeopathy, traditional Chinese/Korean herbal medicine, honeybee larvae, and other various vitamins and minerals. Evidence for efficacy of these therapies for tinnitus does not exist.

Further study is needed to investigate the side effects that may occur in the use of *G. biloba*, melatonin, or dietary supplements, as well as the use of such products in the treatment of patients with primary tinnitus.

1.1.6.6. Acupuncture

Acupuncture is a form of alternative medicine in which thin needles are inserted into the body. It is a key component of traditional Chinese medicine. The role of acupuncture in tinnitus patients is still controversial. Although unblinded studies have suggested positive results, they have not been reproduced in blinded studies [52]. There is general consensus that acupuncture is a relatively safe treatment when administered by well-trained and experienced practitioners [53–58].

The objective of the current chapter is to evaluate the effect of TMS on the treatment of subjective tinnitus, so you can find detailed information about other treatments of tinnitus in the literature.

2. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a method based on the stimulation of neuronal tissue without depending on the transfer of electrical current by means of electrodes or the skin. Magnetic stimulation causes transient disturbances of neural activity in different regions of the cortex. The depth of penetration is limited to less than 2 cm [59]. With stimulation, it forms a temporary lesion in the region. This reversible lesion allows the investigator to provide information about whether the cortical region contributes to a particular perception or behavior [60]. To better understand motor responses and corticospinal mechanisms to deep brain stimuli in Parkinson's patients [61, 62], phantom muscle contractions were used for cortical silent period studies [63]. In 1980, Merton and Morton have shown that motor neurons can be stimulated by a single, high-voltage, short-duration electrical stimulus applied to a rigid scalp with an electrical stimulator [64]. In 1985, Barker and colleagues began to use transcranial magnetic stimulation, which is transmitted through tissues like the same electrical stimulator and applied with a magnetic stimulator that stimulates the cerebral motor cortex and is more painless [65]. Since then, transcranial magnetic stimulation became widely used in areas such as clinical neurophysiology, neurology, and psychiatry. In the following years, transcranial magnetic stimulation became widely used in the evaluation of many other cerebral functions as well as studies in the developing peripheral nerves and muscles that stimulate magnetic stimulation producing coils to stimulate a small area of the cortex [66–68]. Today, advanced TMS machines can deliver up to 60 stimuli.

The magnetic field affected by a single pulse is measured for milliseconds for a short time. Repeated stimuli cause superficial cortex to change from a few seconds to a few minutes of neuronal depolarization. Repeated stimuli produce different responses depending on the frequency of the region. The application of repetitive stimuli is termed repetitive TMS (rTMS). Low-frequency (<1 Hz) repetitive TMS decreases cortical excitability [69], whereas high-frequency (5–20 Hz) repetitive TMS increases cortical excitability [70]. 1 Hz or slower is called slow rTMS; faster than 1 Hz is called fast rTMS. In the practice of TMS, when the head piece was placed on the scalp corresponding to the projection of the motor cortex and stimulated, the opposite extremities were seen to move painlessly [65]. The diameter of the electrodes used for magnetic stimulation is the most important factor affecting the magnetic field configuration. Electrodes are divided into "circular" or "butterfly" type. Those in butterfly type are called "double shape" or "eight shaped." Their difference from the circular types is that the maximum current intensity is below the center point. These electrodes are more suitable for selective excitation by producing more localized currents [71, 72]. A magnetic exciter consists of a high-capacity series capacitor and a copper winder. With the discharge of the capacitor, a sudden and high-power (1–4.3 T) magnetic field exchange occurs around the coil. With this effect, ion currents emerge in the neural tissues adjacent to the region where it is placed on the

coil and stimulate the neural tissue. If enough magnitude and a rapidly changing magnetic pulse are generated at a sufficient depth, this pulse will cause a secondary ion current in the neuronal tissue [68]. This leads to depolarization of the membrane in the stimulated region of the neuronal tissue. Magnetic stimulation reaches the neuronal tissue without being hindered by intervening tissues such as skin and bone, which does not cause any obvious pain because it does not stimulate the surrounding tissues [73].

The therapeutic response of magnetic stimulation has been observed to be more pronounced with frequent repetitive stimulation (repetitive magnetic stimulation) and studies have shifted to this direction. For this purpose, it was most commonly used in psychiatric disorders [74]. In drug-resistant depressions, repetitive transcranial magnetic stimulation resulted in improvements of 40–50% [75]. TMS has been studied and is still being studied in psychiatric disorders such as schizophrenia, obsessive-compulsive disorder, posttraumatic stress disorder, and mania even though it is not the same size as depression. TMS is one of the safest and painless methods used in the evaluation of the nervous system and in the treatment of the mentioned psychiatric disorders [76–79]. It is not recommended to be applied in patients who have clips with neurosurgical operation and patients with heart pace because they can stimulate an epileptic seizure on the stroke [80, 81]. Although the use of repetitive TMS (rTMS) in tinnitus is very recent, there are many studies on the efficacy [8, 9, 82]. TMS has opened a new vision into investigating the causes and associations of tinnitus-related cortical activity, and it may provide an effective tinnitus therapy for some patients.

Imaging methods can show asymmetric metabolic activity in the hearing cortex of patients with tinnitus. Functional magnetic resonance imaging and fluorodeoxyglucose positron emission tomography provide it [83, 84]. The fact that rTMS has an inhibitory effect on the area it is applied to suggests that it may also be effective in the treatment of tinnitus [8, 9, 85].

2.1. TMS in the treatment of tinnitus

Tinnitus is still a subject of research on neurotology; however, recent studies in literature are not sufficient enough to enlighten the etiology or pathophysiology of tinnitus, and because of this uncertainty, treatment options are limited. Success rate of medical treatment of tinnitus according to the literature is between 30 and 80%, and most of these studies underline the effectiveness of placebo [86, 87]. TMS application for tinnitus treatment is a relatively new subject, studies are providing very little information, but the results seem promising.

It is important to determine the frequency and loudness of tinnitus because these are correlated with affects of tinnitus on the patients' life [88, 89]. Tinnitus is present in 65% of the population with hearing problems, and tinnitus in 50% of them is a serious problem [90]. According to one study, tinnitus is a serious problem for 2.6% of the local population [91].

The probability of tinnitus is increasing in patients with hearing loss [92]. If external hair cell damage is not up to 30%, the hearing thresholds do not get affected. This could explain tinnitus in patients who do not have hearing loss [20]. The loudness and frequency of tinnitus must be determined for rehabilitation [93]. In Yilmaz et al.'s study, the mean (SD) scores in the TMS group before the treatment was 7.069 (1.42) and 7.073 (1.52) points in the placebo group,

and these results were higher when compared with the literature [44, 50]. In general literature, THI is used in the evaluation of tinnitus before and after the treatment [16, 50, 94–96].

Detection of the frequency at which tinnitus is occurring is almost always difficult [93]. It has been determined that the frequency of tinnitus changes in 60% of cases according to the studies [97]. According to general opinion, tinnitus frequency is above 2000 Hz and mostly at 4000 Hz [86]. In Yilmaz et al.'s study [50], the mean (SD) frequency of tinnitus in the TMS group before the treatment was 7234 (2818) and 5626 (2494) Hz in the placebo group. The mean frequency of tinnitus of all patients before the treatment was 6450 Hz.

Good news is coming from recent studies on TMS application with repetitive low frequency in tinnitus treatment. TMS inhibits abnormal cortical activities in the affected area. Tinnitus treatment is applied to the auditory cortex. Positive results have been revealed during the studies [8, 9]. Animal models and functional human brain imaging studies, which were designed to investigate the pathophysiology of tinnitus, suggest that there is increased signals and activity in the central auditory pathways and also nonauditory brain areas [98].

Many studies suggested radiological findings were used to determine the coil positioning in order to increase efficacy. One suggested method is using positron emission tomography (PET) to determine the hyperactive auditory cortex [99]. Electroencephalography (EEG) also suggested resting state auditory gamma activity as a marker for tinnitus [100]. However, no association was demonstrated between tinnitus loudness and auditory gamma band. Also Langguth's study showed no superiority of EEG over PET, and this study could not demonstrate PET-guided coil positioning's superiority over standard-positioned coils [101]. Anatomical magnetic resonance imaging (MRI) is used as a guide in recent studies to position the coil to the primary auditory cortex [102–104]. Functional MRI activity could demonstrate tinnitus-matched sounds' effect on specific cortex areas, but evidence of this kind of navigation for tinnitus is not available [105]. Noh et al.'s recent study showed that there was no significant difference between EEG-guided or neuronavigation-guided coil placement [106].

Functional magnetic resonance imaging and F-18 fluorodeoxyglucose positron emission tomography have shown asymmetric metabolic activity in the hearing cortex of patients with unilateral or bilateral tinnitus [83]. Coactivation of prefrontal areas was detected in imaging studies. This may be related to the affective compacts of tinnitus [107–109]. Frontothalamic gating system may be formed by limbic and paralimbic structures for tinnitus [110]. James et al.'s study demonstrated with functional MRI that left superior dorsolateral prefrontal cortex had a greater role in predicting tinnitus awareness [111]. Combined prefrontal and temporal cortex rTMS was found to be more effective than temporal cortex rTMS alone [101, 112–114].

rTMS's antiapoptotic mechanism was demonstrated in Yoon et al.'s recent animal model [115]. Repeated stimulation induces neuroplastic changes. Single session effects seem to be short and immediate, and daily treatment over 4 weeks seem to have longer results that last over months to years [116–118].

Kleinjung et al. reported that, after rTMS application to the patients with chronic tinnitus, the mean score of tinnitus decreased at the rate of 7.5% [8]. De Ridder and colleagues found

positive results in half of the patients with rTMS in unilateral tinnitus treatment in 114 patients [9]. Kleinjung and colleagues found that application of low-frequency rTMS for 5 days had significant effects on tinnitus treatment [8]. In another study, 3 patients were treated with 1 Hz rTMS (2000 stimulus/day) for 5 days and 2 of the patients had a positive result [99]. In Langguth et al.'s study, 28 patients were treated with 1 Hz rTMS (2000 stimulus/day) for 10 days and 67.8% of the patients had a positive result [119]. Folmer et al.'s study demonstrated that 1 Hz rTMS for chronic tinnitus is an effective treatment method. The application of rTMS daily for 10 days had significantly better outcomes of chronic tinnitus patients [120].

In order to suppress tinnitus, various stimulation patterns have been reported as effective such as 1 Hz, 10 Hz, and burst stimulation [82, 103, 121–124].

A new TMS protocol was introduced by Huang et al. in 2008 [125]: the protocol named theta burst stimulation [TBS], which is a repeated application of triplets of 50 Hz pulses with 200 ms (5 Hz; theta) pulse interval [125]. Huang et al. suggested that this protocol is superior to tonic rTMS [125]. However, literature findings are controversial. De Riddler et al., Lorenz et al., and Poreiz et al. showed the efficacy of TBS but Chung et al.'s and Plewnia et al.'s studies did not find the same efficacy [103, 126–130]. Many studies showed low-frequency 1 Hz rTMS to be effective for tinnitus. Khedr et al. suggested that 10 or 20 Hz stimulation could also be effective [123]. James et al.'s study demonstrated that 1 Hz rTMS seemed to significantly decrease the awareness, loudness, and annoyance of tinnitus, but 10 Hz stimulus seemed to decrease only the awareness of tinnitus [111].

Kreuzer et al.'s study suggested that individualized rTMS sessions' outcomes were better, since tinnitus is a personal symptom and hard to generalize [131]. In Yilmaz et al.'s study, THI score decreased by 8 points after the application of low-frequency rTMS, and also a statistically significant decrease was observed in tinnitus loudness and subjective score after the application of rTMS [50]. Park et al. studied the difference between 6000 pulse and 12,000 pulse rTMS to temporal and prefrontal cortex. Patients who received 12,000 pulses of rTMS seemed to have better outcomes. This study seems to be the first in literature that underlines the importance of pulse rate, at least 12,000 pulses of rTMS seems to achieve a favorable outcome [132].

The chapter showed that low-frequency rTMS is useful in the treatment of chronic tinnitus.

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References

[1] Jastreboff PJ, Gray WC, Mattox DE. Tinnitus and hyperacusis. In: Cummings CW, Fredrickson JM, Harker LA, et al., editors. Otolaryngology Head and Neck Surgery. 3rd ed. St Louis: Mosby-Year Book; 1998. pp. 3198-3222

[2] Nondahl DM, Cruickshanks KJ, Wiley TL, et al. Prevalence and 5-year incidence of tinnitus among older adults: The epidemiology of hearing loss study. Journal of the American Academy of Audiology. 2002;**13**(6):323-331

[3] Cooper JC Jr. Health and nutrition examination survey of 1971-75: Part II. Tinnitus, subjective hearing loss, and well-being. Journal of the American Academy of Audiology. 1994;**5**(1):37-43

[4] Hoare DJ, Gander PE, Collins L, Smith S, Hall DA. Management of tinnitus in English NHS audiology departments: An evaluation of current practice. Journal of Evaluation in Clinical Practice. 2012;**18**:326-334

[5] Henry JA, Dennis KC, Schechter MA. General review of tinnitus: Prevalence, mechanisms, effects, and management. Journal of Speech, Language, and Hearing Research. 2005;**48**:1204-1235

[6] Kim KS. Occupational hearing loss in Korea. Journal of Korean Medical Science. 2010;**25**: S62-S69

[7] Steinmetz LG, Zeigelboim BS, Lacerda AB, Morata TC, Marques JM. Evaluating tinnitus in industrial hearing loss prevention programs. The International Tinnitus Journal. 2008; **14**:152-158

[8] Kleinjung T, Eichhammer P, Langguth B, et al. Long-term effects of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic tinnitus. Otolaryngology and Head and Neck Surgery. 2005;**132**:566-569

[9] De Ridder D, Verstraeten E, Van der Kelen K, et al. Transcranial magnetic stimulation for tinnitus: Influence of tinnitus durationon stimulation parameter choice and maximal tinnitussuppression. Otology & Neurotology. 2005;**26**:616-619

[10] Çakır Ö. "Tinnitus Tedavisinde Çinko Kullanımı" Ankara Numune Hastanesi 1. Kulak Burun Boğaz Baş Boyun Cerrahisi Kliniği. Ankara: Uzmanlık Tezi; 2001

[11] Jerger J. Clinical experience with impedance audiometry. Archives of Otolaryngology. 1970;**92**:311-324

[12] Mitchhell SM, Michael JC. Subspecialty clinics: Otorhinolaryngology, tinnitus. Mayo Clinic Proceedings. 1991;**66**:614-620

[13] Jastreboff PJ, Hazell WP. A neurophysiological approach to tinnitus: Clinical implications. British Journal of Audiology. 1993;**27**:7-17

[14] Akyıldız N. Tinnitus, Kulak hastalıkları ve mikrocerrahisi II. Ankara: Bilimsel tıp yayınevi; 2002. pp. 67-81

[15] Ridder DD, Mulder GD. Primary and secondary auditory cortex stimulation for intractable tinnitus. ORL. 2006;**68**:48-55

[16] Moller AR. Pathophysiology of tinnitus. Otolaryngologic Clinics of North America. 2003; **36**:349-266

[17] Celik O. Tinnitus, Kulak burun boğaz hastalıkları ve baş boyun cerrahisi, Turgut yayıncılık, Đstanbul, Ozluoğlu L. Ataş A. 2002;**1**(5):88-98

[18] Tonndorf J. Acute cochlear disorders; the combination of hearing loss, recruitment, poor speech discrimination, and tinnitus. The Annals of Otology, Rhinology, and Laryngology. 1980;**89**:353-358

[19] Melzack R, Wall PD. Pain mechanisms: A new theory. Science. 1965;**150**:971-979

[20] Tonndorf J. The analogy between tinnitus and pain: A suggestion for a physiological basis of chronic tinnitus. Hearing Research. 1987;**28**(2–3):271-275

[21] Salvi RJ, Ahroon WA. Tinnitus and neural activity. Journal of Speech and Hearing Research. 1983;**26**:629-632

[22] Perucca E, Jackson P. A controlled study of the suppression of tinnitus by lidocaine infusion (relationship of therapeutic effect with serum lidocaine levels). The Journal of Laryngology and Otology. 1985;**99**:657-661

[23] Eggermont JJ. Tinnitus: Some thought about its origin. The Journal of Laryngology and Otology. Supplement. 1984;**9**:31

[24] Charles WC. Otolaringoloji Bas Ve Boyun Cerrahisi Cilt 4, Koc C (Cev), 4. Đstanbul, Gunes Tıp Kitapevi: Basım; 2007

[25] Shulman A, Seitz MR. Central tinnitus diagnosis and treatment. Laryngoscope. 1981;**91**: 2025-2034

[26] Tunkel DE, Bauer CA, Sun GH, Rosenfeld RM, Chandrasekhar SS, Cunningham ER Jr, et al. Clinical practice guideline: Tinnitus. Otolaryngology and Head and Neck Surgery. Oct 2014;**151**(2 Suppl):S1-S40

[27] Evered D, Lawrenson G. Tinnitus. Ciba Foundation Symposium; 85, Summit, NJ. Ciba Pharmaceutical Co. Medical Education Administration. viii; 1981. p. 325

[28] Sindhusake D, Golding M, Newall P, et al. Risk factors for tinnitus in a population of older adults: The blue mountains hearing study. Ear and Hearing. 2003;**24**(6):501-507

[29] Eggermont JJ. Central tinnitus. Auris Nasus Larynx. 2003;**30**(suppl):7-12

[30] Chung JH, Des Roches CM, Meunier J, et al. Evaluation of noise-induced hearing loss in young people using a web-based survey technique. Pediatrics. 2005;**115**(4):861-867

[31] Axelsson A, Sandh A. Tinnitus in noise-induced hearing loss. British Journal of Audiology. 1985;**19**(4):271-276

[32] Chole RA, Parker WS. Tinnitus and vertigo in patients with temporomandibular disorder. Archives of Otolaryngology—Head & Neck Surgery. 1992;**118**(8):817-821

[33] Flint Paul W. Cummings Otolaryngology—Head & Neck Surgery. 6th ed. Philadelphia, PA: Elsevier/Saunders; 2015. pp. 2336-2345

[34] House JW. Tinnitus: Evaluation and treatment. The American Journal of Otology. 1984;**5**: 1472-1475

[35] Basut O, Ozdilek T, Coşkun H, et al. The incidence of hyperinsulinemia in patients with tinnitus and the effect of a diabetic diet on tinnitus [Turkish]. Kulak Burun Boğaz Ihtisas Dergisi. 2003;**10**:183-187

[36] Shulman A. Tinnitus medical evaluation. Otolaryngologic Clinics of North America. 1991;**36**:239-292

[37] Cenik Z, Gul O. Tinnitus etyolojisi. S.U. Tıp Fakultesi Dergisi. 1989;**5**(4):4-10

[38] Luxon LM. Tinnitus: Its causes, diagnosis and treatment. BMJ. 1993;**306**:1490-1491

[39] Meyerhoff WL, Cooper JC. Tinnitus. In: Paperalla M, Shumrick DA, Gluckman JL, Meyerhoff W, editors. Otolaryngology, Vol. 2, 3rd ed. W.B. Saunders Comp, Philadelphia; 1991. pp. 1169-1179

[40] House JW. Therapies for tinnitus. The American Journal of Otology. 1989;**10**(3):163-165

[41] Mattox DE, Richtsmeier WJ. Tinnitus—The initial evaluation. Otolaryngology and Head and Neck Surgery. 1987;**96**:172-174

[42] Coles RRA, Baskill JL, Sheldrake JB. Measurement and management of tinnitus, part I measurement. The Journal of Laryngology and Otology. December 1984;**98**:1171-1176

[43] Weissman JL, Hirsch BE. Imaging of tinnitus: A review. Radiology. 2000;**216**:342-349

[44] Goodwin PE, Johnson RM. The loudness of tinnitus. Acta OtoLaryngologica. 1980;**90**(5-6):353

[45] Tyler RS, Conrad-Armes D. Spontaneous acoustic Cochlear emissions and sensorineuraltinnitus. British Journal of Audiology. 1982;**16**:193

[46] Penner MJ, Burns EM. The dissociation of SOAEs and tinnitus. Journal of Speech and Hearing Research. 1987;**30**:396-403

[47] Penner MJ. Linking spontaneous otoacoustic emissions and tinnitus. British Journal of Audiology. 1992;**26**:115-123

[48] Shiomi Y, Tsuji J, Naito Y. Characteristics of DPOAE audiogram in tinnitus patients. Hearing Research. 1997;**108**:83-88

[49] Barnea G, Attias J, Gold S, Shahar A. Tinnitus with normal hearing sensitivity: Extended high frequency audiometry and auditory-nerve brain stem-evoked response. Audiology. 1990;**29**:36-45

[50] Yilmaz M, Yener MH, Turgut NF, Aydin F, Altug T. Effectiveness of transcranial magnetic stimulation application in treatment of tinnitus. The Journal of Craniofacial Surgery. Jul 1984;**25**(4):1315-1318

[51] Andersson G, Lyttkens L. A meta-analytic review of psychological treatments for tinnitus. British Journal of Audiology. 1999;**33**:201-210

[52] Park J, White AR, Ernst E. Efficacy of acupuncture as a treatment for tinnitus: A systematic review. Archives of Otolaryngology—Head & Neck Surgery. Apr 2000;**126**(4):489-492

[53] Witt CM, Pach D, Brinkhaus B, et al. Safety of acupuncture: Results of a prospective observational study with 229,230 patients and introduction of a medical information and consent form. Forschende Komplementärmedizin. 2009;**16**:91-97

[54] Endres HG, Molsberger A, Lungenhausen M, Trampisch HJ. An internal standard for verifying the accuracy of serious adverse event reporting: The example of an acupuncture study of 190,924 patients. European Journal of Medical Research. 2004;**9**:545-551

[55] Macpherson H, Scullion A, Thomas KJ, Walters S. Patient reports of adverse events associated with acupuncture treatment: A prospective national survey. Quality & Safety in Health Care. 2004;**13**:349-355

[56] Melchart D, Weidenhammer W, Streng A, et al. Prospective investigation of adverse effects of acupuncture in 97 733 patients. Archives of Internal Medicine. 2004;**164**:104-105

[57] White A, Hayhoe S, Hart A, Ernst E. Survey of adverse events following acupuncture (SAFA): A prospective study of 32,000 consultations. Acupuncture in Medicine. 2001;**19**:84-92

[58] Norheim AJ. Adverse effects of acupuncture: A study of the literature for the years 1981–1994. Journal of Alternative and Complementary Medicine. 1996;**2**:291-297

[59] Wagner T, Gangitano M, Romero R, et al. Intracranial measurement of current densities induced by transcranial magnetic stimulation in the human brain. Neuroscience Letters. 2004;**354**(2):91-94

[60] Bestmann S, Ruff CC, Blakemore C, et al. Spatial attention changes excitability of human visual cortex to direct stimulation. Current Biology. 2007;**17**(2):134-139

[61] Costa J, Valls-Sole J, Valledeoriola F, Rumia J, Tolosa E. Motor responses of muscles supplied by cranial nerves to subthalmic nucleus deep brain stimuli. Brain. 2007;**130**: 245-255

[62] Molnar GF, Sailer A, Gunraj CA, et al. Changes in cortical excitability with thalamic deep brain stimulation. Neurology. 2005;**64**:1913-1919

[63] Tazoe T, Endoh T, Nakajima T, Sakmoto M, Komiyama T. Disinhibition of upper limb motor area by voluntary contraction of the lower limb muscle. Experimental Brain Research. 2007;**177**:419-430

[64] Muray NMF. Motor evoked potentials. In: Aminoff MJ, editor. Electrodiagnosis in Clinical Neurology. USA: Churchill Livingstone; 1992. pp. 605-626

[65] Barker AT, Jalinous II. Non-invasive magnetic stimulation of human motor cortex. The Lancet. May 1985;**11**:1106-1107

[66] Gürelik M, Karadağ Ö, Polat S, Özüm Ü, Aslan A, et al. The effect of the electrical stimulation of the nasal mucosa on cortical cerebral blood flow in rabbits. Neuroscience Letters. 2004;**365**:210-213

[67] Legatt AD, Ellen R. Grass lecture: Motor evoked potential monitoring. American Journal of Electroneurodiagnostic Technology. 2004;**44**:223-243

[68] Taylor JL, Gandevia SC. Noninvasive stimulation of the human corticospinal tract. Journal of Applied Physiology. 2004;**96**:1496-1503

[69] Chen R, Cohen LG, Hallett M. Role of the ipsilateral motor cortex in voluntary movement. The Canadian Journal of Neurological Sciences. 1997;**24**(4):284-291

[70] Pascual-Leone A, Valls-Solé J, Wassermann EM, et al. Responses to rapid-rate transcranial magnetic stimulation of the humanmotor cortex. Brain. 1994;**117**(Pt 4):847-858

[71] Epstein CM, Schwartzberg DG, Davey KR, Sudderth DB. Localizing the site of magnetic brain stimulation in humans. Neurology. 1990;**40**:666-670

[72] Geddes LA. Optimal stimulus duration for extracranial cortical stimulation. Neurosurgery. 1987;**20**:94-99

[73] Cohen LG, Roth BJ, Nilsson J, Dang N, et al. Effects of coil design on delivery of focal magnetic stimulation. Technical considerations. Electroencephalography and Clinical Neurophysiology. 1990;**75**:350-357

[74] Maeda F, Pascual-Leone A. Transcranial magnetic stimulation: Studying motor neurophysiology of psychiatric disorders. Psychopharmacology. 2003;**168**:359-376

[75] George MS, Nahas Z, Molloy M. A controlled trial of daily left prefrontal cortex TMS for treating depression. Biological Psychiatry. 2000;**48**:962-970

[76] Pennisi G, Rapisarda G, Bella R, Calabrese V, et al. Absence of response to early transcranial magnetic stimulation in ischemic stroke patients: Prognostic value for hand motor recovery. Stroke. Dec 1999;**30**(12):2666-2670

[77] Trompetto C, Assini A, Buccolieri A, Marchese R, Abbruzzese G. Motor recovery following stroke: A transcranial magnetic stimulation study. Clinical Neurophysiology. Oct 2000;**111**(10):1860-1867

[78] Escudero JV, Sancho J, Bautista D, Escudero M, López-Trigo J. Prognostic value of motor evoked potential obtained by transcranial magnetic brain stimulation in motor function recovery in patients with acute ischemic stroke. Stroke. Sep 1998;**29**(9):1854-1859

[79] Feydy A, Carlier R, Roby-Brami A, Bussel B, Cazalis F, et al. Longitudinal study of motor recovery after stroke: Recruitment and focusing of brain activation. Stroke. 2002; **33**(6):1610-1617

[80] Eisen A. Cortical and peripheral nerve magnetic stimulation. Journal of Clinical Neurophysiology. 1992;**3**:65-80

[81] Barker AT, Berardelli A, Caramia MD, Caruso G, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: Basic principles and procedures for routine clinical application. Report of an IFCN committee. Electroencephalography and Clinical Neurophysiology. Aug 1994;**91**(2):79-92

[82] Plewnia C, Bartels M, Gerloff C. Transient suppression of tinnitus by transcranial magnetic stimulation. Annals of Neurology. 2003;**53**:263Y6

[83] Arnold W, Bartenstein P, Oestreicher E, et al. Focal metabolic activation in the predominant left auditory cortex in patients suffering from tinnitus: A PET study with [18F] deoxyglucose. ORL: Journal for Otorhinolaryngology and its Related Specialties. 1996; **58**:195-199

[84] Langguth B, Eichhammer P, Wiegand R, et al. Neuronavigated rTMS in a patient with chronic tinnitus. Effects of 4 weeks treatment. Neuroreport. 2003;**14**:977-980

[85] Chen R, Classen J, Gerloff C, et al. Depression of motor cortex excitability by low frequency transcranial magnetic stimulation. Neurology. 1997;**48**:1398-1403

[86] Yilmaz Đ, Akkuzu B, Cakmak O, et al. Misoprostol in the treatment of tinnitus: A double-blind study. Otolaryngology and Head and Neck Surgery. 2004;**130**:604-610

[87] Cekkayan S, Ozluoğlu L, Yoloğlu S, et al. Tinnituslu hastalarda beta-histin ve ginkgo biloba ekstresinin etkinliğinin karsilastirilmasi. KBB ve BBC Dergisi. 1996;**4**:19-22

[88] Hazell J. Tinnitus and disability with ageing: Adaptation and management. Acta Oto-Laryngologica. 1991;**476**:202-208

[89] Sadlier M, Stephens SD. An approach to the audit of tinnitus management. The Journal of Laryngology and Otology. 1995;**109**:826-829

[90] Salomon G. Hearing problems in the elderly: Qualitative aspects of hearing problems and influence of tinnitus on hearing. Danish Medical Bulletin Supplement. 1986;**33**:14-15

[91] Axelsson A, Ringdahl A. Tinnitus: A study of its prevalence and characteristics. British Journal of Audiology. 1989;**23**:53-62

[92] Chung DY, Gannon RP, Mason K. Factors affecting the prevalence of tinnitus. Audiology. 1984;**23**:441-452

[93] Goldstein B, Shulman A. Tinnitus evaluation. In: Vernon JA, Moller AR, editors. Tinnitus Diagnosis and Treatment. Philadelphia: Lea and Febiger, 1991. pp. 293-318

[94] American Tinnitus Association. Tinnitus Patient Survey: Information from the American Tinnitus Association. Portland, OR: ATA; 1986

[95] Newman CW, Sandridge SA, Jacobson GB. Psychometric adequacy of the tinnitus handicap inventory (THI) for evaluating treatment outcome. Journal of the American Academy of Audiology. 1998;**9**:153-160

[96] Hazell JWP, Jastreboff PJ, Meerton LE, et al. Electrical tinnitus suppression: Frequency dependence of effect. Audiology. 1993;**32**:68-77

[97] Lenarz T, Schreiner C, Snyder RL, et al. Neural mechanisms of tinnitus. European Archives of Oto-Rhino-Laryngology. 1993;**249**:441-446

[98] Eggermont JJ. Correlated neural activity as the driving force for functional changes in auditory cortex. Hearing Research. 2007;**229**(1-2):69-80

[99] Eichhammer P, Langguth B, Marienhagen J, et al. Neuronavigated repetitive transcranial magnetic stimulation in patients with tinnitus: A short case series. Biological Psychiatry. 2003;**54**:862-865

[100] Müller N, Lorenz I, Langguth B, Weisz N. rTMS induced tinnitus relief is related to an increase in auditory cortical alpha activity. PLoS One. 2013;**8**(2):e55557

[101] Langguth B, Landgrebe M, Frank E, et al. Efficacy of different protocols of transcranial magnetic stimulation for the treatment of tinnitus: Pooled analysis of two randomized controlled studies. World Journal of Biological Psychiatry. 2014;**15**:276Y85

[102] Barwood CH, Wilson WJ, Malicka AN, et al. The effect of rTMS on auditory processing in adults with chronic, bilateral tinnitus: A placebo-controlled pilot study. Brain Stimulation. Sep 2013;**6**(5):752-759

[103] Chung HK, Tsai CH, Lin YC, et al. Effectiveness of theta-burst repetitive transcranial magnetic stimulation for treating chronic tinnitus. Audiology and Neurotology. 2012;**17**: 112Y20

[104] Lefaucheur JP, Brugières P, Guimont F, Iglesias S, Franco-Rodrigues A, et al. Navigated rTMS for the treatment of tinnitus: A pilot study with assessment by fMRI and AEPs. Neurophysiologie Clinique. Apr 2012;**42**(3):95-109

[105] De Ridder D, Vanneste S, Kovacs S, Sunaert S, Menovsky T, et al. Transcranial magnetic stimulation and extradural electrodes implanter on secondary auditory cortex for tinnitus suppression. Journal of Neurosurgery. Apr 2011;**114**(4):903-911

[106] Noh TS, Rah YC, Kyong JS, Kim JS, Park MK, et al. Comparison of treatment outcomes between 10 and 20 EEG electrode location system-guided and neuronavigation-guided repetitive transcranial magnetic stimulation in chronic tinnitus patients and target localization in the Asian brain. Acta Oto-Laryngologica. Sep 2017;**137**(9):945-951

[107] Langguth B, Landgrebe M, Kleinjung T, Sand GP, Hajak G. Tinnitus and depression. The World Journal of Biological Psychiatry. 2011;**12**(7):489-500. DOI: 10.3109/1562 2975.2011.575178

[108] De Ridder D, Elgoyhen AB, Romo R, Langguth B. Phantom percepts: Tinnitus and pain as persisting aversive memory networks. Proceedings of the National Academy of Sciences of the United States of America. 2011;**108**:8075-8080. DOI: 10.1073/pnas.1018466108

[109] Vanneste S, Plazier M, Der Loo E, De Heyning PV, et al. The neural correlates of tinnitus-related distress. NeuroImage. 2010;**52**:470-480. DOI: 10.1016/j.neuroimage.2010.04.029 24.

[110] Rauschecker JP, Leaver AM, Muhlau M. Tuning out the noise: Limbic-auditory interactions in tinnitus. Neuron. 2010;**66**:819-826. DOI: 10.1016/ j.neuron.2010.04.032

[111] James GA, Thostenson JD, Brown G, Carter G, Hayes H, et al. Neural activity during attentional conflict predicts reduction in tinnitus perception following rTMS. Brain Stimulation. 2017;**10**(5):934-943

[112] Kleinjung T, Eichhammer P, Landgrebe M, et al. Combined temporal and prefrontal transcranial magnetic stimulation for tinnitus treatment: A pilot study. Otolaryngology–Head and Neck Surgery. 2008;**138**:497Y501

[113] Vanneste S, De Ridder D. The involvement of the left ventrolateral prefrontal cortex in tinnitus: a TMS study. Experimental Brain Research. 2012;**221**:345Y50

[114] Lehner A, Schecklmann M, Poeppl TB, et al. Multisite rTMS for the treatment of chronic tinnitus: Stimulation of the cortical tinnitus networkVa pilot study. Brain Topography. 2013;**26**:501Y10

[115] Yoon KJ, Lee YT, Han TR. Mechanism of functional recovery after repetitive transcranial magnetic stimulation (rTMS) in the subacute cerebral ischemic rat model: Neural plasticity or anti-apoptosis? Experimental Brain Research. Oct 2011;**214**(4):549-556

[116] Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. Noninvasive brain stimulation: From physiology to network dynamics and back. Nature Neuroscience. Jul 2013;**16**(7): 838-844

[117] Thut G, Pascual-Leone A. A review of combined TMS-EEG studies to characterize lasting effects of repetitive TMS and assess their usefulness in cognitive and clinical neuroscience. Brain Topography. Jan 2010;**22**(4):219-232

[118] Wassermann EM, Zimmermann T. Transcranial magnetic brain stimulation: Therapeutic promises and scientific gaps. Pharmacology & Therapeutics. Jan 2012;**133**(1):98-107

[119] Langguth B, Zowe M, Landgrebe M, et al. Transcranial magnetic stimulation for the 11 treatment of tinnitus: A new coil positioning method and first results. Brain Topography. 2006;**18**:241-247

[120] Folmer RL, Theodoroff SM, Casiana L, Shi Y, et al. Repetitive transcranial magnetic stimulation treatment for chronic tinnitus: A randomized clinical trial. JAMA Otolaryngology. Head & Neck Surgery. Aug 2015;**141**(8):716-722

[121] Khedr EM, Rothwell JC, El-Atar A. One-year follow up of patients with chronic tinnitus treated with left temporoparietal rTMS. European Journal of Neurology. 2009;**16**:404Y8

[122] Rossi S, De Capua A, Ulivelli M, et al. Effects of repetitive transcranial magnetic stimulation on chronic tinnitus: A randomised, crossover, double blind, placebo controlled study. Journal of Neurology, Neurosurgery, and Psychiatry. 2007;**78**:857Y63

[123] Khedr EM, Rothwell JC, Ahmed MA, El-Atar A. Effect of daily repetitive transcranial magnetic stimulation for treatment of tinnitus: Comparison of different stimulus frequencies. Journal of Neurology, Neurosurgery, and Psychiatry. 2008;**79**:212Y5

[124] Vanneste S, Plazier M, van der Loo E, Ost J, et al. Burst transcranial magnetic stimulation: Which tinnitus characteristics influence the amount of transient tinnitus suppression? European Journal of Neurology. 2010;**17**:1141Y7

[125] Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron. 2005;**45**(2):201-206

[126] De Ridder D, van der Loo E, Van der Kelen K, Menovsky T, et al. Theta, alpha and beta burst transcranial magnetic stimulation: Brain modulation in tinnitus. International Journal of Medical Sciences. 2007 Oct 9;**4**(5):237-241

[127] Lorenz I, Muller N, Schlee W, Langguth B, Weisz N. Short-term effects of single repetitive TMS sessions on auditory evoked activity in patients with chronic tinnitus. Journal of Neurophysiology. 2010;**104**(3):1497-1505

[128] Poreisz C, Paulus W, Moser T, Lang N. Does a single session of theta-burst transcranial magnetic stimulation of inferior temporal cortex affect tinnitus perception? BMC Neuroscience. 2009 May 29;**10**:54

[129] Plewnia C, Vonthein R, Wasserka B, Arfeller C, et al. Treatment of chronic tinnitus with θ burst stimulation: A randomized controlled trial. Neurology. 2012 May 22;**78**(21):1628-1634

[130] Schecklmann M, Giani A, Tupak S, Langguth B, Raab V, et al. Neuronavigated left temporal continuous theta burst stimulation in chronic tinnitus. Restorative Neurology and Neuroscience. 2016;**34**(2):165-175

[131] Kreuzer PM, Poeppl TB, Rupprecht R, Vielsmeier V, et al. Individualized repetitive transcranial magnetic stimulation treatment in chronic tinnitus? Frontiers in Neurology. 2017 Apr 6;**8**:126

[132] Park JH, Noh TS, Lee JH, et al. Difference in tinnitus treatment outcome according to the pulse number of repetitive transcranial magnetic stimulation. Otology & Neurotology. Sep 2015;**36**(8):1450-1456

Chapter 6

TMS for OCD

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73594

Abstract

Introduction: Obsessive compulsive disorder (OCD) is a common disabling condition, which greater than 40% of patients do not respond to the available treatment options. Imbalances in the cortical-striatal-thalamic-cortical circuits have proven to be useful psychosurgical treatment targets making this circuit disorder an optimal target for intervention with TMS.

Methods: PubMed and clinicaltrials.gov were reviewed for sham-controlled therapeutic rTMS studies for OCD.

Results: Eighteen relevant studies are presented in a narrative fashion along with relevant methodological details, and distinctions.

Conclusions: High and low frequency stimulation to lateral prefrontal cortices does not appear to have consistent efficacy in the small studies done to date. Several small studies with non-blinded operators suggest that low frequency high intensity rTMS to the supplementary motor area with a figure-8 coil reduces OCD symptoms. A fully blinded multicenter center study is warranted to confirm this finding. A promising pilot study and a subsequent multicenter study of high frequency high intensity deep rTMS with the HAC/H7 coil to the bilateral prefrontal orbitofrontal and anterior cingulate cortices were completed with positive results. Many areas of uncertainty remain, such as the optimal state of the circuitry during stimulation and identifying a priori biomarkers for responders and non-responders to specific protocols.

Keywords: rTMS, dTMS, TMS, OCD, ACC, SMA, OFC, obsessive compulsive disorder

1. Introduction

The DSM 5 criteria for obsessive compulsive disorder (OCD) are specific. Patients can have either obsessions, compulsions or both. Obsessions are defined as unwanted thoughts, images or urges. Compulsions are repetitive behaviors or mental acts that are done in response to an obsession or a rigid rule with the aim of reducing anxiety. However, the extent of the compulsion

is either unrealistic or excessive. Obsessions and/or compulsions must take up at least 1 h a day, and though it may relieve their anxiety, it should not be pleasurable to the patient. In addition to the time component, the obsessions-compulsions should cause significant impairment in social or occupational functioning. The OCD symptoms should not be due to a substance or another disorder. Specifiers for OCD in the DSM 5 include the degree of insight (good, fair, poor, absent, delusional beliefs) and tic related [1].

2. Epidemiology

The 12-month prevalence of OCD in the United States is 1.2%, with similar prevalence internationally (1.1–1.8%). Females are affected at a slightly higher rate than males in adulthood; although males are more commonly affected in childhood. The mean age at onset of OCD is 19.5 years and 25% of cases start by 14 years old. Onset after 35 years is unusual but does occur. Males have an earlier age of onset than females; nearly 25% of males have onset before the age of 10. The onset of symptoms is typically gradual; however, acute onset has also been reported [1].

If OCD is untreated, the course is usually chronic, often with waxing and waning symptoms. Some have an episodic course and a minority has a deteriorating course. Without treatment, remission rates in adults are low (i.e. 20%). Onset in childhood or adolescence can lead to a lifetime of OCD. However, 40% of individuals with childhood or adolescent onset of OCD may experience remission by early adulthood. The course of OCD is often complicated by the co-occurrence of other disorders. Compulsions are more easily diagnosed in children than obsessions, because compulsions are observable. However, most children have both [1].

2.1. Prognostic factors

Greater internalizing symptoms, higher negative emotionality, and behavioral inhibition in childhood are possible temperamental risk factors. Physical and sexual abuse in childhood and other stressful or traumatic events have been associated with an increased risk for developing OCD. Some children develop the sudden onset of OCD symptoms after streptococcal infection, and subsequently it is not distinguishable from OCD for the duration of their lives. In others, it has more motor symptoms and is amenable to antibiotic treatment if it is treated immediately.

2.2. Comorbidities

Most OCD patients (76%) have a lifetime history of another anxiety disorder. Specifically, 63% have lifetime history of mood disorder, 41% have major depressive disorder, 23–32% has comorbid obsessive-compulsive personality disorder, 29% have lifetime history of tic disorder, and 12% have schizophrenia. Additional common diagnoses include bipolar, anorexia, bulimia and Tourette's [1].

2.3. Heritability

OCD may be the most heritable psychiatric condition, with a monozygotic twin concordance rate of 0.52 and a dizygotic concordance rate of 0.21, with overall heritability for OCD estimated

http://dx.doi.org/10.5772/intechopen.73594

to be 48% [2]. The overall recurrence rate (another first degree family member getting OCD) is about 50%, which is higher with Tourette's and tics as well as childhood onset. It is lower with pure OCD of adult onset [3].

3. Current available treatment options for OCD

At the present time, exposure and response prevention should probably be the first line treatment for non-comorbid OCD. Pharmacologic interventions with significant evidence for efficacy, specifically with 8–12 weeks of medication results with greater than 30% improvement for 40–60% of OCD patients include several selective serotonin reuptake inhibitors: Fluoxetine, Paroxetine, Fluvoxamine and Sertraline in the USA; Citalopram and Escitalopram in Europe; and the tricyclic, Clomipramine.

Neurosurgery has shown promising outcomes where 58–67% of patients showed marked improvement in numerous studies even for patients who have refractory OCD (failed three medications and had 6 months of exposure and response prevention). The primary ablation anatomical targets are the fiber tracts that connect the cortex to thalamic nuclei, the anterior limb of the internal capsule and the cingulate gyrus. Nevertheless, neurosurgical procedures also yield reports of transient and persistent adverse effects [4].

Deep brain stimulation (DBS) has several advantages over ablation. Surgeons using DBS can potentially achieve a clinical effect without producing an irreversible lesion. The efficacy of ablative lesions appears to be similar to DBS.

4. Why do we need TMS for OCD?

Over 1% of the population has no improvement from current approved treatments. Even the 1% that benefits from current approved treatments is actually still quite affected by their OCD. We use improvement criteria in OCD trials rather than response and remission, similar to schizophrenia. Schizophrenia affects 1% of the population, and there are over 20 antipsychotics available in most countries. OCD affects 2.3% of the population, and there are only 5 approved medications.

5. OCD as a circuit disorder

Several inclusive models have been suggested to explain the neurobiology of OCD. One is an executive dysfunction model, where there are deficits in impulse control and inhibition of behaviors. Another is a modulatory control model, where the main dysfunction is in regulating socially appropriate behaviors. A recent model proposes OCD as an uncertainty disorder where there is an imbalance between input and input suppression [5]. Regardless of the model, there is abnormal activity in a region of the cortical-striatal-thalamic-cortical circuits. These are multiple parallel interconnected loops between cortical and subcortical areas whose role is to screen out which actions are selected and which are considered maladaptive and

ignored. These regions include the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), cingulate cortex, caudate nucleus, striatum and thalamus. An abnormality in the functioning of this pathway results in impulsivity, compulsivity, obsessivity, uncertainty, deficits in attentional allocation, sensory-motor gating, modulation of motor activity and more [6, 7].

The greatest evidence for OCD as a circuit disorder comes from the success of circuit interventions at various locations along the pathway. Specifically, circuit interventions have demonstrated efficacy at the striatum, globus pallidus interna, substantia nigra, thalamus, subthalamic nucleus, anterior cingulate cortex (ACC), OFC and anterior capsulotomy [5].

6. TMS systems for OCD

6.1. Coil types

Transcranial magnetic stimulation (TMS) uses magnetic pulses to induce electrical current in the underlying neuronal tissue. There are a variety of different TMS coils on the market, and they differ primarily with the orientation and flexibility of the wire windings in the coil. Several types of coils have been used in sham-controlled OCD studies. The first is a rigid circular coil. These are typically large and very non-focal as the induced current is identical in intensity anywhere under the wire. The orientation of the current in relation to the neurons is important. The coil can be reoriented 180° to switch the direction of the current under one side of the coil, but the other side of the coil will still have an effect. The second is a figure-8 or butterfly shaped coil. This is a rigid coil, usually in a 180° plane, which induces the strongest current beneath the center of the two circular coils. However, the field decays relatively rapidly. The manufacturer for most of the research figure-8 systems is Magstim, but Magventure (formerly Medtronic) makes a double-blind figure-8 system as well. Approximately 20 companies make active figure-8 coils. An option not yet used is a bent or double cone coil, which is also a rigid coil, but it is larger and bent at a 120° fixed angle. It is capable of reaching a greater depth than a figure-8 coil. To date, it has never been used in an OCD clinical trial, but it is made by many companies similarly to the figure-8 coil. The newest coil on the market is the H7 or HAC-coil. It has flexible windings that run along the skull and sum at depth, and these windings are tightened to the head. It can reach 3 cm beneath the cortex at high frequency and high intensity; additionally, the magnetic field decays slowly. The H-coil has gaps between the central groups, which make the field different from the fixed denser distribution of the bent or double cone coil. The H7/HAC coil had the largest and only multicenter sham-controlled OCD study to date.

6.2. Cooling systems

When TMS is done repetitively (rTMS), especially at high frequencies for long periods of time, the coils will heat up. To prevent this from occurring, the coils are cooled using one of three methods; fan cooled with room temperature air (Magstim), liquid cooled (Magventure or Mag and More), or fan cooled with a forced cooled air system (Brainsway). The figure-8 coil and bent coil are available liquid cooled or fan cooled. The H-coil uses a forced air conditioning system.

6.3. Blinding system

Clinical trials with TMS ideally should include blinding for the patient, rater and operator. However, in order for the operator of the TMS device to be blinded a unique research TMS system is required. Because of this many TMS studies do not have a blinded TMS operator and the sham arm has the operator rotate the coil 90° against the scalp delivering cutaneous stimulation with the identical sound. Magventure manufactures a double-blind coil, which is in one device; then, the computer tells the operator which side of the coil to use for the patient. Magstim has separate active and sham coils. When conducting a clinical trial, one can use coil A or coil B, as well as a third coil to determine the motor threshold. Both the Magstim and Magventure, require a cutaneous nerve stimulator to induce a superficial sensation during the sham train. Some single-blind studies do not even create a cutaneous sensation at all. Brainsway has the most practical approach, since the H-coil is in a helmet both the active and sham coil is in the same helmet. The subject is assigned a card that interacts with the stimulator and coil through an interface module. The motor threshold is determined with an operator card; then the coil is advanced to the treatment position, and the subject card is inserted, which selects whether the sham or active coil is activated. The sham coil is made of conical windings that do not penetrate the cortex; so, the identical sound and a superficial sensation are felt, but no neuronal stimulation is induced.

7. Detailed review of sham-controlled trials using TMS for treatment refractory OCD

In the following paragraphs, the sham-controlled or multi-arm therapeutic studies of TMS for OCD are described in detail. For an overview, please see **Table 1**.

In 2001, Pino Alonso published a sham-controlled TMS study whereby 18 OCD patients were administered active (N = 10) or sham (N = 8) rTMS for 18 sessions (3 times a week for 6 weeks). Active and sham treatments were administered using low frequency rTMS (1 Hz, 1200 pulses) to the right prefrontal cortex (PFC) using a 70 mm circular coil. The active group was administered 110% of the left hand resting motor threshold (MT) and the sham group was administered 20%MT. Raters and patients were blinded, and operators were unaware of the expected effects of the prescribed intensity. Neither the sham nor active treatment groups had significant reduction in their OCD symptoms following 18 sessions of low frequency rTMS over the right PFC with a circular coil for 6 weeks [8].

Sachdev et al. randomly designated 12 treatment-resistant OCD subjects to right (n = 6) or left (n = 6) prefrontal rTMS treatment groups. Both groups were administered a figure-8 coil for 10 treatments over 2 weeks at 10 Hz for 1500 pulses at 110% MT. An independent rater evaluated progress once a weekly during treatment then at the 1 month follow up. In both groups, there was a significant improvement after 2 weeks and at the 1 month follow up in the obsessions, compulsions, and total scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS). There was not a significant difference between left and right-sided high frequency rTMS [9].

Study	Device	Location	Protocol	Sample size	Blinding			Outcome
					Patient	Operator	Rater	
Alonso [8]	Magstim circular	Right PFC	1 Hz, 1200P, 110%MT	10	+		+	No significant reduction in OCD
			Sham: 20%MT	8				
Sachdev [9]	Magstim figure 8	Right PFC	10 Hz, 1500P, 110%MT	6	- (ignorant to significance of laterality)	—	+	No significant difference between right and left high frequency. Both left and right groups had significant OCD improvement
		Left PFC	10 Hz, 1500P, 110%MT	6				
Prasko [10]		Left DLPFC	1 Hz, 110%MT	15				Active did not have any greater benefit than sham
			Sham	15				
Sachdev [11]	Magstim figure 8	Left DLPFC	10 Hz, 1500P, 110%MT	10	+	—	+	No significant difference between active and sham after 10 sessions. There was a significant difference after 20 treatments
			Sham	8				
Ruffini [12]	Magstim figure 8	Left OFC	1 Hz, 600P, 80%MT	16	+	—		There was a significant difference between active and sham, which lasted 10 weeks after TMS ended
			Sham: (coil perpendicular to scalp)	7				
Mantovani [13]	Magstim figure 8	Pre-SMA	1 Hz, 1200P, 100%MT	9	+	—	+	The active TMS group had 25% reduction in YBOCS compared to 12% reduction in sham
			Sham: coil with a mu shield	9				
Mansur [14]	Medtronic figure 8	Right DLPFC	10 Hz, 2000P, 110%MT	13	+	—	+	There was no difference in any of the outcome measures between active and sham
			Sham	14				
Gomes [15]	Neuro-MS figure 8	Pre-SMA	1 Hz, 1200P, 100%MT	12	+	—	+	Significant reduction in YBOCS compared to sham
			Sham	10				
Ma [16]	αEEG guided rTMS (Cadwell 9 cm circular coil)	Midfrontal region	648–872P, 80%MT	25	+	+	+	Significant reduction of YBOCS compared to sham
			Sham	21				

Study	Device	Location	Protocol	Sample size	Blinding			Outcome
					Patient	Operator	Rater	
Haghihagi [17]	Magstim figure 8	Left DLPFC	Crossover study: 20 Hz, 100%MT then sham	21	+	—	+	YBOCS improved after active rTMS
			Crossover study: sham then 20 Hz, 100%MT	21				
Elbeh [18]	Magstim figure 8	Right DLPFC	1 Hz, 2000P, 100%MT	15	+	—	+	Significant improvement compared to sham
			10 Hz, 2000P, 100%MT	15				No significant improvement compared to sham
			Sham	15				
Hawken [19]	Medtronic figure 8	SMA	1 Hz, 1200P, 110%MT	10	+	—	+	Active TMS had significant reduction in YBOCS compared to sham
			Sham: (coil rotated away from head)	12				
Seo [20]	Tamas/remed figure 8	Right DLPFC	1 Hz, 1200P, 100%MT	14	+	—	+	Significant reduction in YBOCS compared to sham
			Sham	13				
Pallanti [21]	Magstim 70-mm figure 8	SMA	1 Hz, 1200P, 100%MT	25	—	—	—	Effective in 2/3 patients.
			TAU: Antipsychotics	25				Effective in ¼ patients.
Pelissolo [22]	Magstim 70-mm figure 8	Pre-SMA	1 Hz, 1500P, 100%MT	20	+	—	+	No significant difference.
			Sham: coil with mu shield	19				
Shayganfard [23]	Magstim figure 8	Left DLPFC	Crossover study: 20 Hz, 750P, 100%MT then Sham	10	+	—	+	YBOCS improved after active rTMS
			Crossover study: sham then 20 Hz, 750P, 100%MT	10				

http://dx.doi.org/10.5772/intechopen.73594

Study	Device	Location	Protocol	Sample size	Blinding			Outcome
					Patient	Operator	Rater	
Carmi [25]	Brainsway dTMS H7	dmPFC/ ACC	20 Hz	16	+	+	+	Improvement compared to sham
			Sham: 20 Hz	7				
			1 Hz	8				No difference between 1 Hz & 1 Hz sham
			Sham: 1 Hz	7				
Brainsway Ltd. [26]	Brainsway dTMS H7	dmPFC/ ACC	20 Hz, 2000P, 100%MT	47	+	+	+	Improvement compared to sham
			Sham	47				

Table 1. Individual characteristics of sham-controlled therapeutic TMS studies for OCD.

http://dx.doi.org/10.5772/intechopen.73594

In 2006, Prasko conducted a sham-controlled study of 30 OCD patients, half were assigned to sham and half to active low frequency rTMS. Ten treatments over 2 weeks were administered of low frequency rTMS to the left DLPFC (1 Hz, 110% MT, total pulses not available to this author). The active group did not have any greater benefit than the sham group [10].

In 2007, Perminder Sachdev published the results of a 2-week sham-controlled study for OCD in which the patients and raters were blinded; but the operators were not. Ten subjects were randomized to active and eight to sham. High- frequency (10 Hz, 5 second train, 25 second inter-train interval, 30 trains, 1500 total pulses, at 110% of resting right hand MT) rTMS was administered to the left DLPFC in 10 sessions over 2 weeks with a figure-8 coil. Patients were offered to extend treatment up to 20 sessions. No significant difference was found between the treatment groups in YBOCS or Maudsley Obsessive-Compulsive Inventory scores after 10 sessions. There was a significant difference in YBOCS after 20 treatments; however, it was not significant after controlling for depression [11].

In 2009, Chiara Ruffini published the results of a single-blind left OFC rTMS study of 23 patients with medication resistant OCD. Using a figure-8 coil, he administered low frequency, subthreshold rTMS (1 Hz, 80% MT, 600 pulses) to the left OFC (fp1 on EEG system) with the coil parallel to the scalp for the 16 subjects randomized to active. The coil was positioned perpendicular to the scalp for the seven subjects randomized to sham. There was a significant difference between active and sham low frequency stimulation of the left OFC which lasted until 10 weeks after rTMS ended. Only one of the seven patients had a placebo response, and of the 16 active patients, four had a greater than 35% reduction in the YBOCS from baseline. It is not clear (to this writer) why no one replicated the results of this study on a larger scale, longer treatment duration in double blinded format [12].

In 2010, Antonio Mantovani published the results of a 4 week double blinded study of 1HZ rTMS to the bilateral pre supplementary motor area (SMA) at 100%MT of the thumb for 1200 pulses in 18 medication and cognitive behavioral therapy (CBT) resistant OCD patients with a figure-8 coil. The operators were not blinded, and they used a sham coil with a mu shield; but the patients and raters were blinded. On average at 4 weeks, the active TMS group had a 25% reduction in YBOCS compared to a 12% reduction in the sham group. Patients who subsequently continued an additional 4 weeks of open label treatment generally had an additional three-point decrease in their YBOCS. The results were promising but the active group only had nine completers [13].

In 2011, Carlos Gustavo Mansur published the results of a sham-controlled study of high frequency, high intensity right DLPFC rTMS for OCD using a figure-8 coil. In this study, operators were not blinded but the patients and raters were blinded. Thirteen patients received active and 14 patients received sham. rTMS was administered at 110% of resting left hand MT, 10HZ, 5 second trains, 25 second intervals, 40 trains, 2000 total pulses for 30 treatments over 6 weeks. There was no difference in any of the outcome measures between the active and sham groups [14].

In 2012, Pablo Vinicius Oliveira Gomes randomized 22 patients with moderate OCD into active (n = 12) or sham (n = 10) groups. The study was blinded to the subjects and raters; however, the TMS operators were not blinded. Patients received 10 rTMS treatment sessions

over 2 weeks utilizing a figure-8 coil with low frequency (1 Hz), 1200 pulses at 100% MT over the bilateral pre SMA. They were assessed 3 months after completing TMS. At the 2 week and 14 week assessments, the active group had a significant reduction of 35% in YBOCS scores compared to the sham group who had a 6.2% reduction [15].

In 2014, Xiaoyan Ma published a randomized single-blind sham-controlled study that enrolled 46 subjects with moderate to severe OCD. The study's goal was to determine the treatment effect of using the patient's individualized alpha electroencephalogram (αEEG)-guided rTMS (αTMS) in OCD patients. Treatment was administered with a 9 cm circular coil placed over the midfrontal region. Twenty-five OCD patients received αTMS at 80% resting MT of the hand, 4 seconds stimulation, 56 seconds interval, 20 minutes stimulation daily, total pulses varied by patient's alpha between 648 and 872 pulses per day for 10 treatment sessions over 2 weeks. Twenty-one patients received sham stimulation using an unplugged coil with acoustic effects from another coil at a distance. At the end of treatment and the 1 week follow up, the obsession component of the YBOCS was significantly reduced in the active treatment group compared to the sham group [16].

In 2015, Mohammad Haghihagi published the results of a single blinded crossover trial of 21 OCD patients. Stimulation was administered at 20 Hz, 100% resting right hand MT, 1.5 second train, 25 trains, totaling 750 pulses, 5 days a week for 2 weeks. Sham stimulation was done with the coil angled away from the skull. After 2 weeks, patients switched conditions for an additional 2 weeks. In both groups, the patient's YBOCS improved after the active rTMS condition and not during the sham condition [17].

In 2016, Khaled Elbeh randomized 45 patients into a trial to evaluate the effects of different rTMS frequencies over the right DLPFC at 100% resting left hand MT using a figure-8 coil. Fifteen patients received low frequency (1 Hz), 15 high frequency (10 Hz), and 15 received sham. The operators were not blinded. All groups were administered 10 sessions over 2 weeks of 2000 pulses each at 100% MT; then, patients were followed for 3 months post rTMS. The low frequency group but not the high frequency group's YBOCS was significantly different than sham. The effects did not last 3 months [18].

In 2016, Emily Hawken published a two-site randomized, placebo-controlled clinical trial for patients with refractory OCD using low frequency rTMS to the bilateral SMA. Ten patients received active and 12 patients were in the placebo group, where the operators rotated the coil away from the skull. rTMS was administered at 1HZ, 110% of resting hand MT, 1200 pulses for 25 sessions over 6 weeks with a figure-8 coil. Active TMS recipients obtained significant reductions in their YBOCS compared to sham. Benefits were maintained for 6 weeks after treatment [19]. This is the third small sham-controlled study showing the benefits low frequency figure-8 rTMS over the SMA.

In 2016, Ho Jun Seo published a 3-week single-blind study of low frequency rTMS to the right DLPFC with a figure-8 coil (Tamas, Remed). Fourteen patients received active and 13 patients received sham rTMS, 1 Hz, 1200 pulses, 100%MT of the left hand 5 days a week for 3 weeks. The active group had a significant YBOCS reduction compared to sham [20].

In 2016, Stefano Pallanti published the results of an open-label trial with 50 patients with SSRI refractory OCD. Patients were randomized into either the TAU (treatment as usual) (n = 25) or rTMS (n = 25) groups. The TAU group was treated with antipsychotic drugs. In the rTMS

group, patients were administered 15 sessions of rTMS over 3 weeks with a 70 mm Figure 8 coil at 1 Hz, 1200 pulses, 100%MT over the SMA. One quarter of the refractory OCD patients who were treated with antipsychotics responded compared to the subjects treated with rTMS where two thirds were responders [21].

In 2016, Antoine Pelissolo published the results of a randomized double-blind study of 40 SSRI treatment-resistant OCD patients. Subjects were randomized into active (n = 16) or sham (n = 15) groups. The patients and raters were blinded; however, the operators were not. Both groups were administered rTMS with the 70 mm figure-8 coil at 1 Hz for 1500 pulses, 100%MT to the pre-SMA for 4 weeks. The sham coil utilized a mu-metal shield over the figure-8 coil. The active group did not have a significant reduction in YBOCS compared to sham [22].

In 2017, Mehran Shayganfard published the results of a single-blind crossover study of high frequency rTMS to the left DLPFC of 10 OCD patients using a figure-8 coil. Stimulation was administered at 20 Hz, 100% resting right hand MT, 1.5 second train, 25 trains, totaling 750 pulses, 5 days a week for 2 weeks. Sham stimulation was done with the coil angled away from the skull. After 2 weeks, patients switched conditions for an additional 2 weeks. In both groups, the patient's YBOCS improved after the active rTMS condition and not after the sham condition [23, 24]. This was the second single blinded study this group did with the same crossover after 2 weeks [17, 23]. Methodologically, they should do a double-blind non-crossover study, and at a significantly later date offer the sham patients active treatment.

Between 2012 and 2014, a feasibility study used an H-coil designed to target the medial prefrontal cortices and anterior cingulate cortices (ACC) bilaterally (HAC or H7 coil) in 41 treatment-resistant obsessive-compulsive-disorder (OCD) patients with moderate to severe symptoms. Treatments were administered after the patient's individual symptoms were provoked, and improvements were measured using the YBOCS. Initially the study had four arms, a high frequency arm of 20 Hz, a sham 20 Hz arm, a low frequency arm of 1 Hz and a sham 1 Hz arm. Because the interim analysis showed no difference between the sham and 1 Hz arms, the study was continued with just high frequency and sham. At the end of the study, the response rate in the 20 Hz arm was much greater than in the sham group and the improvements were still present a month after treatments ended [25, 26].

Subsequently, from 2014 to 2017 94 patients with moderate to severe treatment-resistant OCD were randomized in a multicenter double-blind study to either 20 Hz active or sham dTMS, at 100% resting MT of the foot, 2 second trains, 20 second inter train intervals, 2000 total pulses per day. Treatments were administered daily for 29 days over 6 weeks after the patient's individual symptoms were provoked, with a follow up at week 10. Although the study has been completed with a public announcement of positive results, the details have not been published yet.

8. Conclusion-key results

OCD is uniquely suited for intervention with TMS. However, rTMS interventions in OCD that focus on the lateral prefrontal cortices in both high and low frequency are not consistently efficacious. Most of the small sham-controlled studies treating the SMA, left DLPFC, and right DLPFC with low frequency as well as high frequency showed benefit. This is consistent with

the results of a recently published meta-analysis. The meta-analysis noted the right DLPFC had a greater therapeutic effect than other treatment locations [27]. The next step should be a fully blinded (including the operators) sham-controlled multicenter study of low frequency rTMS to the SMA (the pre-SMA is the anterior portion of the SMA, and it is a midline region so it is always treated bilaterally even with a figure-8 coil). Two high frequency, high intensity studies using the HAC/H7 deep rTMS coil showed efficacy for OCD including a multisite study for FDA clearance. We await the detailed presentation of those results.

Further directions for the field include optimizing stimulation parameters for greater efficacy. What state should the circuitry be in during the stimulation? Does the treatment have durability or is maintenance necessary? If children and adolescents are treated early will it change the trajectory of their illness? Does the same protocol work for OCD related disorders such as hoarding, trichotillomania and body dysmorphic disorder? Does this work for OCD without insight or with delusions? Does it help with tics? What happens to the neural circuitry of the OCD patients responding to TMS? Can non-responders benefit from an individualized protocol? Can we predict responders from non-responders before we go through an entire treatment course?

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References

[1] Association AP. Diagnostic and Statistical Manual of Mental Disorders. 5th(DSM-5(TM)) ed. Washington, DC: American Psychiatric Association Publishing; 2013

[2] Bais M, Figee M, Denys D. Neuromodulation in obsessive-compulsive disorder. The Psychiatric Clinics of North America. 2014;**37**(3):393-413

[3] Browne HA et al. Genetics of obsessive-compulsive disorder and related disorders. The Psychiatric Clinics of North America. 2014;**37**(3):319-335

[4] Grant JE. Clinical practice: Obsessive-compulsive disorder. The New England Journal of Medicine. 2014;**371**(7):646-653

[5] De Ridder D et al. Psychosurgery reduces uncertainty and increases free will? A review. Neuromodulation: Journal of the International Neuromodulation Society. 2016; **19**(3):239-248

[6] Dunlop K et al. Reductions in cortico-striatal hyperconnectivity accompany successful treatment of obsessive-compulsive disorder with dorsomedial prefrontal rTMS. Neuropsychopharmacology. 2016;**41**(5):1395-1403

[7] Fettes P, Schulze L, Downar J. Cortico-striatal-thalamic loop circuits of the orbitofrontal cortex: Promising therapeutic targets in psychiatric illness. Frontiers in Systems Neuroscience. 2017;**11**:25

[8] Alonso P et al. Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: A double-blind, placebo-controlled study. The American Journal of Psychiatry. 2001;**158**(7):1143-1145

[9] Sachdev PS et al. Right versus left prefrontal transcranial magnetic stimulation for obsessive-compulsive disorder: A preliminary investigation. The Journal of Clinical Psychiatry. 2001;**62**(12):981-984

[10] Prasko J et al. The effect of repetitive transcranial magnetic stimulation (rTMS) on symptoms in obsessive compulsive disorder. A randomized, double blind, sham controlled study. Neuro Endocrinology Letters. 2006;**27**(3):327-332

[11] Sachdev PS et al. Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: A double-blind controlled investigation. Psychological Medicine. 2007;**37**(11):1645-1649

[12] Ruffini C et al. Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive disorder patients: A controlled investigation. Primary Care Companion to the Journal of Clinical Psychiatry. 2009; **11**(5):226-230

[13] Mantovani A et al. Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. The International Journal of Neuropsychopharmacology. 2010;**13**(2):217-227

[14] Mansur CG et al. Placebo effect after prefrontal magnetic stimulation in the treatment of resistant obsessive-compulsive disorder: A randomized controlled trial. The International Journal of Neuropsychopharmacology. 2011;**14**(10):1389-1397

[15] Gomes PV et al. A randomized, double-blind trial of repetitive transcranial magnetic stimulation in obsessive-compulsive disorder with three-month follow-up. The Journal of Neuropsychiatry and Clinical Neurosciences. 2012;**24**(4):437-443

[16] Ma X et al. A randomized double-blinded sham-controlled trial of alpha electroencephalogram-guided transcranial magnetic stimulation for obsessive-compulsive disorder. Chinese Medical Journal. 2014;**127**(4):601-606

[17] Haghighi M et al. Repetitive Transcranial magnetic stimulation (rTMS) improves symptoms and reduces clinical illness in patients suffering from OCD–Results from a single-blind, randomized clinical trial with sham cross-over condition. Journal of Psychiatric Research. 2015;**68**:238-244

[18] Elbeh KAM et al. Repetitive transcranial magnetic stimulation in the treatment of obsessive-compulsive disorders: Double blind randomized clinical trial. Psychiatry Research. 2016;**238**:264-269

[19] Hawken ER et al. Transcranial magnetic stimulation of the supplementary motor area in the treatment of obsessive-compulsive disorder: A multi-site study. International Journal of Molecular Sciences. 2016;**17**(3):420

[20] Seo HJ et al. Adjunctive low-frequency repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex in patients with treatment-resistant obsessive-compulsive disorder: A randomized controlled trial. Clinical Psychopharmacology and Neuroscience. 2016;**14**(2):153-160

[21] Pallanti S et al. Better than treated as usual: Transcranial magnetic stimulation augmentation in selective serotonin reuptake inhibitor-refractory obsessive-compulsive disorder, mini-review and pilot open-label trial. Journal of Psychopharmacology. 2016; **30**(6):568-578

[22] Pelissolo A et al. Repetitive transcranial magnetic stimulation to supplementary motor area in refractory obsessive-compulsive disorder treatment: A sham-controlled trial. International Journal of Neuropsychopharmacology. 2016;**19**(8):pyw025

[23] Shayganfard M et al. Repetitive transcranial magnetic stimulation improved symptoms of obsessive-compulsive disorders but not executive functions: Results from a randomized clinical trial with crossover design and sham condition. Neuropsychobiology. 2016;**74**(2):115-124

[24] Jahangard L et al. Repetitive transcranial magnetic stimulation improved symptoms of obsessive-compulsive disorder, but also cognitive performance: Results from a randomized clinical trial with a cross-over design and sham condition. Neuropsychobiology. 2016;**73**(4):224-232

[25] Carmi L et al. Deep transcranial magnetic stimulation (Tms) in obsessive compulsive disorder (Ocd) patients. European Psychiatry. 2015;**30**:794

[26] Carmi L et al. Clinical and electrophysiological outcomes of deep TMS over the medial prefrontal and anterior cingulate cortices in OCD patients. Brain Stimulation. 2017;**11**(1):158-165

[27] Zhou DD et al. An updated meta-analysis: Short-term therapeutic effects of repeated transcranial magnetic stimulation in treating obsessive-compulsive disorder. Journal of Affective Disorders. 2017;**215**:187-196

Chapter 7

Neurostimulation Techniques for the Modulation of Pain

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.79406

Abstract

Non-invasive brain stimulation (NIBS) is increasingly proposed as a therapeutic intervention for many neurological and psychiatric disorders, including pain, depression, obsessive compulsive disorder, and anxiety. While neuromodulation as an intervention for pain relief has a well-established scientific basis, evidence is largely restricted to invasive stimulation that targets the spinal cord. Novel non-invasive methodologies instead predominately target cortical processing of pain and thus raise interesting questions about how the most effective pain relief can be achieved. Functional magnetic resonance imaging (fMRI) studies show a widespread and distributed activation of brain areas during pain. This diverse activity is often referred to as the "pain neuromatrix" and can lead to the proposal for different possible target areas for pain relief. Neuromodulation could target brain regions of pain processing areas responsible for sensorimotor processing or alternatively regions responsible for the affective and evaluative aspects of the subjective pain experience. The chapter addresses the different approaches currently taken in the use of non-invasive neuromodulation for altering pain both in an experimental setting and the challenges involved in the translation of these techniques to a diverse range of chronic pain conditions.

Keywords: pain, neurostimulation, transcranial magnetic stimulation, transcranial direct current stimulation, quantitative sensory testing

1. Introduction

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [1]. Nociception is an indispensable survival mechanism designed to minimize tissue injury, observed across species from the simplest invertebrate

model systems. Its critical function as a sense for survival is reflected by its emergence early developmentally. In all animals, the characteristic perception of nociceptive stimuli is rapid reflexive movement away from the source of the noxious stimulus (nocifensive behavior) and autonomic responses that optimize the ability to escape from threats [2]. In humans, pain encompasses not only these sensorimotor responses but critically also the cognitive evaluative component, and the IASP definition encompasses the subjectivity of the pain phenomenon.

Chronic pain represents a significant health burden worldwide with over 1.5 million people suffering from chronic pain globally [3]. Nearly 20% of those in Europe are believed to be in chronic pain, and lifetime prevalence of chronic pain worldwide has been put as high as 55.2% of the population [4, 5]. The experience of pain is known to have a substantial detrimental impact on an individual's quality of life and mental health status. Extensive research has documented the high correlation between pain and mental health difficulties, not just within clinical cohorts but also in community-based studies [6]. Pain can therefore be seen as an important risk factor for the development of psychiatric conditions, for instance, depression. Furthermore, there is a reciprocal nature to the interaction, with depression likely to exacerbate the individual's experience of pain [7]. Overall, the consequence is not just on the individual but also the societal economic burden of pain will be further compounded by the economic burden of the concomitant mental health difficulties of those experiencing it chronically.

2. Pain and pain processing

Noxious stimuli are detected by the free endings of pseudounipolar neurons (Aδ or C fibers) which project to the dorsal horn of the spinal cord to synapse with second-order neurons in laminae I–II and V–VII [2]. Type I small-diameter thinly myelinated Aδ fibers respond to strong mechanical stimuli; type II Aδ nociceptors respond to noxious thermal stimuli; unmyelinated C-fiber nociceptors respond to thermal, mechanical, and chemical stimuli [2]. Neurons of laminae I and V relay signals along the spinothalamic and spinoreticulothalamic tracts to supraspinal sites including the thalamus, parabrachial nucleus, and amygdala and to higher cortical centers such as the primary somatosensory cortex (S1), secondary somatosensory cortex (S2), dorsolateral prefrontal cortex (DLPFC), and primary motor cortex (M1). Taken together, the combined activity of both cortical and subcortical regions that form a distributed brain network associated with pain processing is referred to as the pain "neuromatrix" [8]. The ventroposterior lateral and medial nuclei of the thalamus, S1 and S2 are concerned with the sensory-discriminative component of pain, encoding location, and duration of pain, whereas the medial nuclei of the thalamus and anterior cingulate cortex (ACC) are regions suggested to underlie the cognitive-evaluative aspect of pain, including pain-related learning [2]. Descending pathways pass through the periaqueductal gray matter (PAG), which has been long established as important in the endogenous modulation of pain via early electrical stimulation studies [9]. The PAG is part of a central circuit that controls nociceptive transmission at the level of the spinal cord dorsal horn via a relay in the rostral ventromedial medulla (RVM) [10]. The PAG receives direct projections from a number of medial prefrontal cortical areas, including the ACC, the amygdala, and the hypothalamus [11–14], with a primary output to the RVM critical

to descending pain modulation. The PAG-RVM system's critical role in the central control of nociception has been demonstrated by lesion studies [15]. Taken together, these studies indicate that the intensity of pain will be the consequence and composite of interactions between ascending nociceptive inputs and descending antinociceptive controls. Dysregulations in any aspect of these networks may underlie vulnerability factors for the development of chronic pain [16].

2.1. Pain and the chronification of pain

While acute pain is highly functional to survival and an adaptive sense that is protective against tissue damage, the mechanisms behind the development from this protective function to the maladaptive disease of chronic pain in a proportion of individuals remain elusive. Chronic pain is defined as pain that persists for 3–6 months after the initial nociceptive stimuli [17]. Methodologies that have potential to predict individual patients with pain who are at risk of developing chronic pain would be particularly valuable at helping to understand the physiological mechanisms behind this very detrimental disease process. Recent research suggests that the use of computational machine learning methods to analyze large data sets of medical and demographic characteristics collected from patients who develop chronic pain patients may aid understanding of the risk factors underlying chronification and a possible chronic pain phenotype [18]. This is an interesting concept, though ultimately dependent on the relevant predictors of pain chronification being in the analyzed data set. For instance, while there has been recent interest in the use of quantitative sensory testing to characterize individual differences in pain sensitivity, thorough assessment of pain thresholds across a variety of modalities, this is by no means standard. That limitation aside, greater understanding of pain chronification is essential for the development of interventions for chronic pain and increased understanding of how to effectively disrupt the transition into a disease state. In the future, the inclusion of larger data sets will inevitably increase the predictive value of this emerging technique.

Chronic pain is characterized by increases in neuronal excitability leading to increased pain perception. These increases in excitability are believed to occur both peripherally and centrally, factoring into the overall elevated perceived pain. To date, research has predominately focused on spinal cord mechanisms. This perhaps is somewhat related to availability of appropriate animal models and the existing strong scientific basis. However, it is well established that spinal cord excitability can be modulated by descending pathways. Given the role of descending pathways in modulating excitability in the spinal cord, the input and impact of a wide range of cortical areas in perceived pain should be systematically considered and characterized. These cortical areas will not just include those directly related to sensorimotor processing but also encompass those areas important for the cognitive evaluative and emotional response to pain. NIBS techniques may provide a tool that can enable further insight into the mechanisms of pain processing from periphery through to cortex that may in turn reveal potential therapeutics for the treatment of chronic pain conditions.

Further, pain is categorized by the IASP as either neuropathic or nociceptive [19]. Neuropathic pain is a pain that is caused by a disorder of the somatosensory system and typically leads to symptoms that include hyperalgesia, allodynia, and pain in the absence of stimulation. Nociceptive pain is a pain that arises from damage to non neural tissue via the activation of

nociceptors. Another consideration is that although there is a broad distinction into neuropathic and nociceptive pain, there can be overlap in the two forms of pain, as well as the fact that pain can arise from a vast range of different underlying pathologies.

3. Neurostimulation for pain modulation

The use of electricity to alleviate pain has a long history, with the reported use of the electric emissions from the Nile catfish for pain relief in 3100 BC. Although there has been use of electrical stimulation continually, the groundbreaking gate control theory of Melzack and Wall published in 1965 changed the field and provided a strong basis for the design of appropriate interventions [20]. The theory proposes that the balance of activation between small- and larger diameter fibers determines the level of pain signaled. Small-diameter C fibers will open the "gate," and Aβ fibers (that signal innocuous touch), having a larger diameter, will close the "gate." Due to differences in the threshold of activation of these fibers in response to imposed electrical stimulation on a mixed nerve, a simple intervention to shift the balance of activation is possible. Neuromodulation of pain through electrical stimulation of implanted electrodes has substantial supportive evidence since its initial introduction in spinal cord stimulation (SCS) in 1967 [21] and is accepted as a standard form of treatment for intractable chronic neuropathic pain. Many of these implantable neurostimulation devices were adapted from the design of cardiac pacemakers, and their design and stimulation parameters have not changed substantially since their initial introduction. However, differences do exist among SCSs; for instance, some are based on tonic stimulation, whereas others on burst stimulation, and the stimulation frequency can be varied.

Other invasive stimulators have targeted pain pathways in the brain to alleviate pain, often utilizing the knowledge of role of the thalamus as having a critical role in sensory processing. Deep brain stimulation (DBS) has been applied to different thalamic nuclei, including the ventral posteromedial sensory nuclei and ventral posterolateral sensory nuclei and the centromedian-parafascicular intralaminar region. There is widely varying reports of the effectiveness of DBS of the thalamus but with the strongest response believed to be in patients with neuropathic pain [22]. DBS has also included stimulation of the ACC, with the aim of reducing the affective component of chronic pain, and this has been shown to be effective within small studies [23].

The primary motor cortex (M1) was the first cortical target that was proven to be efficacious in chronic pain treatment [24]. Motor Cortex Stimulation (MCS), where epidural electrodes are implanted has been shown to be a particularly useful intervention for neuropathic pain that is not responsive to pharmacological interventions [25, 26]. The primary motor cortex (M1) is somatotopically arranged and receives inputs from three main sources. These are [1] the peripheral body via the thalamic relay nuclei-somatosensory cortex system, from the premotor cortex and from the sensory association areas of the cortex; [2] the basal ganglia; and [3] from the cerebellum. Therefore, there is considerably overlap with motor processing areas and those associated with the pain neuromatrix. It is believed that cathodal MCS is associated with an indirect stimulation of pyramidal neurons via interneurons, whereas anodal MCS is

associated with a direct stimulation of pyramidal neurons. The indirect activation is believed to be optimal for MCS analgesia.

Invasive neuromodulatory devices have been the subject of research for much longer non-invasive neuromodulatory techniques, including randomized controlled trials. By reason of their very invasive nature, and obvious ethical constraints, the effectiveness and consequences of SCS, MCS, and DBS have only be assessed in patients and not experimentally investigated in healthy volunteers, which may have limited the development of different stimulation protocols. Therefore, unlike these invasive stimulators, NIBS techniques potentially enable another important distinction to be considered, the difference in response to neuromodulation in chronic pain patient groups compared with healthy individuals exposed to experimental pain or experiencing acute pain.

4. Functional magnetic resonance imaging (fMRI) and chronic pain

Functional magnetic resonance imaging (fMRI) was first used in the area of pain in order to demonstrate the brain areas responsible for pain perception and part of the pain "neuromatrix" [28]. Subsequently, differences in the structure and function of pain patients compared with healthy controls have been observed through fMRI of experimental pain in both groups [29]. Chronic pain patients show similar activation but with a decrease in thalamic and ACC activation. Activity in the prefrontal cortex (PFC) typically shows an increase in clinical pain conditions. This preferential activation of PFC in chronic pain conditions advocates that chronic pain states have stronger cognitive-evaluative aspect of pain [16].

As well as functional changes, structural changes have been observed through MRI in patients experiencing long-term pain. Chronic pain patients are found to show neuronal loss in significant pain pathways including the thalamus and the lateral prefrontal cortex [30]. Fibromyalgia, a patient group with a particularly complex range of sensorimotor symptoms, shows gray matter loss in the DLPFC [31], and this is believed to be consistent across different chronic pain patient groups. For instance, patients with chronic lower back pain also show reductions in gray matter in distributed regions of the pain "neuromatrix," including DLPFC. This decrease in gray matter also occurs in prolonged pain states in the general population as well as clinical groups [32], and on resolution of persistent pain, for instance when a patient with knee osteoarthritis (OA) undergoes knee arthroplasty, gray matter levels increase in parallel.

fMRI has also been used to demonstrate the effectiveness of neuromodulatory interventions, as well as the scope of the effect of stimulation. For instance, functional connectivity changes were observed in a group of neuropathic pain patients who had undergone SCS. After implantation, decreased connectivity was found between somatosensory and limbic areas of the brain, showing how central changes can be mediated by SCS [28]. Studies using combined NIBS/fMRI may provide interesting insights on the effect of neuromodulation protocols on changes in functional connectivity of the pain neuromatrix as has been done in other treatment interventions [33].

5. Noninvasive brain stimulation: Investigative and therapeutic uses

NIBS is well established as a tool to study the physiology of the CNS, elucidate functional anatomy of specific brain regions and explore brain network organization and plasticity [34]. However, currently the application of NIBS to pain research is much more recent, although this is a rapidly expanding field [35]. The most commonly used forms of NIBS that aim to modulate neuronal plasticity are repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), with the techniques rapidly expanding to variations on these methods. Transcranial alternating current stimulation (tACS) is a particularly exciting new method where an alternating current is applied with the aim of enhancing network oscillations at frequencies close to the stimulation frequency [36]. Therefore, the rationale behind the tACS technique is that it may lead to pain modulation via the alteration of specific rhythmic activity known to be associated with pain processing [37], but currently, there are only a few experimental studies applying this technique to experimental or clinical pain. For all of these methodologies, the noninvasive nature, relatively low cost, and well-established safety and tolerability make these neuromodulatory techniques potentially important tools both for neurophysiological studies and to aid the development of long-term therapeutic interventions [38].

5.1. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) has both neuromodulatory and neurostimulatory properties. The technique, first introduced in 1985, has subsequently been widely used as a tool to study cortical brain areas, particularly motor cortex. The technique involves a stimulating coil of wire positioned over the desired brain target area, with a brief pulse of current passed through the coil, so generating a magnetic field which penetrates through the skull with negligible attenuation. The rapidly changing magnetic field induces a secondary current in the subject's brain, thus stimulating neural tissue via the depolarization of neurons [34]. Thus the technique overcame many of the problems associated with electrical stimulation, where the skull provides a barrier. With an appropriate figure of eight coil [39], TMS can be used to stimulate precise regions, such as the hand area of the motor cortex (C3). The motor cortex is a particularly good target for TMS usage in the absence of neuronavigation software packages that guide coil positioning over the appropriate brain target area as single-pulse TMS eliciting motor evoked potentials (MEPs) that can be recorded using electromyography (EMG), which enable the determination that the correct cortical area has been stimulated. MEPs are further used to determine the stimulation intensity required in an experimental protocol via the measurement of motor threshold and the quantification of changes in corticospinal excitability [34, 40, 41].

Repetitive transcranial magnetic stimulation (rTMS) refers to the application of a train of pulses and dependent on the frequency acts to suppress or facilitate the activity in an underlying brain area. The stimulation of the motor cortex with low frequencies (1 Hz or less) is associated with a decrease in corticospinal excitability, whereas higher frequencies (20–50 Hz) have been associated with an increase in excitability [42]. It has been noted that these effects are somewhat inconsistent, thereby limiting its therapeutic applications [43]. A possible reason behind this is that rTMS is dependent on stimulation parameters other than

frequency, and baseline corticospinal excitability of the targeted brain area is a critical parameter in determining the consequence of rTMS [44].

5.2. Pain modulation through repetitive transcranial magnetic stimulation of motor cortex

Given the known efficacy of MCS for pain relief, the primary motor cortex was an obvious initial choice of target for NIBS interventions. Further given the corticospinal tract is known to have non-motor functions, that include a role in nociception, the stimulation could have an effect on this pathway [45].

High-frequency rTMS of the motor cortex has been shown to be efficacious in the treatment of pain [35, 43, 46, 47]. Significant reductions in pain ratings occur following high-frequency stimulation and these stimulation effects lasting from several minutes up to 8 days and even longer after multiple rTMS sessions. Stimulation of the motor cortex with high-frequency rTMS showed significantly increased pain thresholds with regard to cold thermal stimuli, meaning rTMS reduced the temperature at which the cold sensation became painful [40]. This demonstrates that rTMS not only can modulate chronic pain, but also experimentally induced acute pain.

Evidence for M1 rTMS for pain relief is mounting, but there is still a shortage of large studies, and the duration of the neuromodulatory effect is not well established. Technical considerations with coil positioning may alter the effectiveness of rTMS as an intervention for pain relief which may not be completely controlled for in different studies. In rTMS, the coil is typically placed over M1 in an anteroposterior orientation which is associated with transsynaptic activation of pyramidal neurons, and this placement is believed to be optimal for analgesic effects compared with the placement of the coil in a lateromedial orientation, similar to findings with MCS [27]. Further, there is evidence that when the electrodes are placed over the somatotopic M1 region of the painful area, that optimal analgesic effect can be obtained [27].

The mechanisms behind M1 rTMS-facilitated analgesia are still not established. Previous research on implanted MCS has suggested that the modulation of pain is related to the inhibition of thalamic activity. M1 rTMS could modulate the pathways from the insula and orbitofrontal cortex to the posterior thalamus in order to upregulate these pain thresholds [48]. The modulation of pathways from the insula could be particularly significant, given recent research suggesting that the insula act as the cortical generator of pain perception, integrating sensory and affective components of pain [2].

The neurochemical mediation of the neuromodulation is still uncertain. There is evidence that the endogenous opioid system may be responsible. Additionally, the activation of GABA (*gamma*-Aminobutyric acid)-ergic and glutamatergic pathways may be critical. For instance, high-frequency rTMS is believed to restore defective intracortical inhibition, a measure associated with impairments in GABAergic neurotransmission in patients with chronic pain [47]. Glutamate N-methyl-D-aspartate (NMDA)-receptors are also thought to be involved in rTMS neuromodulatory effects, in that there was observed a decrease in analgesic effects after the administration of the NMDA antagonist, ketamine [49]. This supports the ability of rTMS to induce synaptic plasticity via long-term potentiation (LTP) and long-term depression (LTD) like mechanisms.

5.3. The dorsolateral prefrontal cortex

A second cortical target that has been investigated by NIBS is the DLPFC [50] The DLPFC is connected to the orbitofrontal cortex and to other areas of the pain "neuromatrix," in particular the thalamus and dorsal caudate nucleus. Evidence from multimodal studies, including neuroimaging, TMS, and tDCS, suggests that DLPFC is important in the affective modulation of pain [51–55]. The DLPFC has shared connectivity with regions associated with sensorimotor processing and monitoring of motor performance. This connectivity highlights the potential importance of the DLPFC as a target for neurostimulation for the modulation of pain [56]. Further, in addition to its possible ability to modulate the sensory-discriminative aspects of pain perception and experience, DLPFC has reciprocal networks within the ventromedial prefrontal cortex supporting the integration of memory and stimulus characteristics. Additionally, it has been found that increased activity in the DLPFC is associated with decreased pain intensity and unpleasantness.

High-frequency rTMS of the DLPFC has been shown to alleviate neuropathic pain in patient groups [57]. Experimentally, the effects of low-frequency rTMS on both left and right DLPFC have also been reported where it was found that stimulation inhibited placebo analgesia, and so increased heat pain ratings [51]. This finding related to placebo analgesia highlights some of the difficulties involved in assessing the efficacy of NIBS interventions.

Differing mechanisms have been proposed for the alleviation of pain through increased activity in the DLPFC, one is that it is able to activate descending modulatory pathways through the periacqueductal gray, whereas an alternative mechanism was via modulation of thalamic activity as has been proposed by fMRI studies [58]. There is also a proposed role for the DLPFC in terms of the anticipation of pain, which could provide some explanation for placebo-related alternations in pain thresholds. One of the difficulties that arises in the comparison of active treatments to placebo is the possibility of an analgesic response to the placebo itself, which may be mediated by endogenous opioids [59, 60]. With this in mind, the ability of NIBS to modulate the placebo effect is in itself interesting.

5.4. Neurophysiology of tDCS

tDCS is a non-invasive technique, where weak direct current (<2 mA) is applied on the scalp for 10–20 mins using large saline-soaked sponge electrodes. In contrast to TMS, tDCS is neuromodulatory rather than neurostimulatory and as such influences spontaneous neuronal activity by modulating resting membrane potentials [61]. Animal studies have demonstrated that anodal tDCS depolarizes membrane potentials and increases neuronal firing rates and excitability, whereas cathodal stimulation hyperpolarizes membrane potentials, leading to decreased excitability [62]. Modeling techniques suggest that these short-term effects may be mediated by glia, with tDCS modulating glial transmembrane potential that may in turn alter glial regulation of potassium or glutamate homeostasis [63]. Due to technical difficulties, experimental evidence to examine the precise effect on glia is limited. Both anodal and cathodal long-term effects have been attributed to N-methyl-D-aspartate (NMDA)-receptor activation; the NMDA-receptor antagonist dextromethorphan has been reported to suppress the aftereffects of anodal and cathodal tDCS [64, 65]. Further, studies using magnetic resonance spectroscopy have reported

that anodal stimulation inhibits neurotransmission by the inhibitory neurotransmitter GABA [66], whereas cathodal stimulation inhibits neurotransmission by the excitatory neurotransmitter glutamate [67, 68]. While the precise mechanisms remain elusive, recent research in animal models suggest that weak electrical stimulation acts as a modulator, rather than an inducer of synaptic plasticity with its effects highly dependent on endogenous synaptic activity [69].

5.5. High-definition transcranial direct current stimulation

High-definition transcranial direct current stimulation (HD-tDCS) is a technique used to increase the spatial focality of tDCS by using <12 mm diameter ring electrodes [70]. As an investigative tool, HD-tDCS holds several advantages over conventional tDCS. Neuroimaging and modeling studies have demonstrated that conventional parameters induced neuromodulation extends outside the area covered by the target electrode [2, 71]. In addition, the largest current densities for conventional tDCS may not be produced directly under the target electrodes [70]. In comparison to the diffuse effects of conventional tDCS, HD-tDCS enables a more targeted approach to neurostimulation, potentially avoiding modulation of confounding brain regions and permitting isolation of certain pain processing pathways [72].

The predominant montage for HD-tDCS is a 4x1 array configuration consisting of five ring electrodes: 1 "active electrode" placed over the target area surrounded by a ring of 4 "return" electrodes placed equidistant from the central electrode [71]. This 4x1 montage increases intensity and focality of the stimulation, with peak stimulation situated under the central electrode. Further, the montage also allows for depth, focality, and intensity of stimulation to be titrated depending on the ring diameter [73]. In addition to improved focality, HD-tDCS has lower observed adverse effects, including less itching and scalp discomfort and with the further advantage of a longer duration of neuromodulatory effects [3]. Recent multidimensional electrode arrays are now available but, thus far, very little research has been conducted.

5.6. Pain modulation using transcranial direct current stimulation

Multiple types of experimental pain have been used to study the effects of NIBS on nociceptive signaling in healthy human subjects [74]. tDCS of M1 produces sustained analgesia in chronic migraine, fibromyalgia, and orofacial pain [38]. Currently, the level of evidence for the use of tDCS in neuropathic pain is currently lower than that for rTMS [17, 75]. Similar to the effect of rTMS on DLPFC, there is also evidence that tDCS of the DLPFC modulates pain. For instance, anodal tDCS of the left DLPFC has been shown to increase electrical pain thresholds [76]. There are currently fewer studies targeting DLPFC, but future work on this area is of clear interest.

The mechanisms by which tDCS modulates pain processing have not yet been fully elucidated and likely differs between target brain regions. Anodal M1 tDCS increases cortical excitability [62] that may result in disinhibition of glutamatergic M1 neurons that activate sensory gating mechanisms in the thalamus via corticothalamic projections, reducing incoming nociceptive information to somatosensory cortex [77]. Alternatively, stimulation of M1 may stimulate GABAergic neurons to restore functional intracortical inhibition in chronic neuropathic pain [47]. In addition, tDCS of M1 may directly increase opioid release [46, 78].

5.7. Transcranial direct current stimulation priming of repetitive transcranial magnetic stimulation

The physiological connectivity and neuronal plasticity of the M1 are two important factors that have been overlooked in the development of NIBS pain modulation protocols in the past. The use of tDCS-primed/preconditioned rTMS stimulation has been suggested as a more robust form of intervention [79, 80]. When tDCS was used to augment background motor corticospinal excitability, the cortical plastic changes induced by subsequent rTMSs were standardized. It has been demonstrated that weak 1 mA tDCS reversed the usual effects of rTMS on corticospinal excitability [81]. That is, preconditioning using a session of cathodal tDCS modified the expected suppressive effect of low-frequency rTMS and led to an overall cortical excitation, whereas anodal tDCS resulted in an overall motor cortical inhibition. This manipulation of effects is based on the conceptual form of brain plasticity, "homeostatic plasticity" [82]. This protocol has been applied to the modulation of pain, and weak tDCS (1 mA) was used to "precondition" the brain to enhance the effects of subsequent stimulation via low-frequency rTMS (1 Hz) on the modulation of thermal sensation, thermal pain thresholds, and pressure pain thresholds, thereby producing a form of analgesia [83, 84].

5.8. Dose effects of neuromodulatory interventions

The physiological mechanism underlying the effects of tDCS remains controversial. Unlike pharmacological interventions for pain relief, where the appropriate dosage is carefully considered, the issue of "dosage" of neurostimulation has been somewhat neglected in the literature [85, 86]. Recent research has been working toward establishing factors responsible for variability in tDCS effects; such as the positioning of the electrodes on the scalp as well as the intensity and duration of the stimulation. This is best demonstrated in studies regarding application to the human motor cortex, where they attempt to direct the current to strictly follow the orientation of axons and/or dendrites in the induced electrical field [61]. Recent studies employ current flow models with defined montages [86] and use improved electrode positioning through the use of caps based on the international 10–20 positioning system [84].

Interestingly, there is evidence that when the electrodes are placed over the somatotopic M1 region of the painful area, optimal analgesic effect can be obtained [27]. This could potentially explain some of the differences in treatment efficacy reported in rTMS studies in pain patients where the exact target of the stimulation in relation to the painful area is not controlled for or appropriately selected. A further complication to this is the variation in chronic pain conditions as to the extent of spatial localization of the perceived pain.

TMS has a much longer history of research than other NIBS techniques. However, there has been only slow development in stimulator design. An interesting recent development has recently occurred in TMS that may improve future therapeutic interventions. Until recently, there has been a complete lack of complete experimental control over the stimulation pulse shape in TMS. It will be interesting to see the emerging literature as new devices develop that examine the differential impact of altering stimulation pulse widths and waveforms via

controllable TMS (c-TMS) [87]. These devices may be critical in optimizing TMS to maximize analgesic effects.

5.9. Combining neuromodulation with pharmacological interventions

In addition to independent efficacy, it may be that NIBS can work in a synergistic fashion with pharamacological interventions for pain relief. This question has been examined with regard to stroke recovery in large randomized control trials in an extensive research network. A number of recent studies have combined drug interventions with rTMS in rehabilitation in patients after stroke [88]. Interesting questions can be raised as to whether drug action can prime the brain and enhance the effect of TMS or vice versa. The same approach should be systematically carried out in patients with chronic pain conditions (27).

6. Challenging issues and inconsistencies in NIBS

NIBS is rapidly emerging as an intervention proposed for wide-ranging neurological and psychiatric disorders. However, tDCS studies have recently been scrutinized due to reported high degree of variability in effectiveness in published studies to date [89]. Evidence on the therapeutic use of both tDCS and newer methodologies like tACS are currently very limited, and the optimal parameters for use have yet to be fully elucidated. Many have suggested that there is a currently a general lack of understanding of the mechanisms by which these interventions are effective. However, tDCS has several advantages compared to the better investigated rTMS including ease of use, portability, and reduced expense [90], which support further investigation into the potential of tDCS in the treatment of pain.

Despite this, there is increasing evidence that NIBS are effective in the modulation of experimentally induced pain [91] as well as chronic pain conditions although the caveat to this is that there is reported variability in responsiveness across studies and individuals in both experimental and clinical studies. This efficacy of NIBS for experimental pain challenges the previously held understanding that neurostimulation devices act solely by interfering with the long-term maladaptive plasticity associated with chronic pain. Instead, it points toward a general lack of sufficient mechanistic understanding as to how NIBS modulates pain and how this modulation differs across individuals [92]. Moves toward characterizing differing individual "pain phenotypes," based on a battery of quantitative sensory testing, may provide insights into why some individuals respond to NIBS [7]. The use of protocols designed to give insights into an individual's endogenous descending modulation such as conditioned pain modulation (CPM) [93] may also be useful in conjunction with NIBS, in the same way that these protocols have been used when differentiating groups that respond to pharmacological treatment interventions. Another possible reason for the variability of the effects of rTMS on acute pain could be differential effects on each pain modality. For example, it is possible that rTMS may influence A- δ –fiber-mediated and C-fiber-mediated pain differently [94].

7. Is optogenetics the future of noninvasive brain stimulation?

Optogenetic techniques, where light-activated ion channels from microbial opsins are expressed in neurons enabling their activity to be controlled remotely by light, are rapidly increasing our understanding of neural circuits [95, 96]. In animal models, the technique has been used to investigate pain processing pathways; for instance, optogenetic activation of the prefrontal cortex has been found to lead to antinociceptive effects. This study highlighted the importance of a previously unexplored prefrontal to nucleus accumbens pathway that may in the future provide insights into treatment interventions for intractable pain [97]. As the field expands, optogenetic techniques are likely to lead to substantial increases in our understanding of pain processing by their use in animal models. In addition to the contribution to basic science, optogenetics has been predicted to have translational potential as a therapeutic neuromodulatory intervention for neurological disorders. One of the current limitations of the use of this technology in humans will be in how to safely deliver the channelrhodopsin (ChR2) gene to the targeted neuronal population. Nonetheless, it is likely that progress will occur very rapidly in this field due to its vast therapeutic potential [98].

8. Conclusion

The use of the NIBS for the relief of pain is a relatively new field and provides an exciting opportunity for neuromodulatory interventions to move to targeting cortical areas rather than traditional spinal cord stimulation. NIBS opens up the opportunity to fully probe the contributions of the widespread brain areas that are thought to be associated with pain processing in the pain neuromatrix. With the associated risk factor of mental health difficulties in chronic pain patients, this is particularly interesting as NIBS introduces the possibility of targeting cognitive-evaluative aspects of pain. Further NIBS allows experimental studies in healthy participants, as well as patient intervention, allowing the investigation of the neuromodulation of pain processing in health and disease. Taken together, these studies provide the potential for greater understanding of the role of descending modulation in pain perception and how this modulation is influenced by chronic pain. There is a clear need to look toward NIBS for future therapeutic interventions for chronic pain as there are currently a number of challenging chronic pain syndromes that are often refractory to conventional pharmacological therapy [3]. With the increasing numbers seeking treatment to pain associated with chronic disease and injury, the development of safe and effective forms of treatment is crucial in terms of both public health and the economy.

Acknowledgements

Experimental work in my laboratory examining pain and neurostimulation has been conducted by Dr. Tonya Moloney, Dr. Eissa Al –Hashessi, Niamh O'Connor, Eoin Devy-Gray, Lucy O'Donoghue, Clive Drakeford, Victor Rodrigues, Brendan Grafe, Hannah Ashe, and Louisa-May Hanrahan. All have provided valuable contributions to discussions on literature in the area of pain and neurostimulation.

Funding has been provided by Trinity College, Dublin.

Conflict of interest

The author has no conflict of interest.

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References

[1] Merskey H, Bogduk N. Classification of Chronic Pain IASP. 2nd ed, 1994

[2] Ossipov MH. The perception and endogenous modulation of pain. Scientifica (Cairo). 2012:561761

[3] Borsook DA. Future without chronic pain: Neuroscience and clinical research. Cerebrum. 2012;**7**

[4] Harstall C, Ospina M. How prevalent is chronic pain. Pain Clinical Updates. 2003;**11**(2):1-4

[5] Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: Prevalence, impact on daily life, and treatment. European Journal of Pain (London, England). 2006;**10**(4):287-333

[6] de Heer EW, Have MT, van Marwijk HWJ, Dekker J, de Graaf R, Beekman ATF, et al. Pain as a risk factor for common mental disorders. Results from the Netherlands mental health survey and incidence Study-2: A longitudinal, population-based study. Pain. 2018;**159**(4):712-719

[7] Grosen K, Fischer IWD, Olesen AE, Drewes AM. Can quantitative sensory testing predict responses to analgesic treatment? European Journal of Pain. 2013;**17**:1267-1280

[8] Melzack R. From the gate to the neuromatrix. Pain. 1999;**6**

[9] Reynolds DV. Surgery in the rate during electrial analgesia induced by focal brain stimulation. Science. 1969;**164**(3878)

[10] Fields HL, Heinricher MM. Anatomy and physiology of a nociceptive modulatory system. Philosophical transactions of the Royal Society of London Series B, Biological sciences. 1985;**308**(1136):361-374

[11] Beitz AJ. The organization of afferent projections to the midbrain periaqueductal gray of the rat. Neuroscience. 1982;**7**(1):133-159

[12] Rizvi TA, Ennis M, Behbehani MM, Shipley MT. Connections between the central nucleus of the amygdala and the midbrain periaqueductal gray: Topography and reciprocity. The Journal of comparative neurology. 1991;**303**(1):121-131

[13] Bandler R, Keay KA. Columnar organization in the midbrain periaqueductal gray and the integration of emotional expression. Progress in brain research. 1996;**107**:285-300

[14] Rizvi TA, Murphy AZ, Ennis M, Behbehani MM, Shipley MT. Medial preoptic area afferents to periaqueductal gray medullo-output neurons: A combined Fos and tract tracing study. The Journal of Neuroscience. 1996;**16**(1):333-344

[15] Fields HL, Heinricher MM, Mason P. Neurotransmitters in nociceptive modulatory circuits. Annual review of neuroscience. 1991;**14**(1):219-245

[16] Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. European journal of pain (London, England). 2005;**9**(4):463-484

[17] O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. Cochrane database systematic review. 2010:CD008208

[18] Lotsch J, Ultsch A. Machine learning in pain research. Pain. 2018;**159**(4):623-630

[19] Woolf CJ, Mannion RJ. Neuropathic pain:Aetiology, symptoms, mechanisms, and management. Lancet. 1999;**353**:1959-1964

[20] Melzack R, Wall PD. Pain mechanisms: A new theory. Science. 1965;**150**(3699):971-979

[21] Shealy S, Mortimer JT, Reswick JB. Electrical inhibition of pain by stimulation of the dorsal columns: Preliminary clinical report. Anesthesia and Analgesia. 1967;**46**:489-491

[22] Levy RM. Deep brain stimulation for the treatment of intractable pain. Neurosurgery Clinics of North America. 2003;**14**:vi

[23] Boccard SG, Pereira EA, Aziz TZ. Deep brain stimulation for chronic pain. Journal of Clinical Neuroscience. 2015;**22**(10):1537-1543

[24] Lefaucher JP, Antal A, Ahdab R, Ciampi de Andrade D, Fregni F, Khedr EM, et al. The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (TDCS) to relieve pain. Brain Stimulation. 2008;**1**:337-344

[25] Tsubokawa T, Katayama Y, Yamamoto T, Hirayama T, Koyama S. Treatment of thalamic pain by chronic motor cortex stimulation. Pacing and Clinical Electrophysiology. 1991;**14**:131-134

[26] Nguyen JPM, Lefaucheur JPM, Keravel YM. Motor cortex stimulation. In: Simpson BA, editor. Electrical Stimulation and the Relief of Pain Research and Clinical Management. p. 152003

[27] Nardone R, Holler Y, Leis S, Holler P, Thon N, Thomschewski A, et al. Invasive and non-invasive brain stimulation for treatment of neuropathic pain in patients with spinal cord injury: A review. The Journal of Spinal Cord Medicine. 2014;**37**(1)

[28] Barthelemy EJ, Rasouli JJ, Yaeger KA, Kopell BH. Functional magnetic resonance imaging in the neuromodulation of pain. In: Krames ES, Hunter Peckham P, Rezai AR, editors.

Neuromodulation Comprehensive Textbook of Principles, Technologies and Therapies. 2. London, UK: Academic Press; 2018

[29] Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. European Journal of Pain. 2005;**9**:463-484

[30] Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. The Journal of Neuroscience. 2004;**24**(46):10410-10415

[31] Seminowicz DA, Wideman TH, Naso L, Hatami-Khoroushahi Z, Fallatah S, Ware MA, et al. Effective treatment of chronic low back pain in humans reverses abnormal brain anatomy and function. The Journal of Neuroscience. 2011;**31**(20):7540-7550

[32] Ruscheweyh R, Deppe M, Lohmann H, Stehling C, Floel A, Ringelstein EB, et al. Pain is associated with regional grey matter reduction in the general population. Pain. 2011;**152**(4):904-911

[33] Gonzalez-Garcia N, Armory JL, Soto J, Trejo D, Alegria MA, Drucker-Colin R. Effects of rTMS on Parkinson's disease: A longitundinal fMRI study. Journal of Neurology. 2011;**258**:1268-1280

[34] Pascual-Leone A, Walsh V, Rothwell J. Transcranial magnetic stimulation in cognitive neuroscience–virtual lesion, chronometry, and functional connectivity. Current Opinion in Neurobiology. 2000;**10**(2):232-237

[35] Mylius V, Borckardt JJ, Lefaucheur JP. Noninvasive cortical modulation of experimental pain. Pain. 2012;**153**:1250-1263

[36] Frohlich F, Sellers KK, Cordle AL. Targeting the neurophysiology of cognitive systems with transcranial alternating current stimulation. Expert review of neurotherapeutics. 2015;**15**(2):145-167

[37] Angelakis E, Liouta E, Andreasdis N, Leonardos A, Ktonas P, Stavrinou LC, et al. Transcranial alternating current stimulation reduces symptoms in intractable idiopathic cervical dystonia: A case study. Neuroscience Letters. 2013;**533**:39-43

[38] Nizard J, Lefaucheur JP, Helbert M, de Chauvigny E, Nguyen JP. Non-invasive stimulation therapies for the treatment of refactory pain. Discovery Medicine. 2012;**14**:21-31

[39] Epstein CM, ed. TMS stimulation coils; 2008

[40] Summers J, Johnson S, Pridmore S, Oberoi D. Changes to cold detection and pain thresholds following low and high frequency transcranial magnetic stimulation of the motor cortex. Neuroscience Letters. 2004;**368**(2):197-200

[41] Pascual-Leone A, Walsh V, Rothwell J. Transcranial magnetic stimulation in cognitive neuroscience - virtual lesion, chronometry and functional connectivity. Current Opinion in Neurobiology. 2000;**10**:232-237

[42] Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology. 2000; **111**(5):800-805

[43] O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. The Cochrane database of systematic reviews. 2014;**4**: Cd008208

[44] Zaghi S, Heine N, Fregni F. Brain stimulation for the treatment of pain: A review of costs, clinical effects, and mechanisms of treatment for three different central neuromodulatory approaches. Journal of Pain Mangement. 2009;**2**(3):339-352

[45] Lemon RN. Descending pathways in motor control. Annual Review in Neuroscience. 2008;**11**:195-218

[46] DosSantos MF, Love TM, Martikainen IK, Nascimento TD, Fregni F, Cumminford C, et al. Immediate effects of tDCS on the opiod system of a chronic pain patient. Frontiers in Psychiatry. 2012;**3**:93

[47] Lefaucher JP, Drouot X, Menard-Lefaucheur I, Keravel Y, Nguyen JP. Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. Neurology. 2006;**14**(6):1568-1574

[48] Saitoh Y, Hosomi K, Kishima H, Goto T, Yoshimine T. Repetitive transcranial magnetic stimulation (rTMS) for neuropathic pain. Clinical Neurophysiology. 2010;**121**(1):22

[49] Ciampi de Andrade D, Mhalla A, Adam F, Texeira MJ, Bouhassira D. Repetitive transcranial magnetic stimulation induced analgesia depends on N-methyl-d-aspartate glutamate receptors. Pain. 2014;**155**(3):598-605

[50] Taylor J, Borckardt JJ, George MS. Endogenous opiods mediate left dorsolateral prefrontal cortex rTMS induced analgesia. Pain. 2012;**153**:1219-1225

[51] Krummenacher P, Candia V, Folkers G, Schedlowski M, Schoenbaechler G. Prefrontal cortex modulates placebo analgesia. Pain. 2010;**148**(3):368-374

[52] Lorenz J, Minoshima S, Casey KL. Keeping pain out of mind: The role of the dorsolateral prefrontal cortex in pain modulation. Brain. 2003;**126**:1079-1091

[53] Wagner J, Rilling E, Smith A, Sokolik K, Casey R, Davidson S, et al. Placebo induced changes in fMRI in the anticipation and experience of pain. Science. 2004;**303**:1162-1167

[54] Hardy SG, Haigler HJ. Prefrontal influences upon the midbrain: A possible route for pain modulation. Brain Research. 1985;**339**(2):285-293

[55] Wiech K, Kalisch R, Weiskopf N, Pfleger B, Stephan KE, Dolan RJ. Anterolateral prefrontal cortex mediates the analgesic effect of expected and perceived control over pain. The Journal of Neuroscience. 2006;**26**(44):11501-11509

[56] Ong W-Y, Stohler CS, Herr DR. Role of the prefrontal cortex in pain processing. Molecular Neurobiology. 2018

[57] Borckardt JJ, Reeves ST, Weinstein M, Smith A, Shelley N, Kozel FA. Fifteen minutes of left prefrontal repetitive transcranial magnetic stimulation acutely increases thermal pain thresholds in healthy adults. Pain Research and Management. 2007;**12**:287-290

[58] Stagg CJ, Lin RL, Mezue M, Segerdahl A, Kong Y, Xie J, Tracey, I. Widespread modulation of cerebral perfusion induced during and after transcranial direct current stimulation applied to the left dorsolateral prefrontal cortex. The Journal of Neuroscience. 2013; **33**(28):11425-11431

[59] Benedetti F, Pollo A, Maggi G, Vighetti S, Rainero I. Placebo analgesia: From physiological mechanisms to clinical implications. In: Dostrovsky J, Carr D, Koltzenburg M, editors. Progress in Pain Research and Management. Seattle: IASP Press; 2003. pp. 315-323

[60] Petrovic P, Kalso E, Petersson KM, Ingvar M. Placebo and opioid analgesia-- imaging a shared neuronal network. Science. 2002;**295**(5560):1737-1740

[61] Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. Journal of Physiology. 2000;**527**(3):633-639

[62] Dayan E, Censor N, Buch ER, Sandrini M, Cohen LG. Noninvasive brain stimulation: From physiology to network dynamics and back. Nature Neuroscience. 2013;**16**:838-844

[63] Ruohonen J, Karhu J. tDCS possibly stimulates glial cells. Clinical Neurophysiology. 2012;**123**:2006-2009

[64] Liebetanz D, Nitsche MA, Tergau F, Paulus W. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. Brain. 2002;**125**:2238-2247

[65] Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. The Journal of Physiology. 2003;**553**(Pt 1):293-301

[66] Stagg CJ, Bestmann S, Constantinescu AO, Moreno LM, Allman C, Mekle R, et al. Relationship between physiological measures of excitability and levels of glutamate and GABA in the human motor cortex. Journal of Physiology. 2011;**589**:5845-5855

[67] Stagg CJ, Best JG, Stephenson MC, O'Shea J, Wylezinska M, Kincses ZT, et al. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. The Journal of Neuroscience. 2009;**29**(16):5202-5206

[68] Stagg CJ, Bestmann S, Constantinescu AO, Moreno LM, Allman C, Mekle R, et al. Relationship between physiological measures of excitability and levels of glutamate and GABA in the human motor cortex. The Journal of Physiology. 2011;**589**(Pt 23):5845-5855

[69] Kronberg G, Bridi M, Abel T, Bikson M, Parra LC. Direct current stimulation modulates LTP and LTD: Activity dependence and dentritic effects. Brain Stimulation. 2017;**10**(1):51-58

[70] Abdel-Nasser AM, El-Azim SA, Taal E, El-Badawy SA, Rasker JJ, Valkenburg HA. Depression and depressive symptoms in rheumatoid arthritis patients: An analysis of their occurrence and determinants. British Journal of Rheumatology. 1998;**37**(4):391-397

[71] Alam M, Truong DQ, Khadka N, Bikson M. Spatial and polarity precision of concentric high-definition transcranial direct current stimulation (HD-tDCS). Physics in Medicine and Biology. 2016;**61**:4506-4521

[72] Borckardt JJ, Bikson M, Frohman H, Reeves ST, Data A, Bansal V, et al. A pilot study of the tolerability and effects of high-definition transcranial direct current stimulation (HD-tDCS) on pain perception. The Journal of Pain. 2012;**13**:112-120

[73] Kuo H-I, Bikson M, Data A, Minhas P, Paulus W, Kuo M-F, et al. Comparing cortical plasticity induced by conventional and high definition 4X1 ring tDCS: A neurophysiological study. Brain Stimulation. 2013;**6**:644-648

[74] Sacco P, Prior M, Poole H, Nurmikko T. Repetitive transcranial magnetic stimulation over primary motor vs non-motor targets; effects on experimental hyperalgesia in healthy subjects. BMC Neurology. 2014;**14**:166

[75] O'Connell NE, Wand BM, Marston L, Spencer S, Desouza LH. Non-invasive brain stimulation techniques for chronic pain. Cochrane database systematic review. 2014; **4**:CD008204

[76] Boggio PS, Zaghi S, Lopes M, Fregni F. Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. European Journal of Neurology. 2008;**15**:1124-1130

[77] Pleger B, Jansenn F, Schwenkreis P, Volker B, Maier C, Iegenthoff M. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. Neuroscience Letters. 2004;**356**:87-90

[78] de Andrade DC, Mhalla A, Adam F, Texeira MJ, Bouhassira D. Neuropharmacological basis of rTMS induced analgesia: The role of endogenous opiods. Pain. 2011:320-326

[79] Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, et al. Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: Evidence for homeostatic plasticity in the human motor cortex. The Journal of Neuroscience. 2004;**24**(13):3379-3385

[80] Vines BW, Cerruti C, Schlaug G. Dual-hemisphere tDCS facilitates greater improvements for healthy subjects' non-dominant hand compared to uni-hemisphere stimulation. BMC Neuroscience. 2008;**9**

[81] Siebner HR, Lang N, Rizzo V, Nitsche MA, Paulus W, Lemon RN, et al. Preconditioning of low-frequency repetitive transcranial magnetic stimulation with transcranial direct current stimulation: Evidence for homeostatic plasticity in the human motor cortex. The Journal of Neuroscience. 2004;**24**:3379-3385

[82] Turrigiano GG, Nelson SB. Hebb and homeostasis in neuronal plasticity. Current Opinon in Neurobiology. 2000;**10**:358-364

[83] Moloney TM, Witney AG. Transcranial direct current stimulation (tDCS) priming of 1Hz repetitive transcranial magnetic stimulation (rTMS) modulates experimental pain thresholds. Neuroscience Letters. 2013;**534**:289-294

[84] Moloney TM, Witney AG. Pressure pain thresholds increase after preconditioning 1 Hz repetitive transcranial magnetic stimulation with transcranial direct current stimulation. PLoS One. 2014;**9**:e92540

[85] Kessler SK, Minhas P, Woods AJ, Rosen A, Gorman C, Bikson M. Dosage considerations for transcranial direct current stimulation in children: A computational modelling study. PLoS One. 2013;**8**(9):e76112

[86] Rawji V, Ciocca M, Zacharia A, Soares D, Truong D, Bikson M, et al. tDCS changes in motor excitability are specific to orientation of current flow. Brain Stimulation. 2018;**11**(2):289-298

[87] Casula EP, Rocchi L, Hannah R, Rothwell JC. Effects of pulse width, waveform and current direction in the cortex: A combined cTMS-EEG study. Brain Stimulation. 2018:1-8

[88] Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, Lamy C, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): A randomised placebo controlled trial. Lancet Neurology. 2011;**10**(3):205

[89] Wiethoff S, Hamada M, Rothwell JC. Variability in response to transcranial direct current stimulation of the motor cortex. Brain Stimulation. 2014;**0**

[90] Minhas P, Bansal V, Patel J, Ho JS, Diaz J, Datta A, et al. Electrodes for high-definition transcutaneous DC stimulation for applications in drug delivery and electrotherapy, including tDCS. Journal of Neuroscience Methods. 2010;**190**:188-197

[91] Bachmann CG, Muschinsky S, Nitsche MA, Rolke R, Magerl W, Treede RD, et al. Transcranial direct current stimulation of the motor cortex induces distinct changes in thermal and mechanical sensory percepts. Clinical Neurophysiology. 2010;**121**:2083-2089

[92] Leo RJ, Latif T. Repetitive transcranial magnetic stimulation (rTMS) in experimentally induced and chronic neuropathic pain: A review. The journal of pain: official journal of the American Pain Society. 2007;**8**(6):453-459

[93] Nahman-Averbuch H, Martucci KT, Granovsky Y, Weissman-Fogel I, Yarnitsky D, Coghill RC. Distinct brain mechanisms support spatial vs temporal filtering of nociceptive information. Pain. 2014;**155**:2491-2501

[94] Tamura Y, Hoshiyama M, Inui K, Nakata H, Qiu Y, Ugawa Y, et al. Facilitation of a delta-fiber-mediated acute pain by repetitive transcranial magnetic stimulation. Neurology. 2004;**62**(12):2176-2181

[95] Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K. Millisecond-timescale, genetically targeted optical control of neural activity. Nature Neuroscience. 2005;**8**:1263-1268

[96] Boyden ES. A history of optogenetics: The development of tools for controlling brain circuits with light. F1000 Biol Rep. 2011

[97] Lee M, Manders TR, Eberle SE, Su C, D'amour J, Yang R, et al. Activation of corticostriatal circuitry relieves chronic neuropathic pain. The Journal of Neuroscience. 2015;**35**(13):5247-5259

[98] Delbeke J, Hoffman L, Mols K, Braeken D, Prodanov D. And then there was light: Perspectives of Optogenetics for deep brain stimulation and Neuromodulation. Frontiers in Neuroscience. 2017;**11**:663

Chapter 8

Chronic Headache and Neuromodulation

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.72150

Abstract

The immense majority of patients with chronic headaches can be controlled with medical treatments. However, there is a subset of them with poor response, and it is for those patients that new therapeutic strategies are being designed. Neuromodulation has been used for chronic pain management in many areas for the past 50 years. The application of these techniques to the treatment of the most refractory chronic headache disorders has offered hope to these patients. There is a large variety of different techniques, each of them particularly suitable to specific types of chronic headaches. The surgically implanted devices are still in use in some particularly recalcitrant cases. Nevertheless, new percutaneous devices allow new treatment strategies. Percutaneous devices do not always show the same effectivity as surgically implanted stimulating devices, but they are user friendly and have no serious adverse effects. Thus, they are becoming the treatment of choice once the pharmacological means are no longer effective. In case of failure, the surgical procedures would still be available as a last resort.

Keywords: chronic headache, chronic migraine, cluster headache, neuromodulation, neurostimulation

1. Introduction

Chronic headache is one of the most frequent pain syndromes, affecting 3% of the population. It can be rather disabling [1, 2], particularly for young people who are most affected by it. The International Classification of Headache subdivides headaches into 300 different entities [3], each of those with a different pathophysiology and involving different anatomical structures. Pain can originate from the central nervous system, the cranium or the cervical area [4].

Primary headaches like tension headache, migraine (CM) or trigeminal autonomic cephalagias (TACs) show the highest incidence. TACs are particularly incapacitating [5]. Most cases can be controlled with medication and physiotherapy. Abuse of medication is common with these patients, via the dose, the drugs or both [6]. When the pharmacological and conservative treatments fail, surgery may be considered. In the past, ablative surgical techniques have been applied. These techniques have been replaced by neuromodulation techniques. In them, the anatomical structures are not lesioned, but instead, the electric impulses block the nervous structures in a reversible fashion [7]. These techniques can be subdivided into two broad categories: noninvasive and invasive [1]. The noninvasive options include transcranial stimulation either electric [8–10] or magnetic [11–13] and transdermal stimulation of occipital [14, 15], supraorbital [9, 14–19] or vagus [20–23] nerves. Invasive procedures include stimulation of occipital [5, 17, 24, 25–35], supraorbital [19, 31, 36], infraorbital [31] or greater auricular [37] nerves as well as sphenopalatine ganglion [38–44], cervical spinal cord [45–48] or hypothalamus [4, 25, 27, 49–52].

Noninvasive neuromodulation techniques are user friendly and have low costs and few and minor side effects [8–15, 19–23]. Unfortunately, their effectivity is lower than their invasive counterparts. Invasive neuromodulation is reserved for the most refractory cases, as they are associated with increased aggressiveness, more severe adverse events (AE) and higher costs [7].

All costs have to be taken into consideration. The full cost of neuromodulation would include the disability grants, as well as further possible treatments for AEs [33, 34, 53].

Taking the net expenditure into consideration, some have reported that the reductions in cost are evident at 5-year postimplantation [53]. In any case, invasive neuromodulation must only be used in the most refractory cases and only after all other medical and noninvasive treatments have failed [46]. This is particularly important due to the high incidence of AEs and the possibility of new surgical procedures to solve them [29, 33]. A trial of temporary stimulation is required to evaluate the possible response of a definitive implant [45, 46, 54] to avoid wasting time and resources.

These techniques present promising new treatment strategies. The available evidence will be analysed, describing the possible future trends.

2. Historical aspects of neuromodulation

Electricity to treat chronic headaches was first used in ancient Rome [55], but it was not until the 1950s that neuromodulation was used in the treatment of chronic pain disorders [55, 56]. Thalamic stimulation to treat chronic headaches was introduced in 1976 [57] and percutaneous peripheral nerve stimulation a year later [58]. At the beginning of the 1990s, hypothalamic deep brain stimulation (hDBS) was applied to the treatment of some chronic headache syndromes and particularly in TACs [59]. The first report of occipital nerve stimulation (ONS) to treat occipital neuralgia was in 1999 [60]. In the year 2000, the hypothalamic stimulation was applied in the treatment of drug-resistant cluster headache (CH) [61]. The first two cases of supraorbital nerve stimulation (SONS) were reported in 2002 [62]. The first cases of hDBS in the treatment of CH were reported in 2003 [61]. In 2004, the ONS was applied in the treatment

of CM [63]. The first case reported with cervical spinal stimulation (SCS) in the treatment of CH was in 2008 [64]. The first report on stimulation of the sphenopalatine ganglion was presented at 2009 [38]. Ever since, there has been an explosion of reports on the effectiveness, indications and AEs of all these techniques. Simultaneously new devices that allow percutaneous stimulation have reached the market, allowing new solutions to old problems.

3. Indications for neuromodulation

The first step is to diagnose the patient and select an appropriate treatment by an experienced team that is familiarised with all available treatments. Neuromodulation techniques are indicated in cases that have failed all other medical treatments available for this specific headache type. It is also recommended that patients receive a psychological assessment.

The next step is to attempt noninvasive neuromodulation techniques particularly useful in this type of chronic headache. Should all fail, a period of temporary trial stimulation is suitable [33]. Patients showing no response are not implanted and are redirected to other forms of treatment. This temporary stimulation also helps to predict the results to be expected if the definitive implant is attempted [32, 46].

4. Classification of the different techniques

4.1. Noninvasive procedures

4.1.1. Transcranial electric stimulation (TES)

This technique involves applying a low amperage continuous electric stimulation directly to the scalp [10]. In most cases, the electric stimulus spreads out of the area covered by the electrodes [10]. AEs have been moderate, such as skin burns due to inadequate electrode skin contact, fatigue or local prickling and burning sensation during the stimulation [8, 10]. Its effectivity and experience are limited [8, 10].

4.1.2. Transcranial magnetic stimulation (TMS)

A magnetic field is applied to the head, inducing depolarization and electrical activity of the underlying brain cortex [65, 66]. Most have applied it to the left frontal motor area [11, 67, 68], but some have done it to the occipital region, particularly in migraine patients [69]. In chronic headache related to mild posttraumatic head injury (MTHI-H), it has shown ≥50% improvement in pain intensity and frequency in 58.3% of the patients [11]. In migraine, some have reported a reduction of 31.2% in pain frequency and 37.8% in attack duration [70] in two-third of the patients [66]. The acute variant, with or without aura, seems to have a better response than the chronic one [67–72]. There seems to be a cumulative effect, so that the longer this treatment modality is applied, the greater is the attack duration reduction [69]. In migraine

patients, a randomised study comparing transcranial magnetic stimulation versus placebo showed a 76.6% versus 27.1% pain improvement [75], but these data were not confirmed by others [68]. Another study in this same disease compared this treatment modality with botulinum toxin injection, finding that although both treatment modalities provide pain relief, the last one is more effective [76]. In atypical facial pain, trigeminal neuropathic pain and cluster headache, it has shown ≥30% pain reduction in 73% of the patients [77]. Interestingly, enough older age and longer treatment duration were associated with a better response, while the type of facial pain showed little influence [77]. It has been applied to pregnant migraine patients with no untoward side effects [69]. Complications are rare and include a case of induced trigeminal autonomic cephalalgia that ceased after stopping the transcranial magnetic stimulation [78]. Some patients have reported transient drowsiness [75]. A continuous application is required for the effects to be persistent [69].

4.1.3. Transcutaneous supraorbital-supratrochlear stimulation

This technique involves a special equipment that looks like a pair of glasses, which has to be worn on the forehead. It provides a 50% chronic headache pain reduction, including CM [14, 16, 18]. When used for CM prevention, it reduces the number of attacks but not their intensity [16, 18]. In episodic CM, patients induced a 50% headache frequency reduction in 38.2% of the patients [18]. Although not very effective, the only side effects are local discomfort, redness or temporary skin irritation [16].

4.1.4. Transcutaneous vagus nerve stimulation (VNS)

The first reports entailed electrodes implanted surgically around the vagal nerve in the neck [79]. However, it never gained acceptance because the procedure was invasive and the results are limited. In 2013, a percutaneous VNS device was introduced, showing promising results in the treatment of chronic CM (CM) [20, 23]. Its best advantage is that it is applied directly to the neck by the patient him/herself [21, 23]. Its main drawback is its low effectiveness (22%) [22, 23, 80]. It is well tolerated with minor side effects like neck twitching, raspy voice or redness at the application site [22, 23, 81].

In CH, it is helpful in the episodic but not in the chronic type [80, 81]. In the episodic type, it induces a positive response in 26.7% of the cases [80]. Some have used it in the acute treatment of the chronic variant of this disease with a higher than 50% pain reduction in 40% of the patients [81]. In CM, it provides a 50% or more pain reduction in 22–56.3% of the patients, which is better in the episodic than in chronic variant [20, 22, 82]. It has been helpful in a single case of hemicrania continua (HC) unresponsive to indomethacin [83].

4.2. Invasive procedures

4.2.1. Sphenopalatine ganglion stimulation (SPGS)

The sphenopalatine ganglion has been a target in the treatment of chronic headaches for over a century. Initially, destructive lesions were applied [84], but since 2009, neuromodulation is also available [38]. It is effective in two thirds of episodic CH cases, preventing at least 50% of attacks, showing a decrease in intensity of at least 50% or both [38, 41–43, 73, 74].

SPGS is both preventive and therapeutic in acute phases [85, 87]. About 30% of the patients can stop the medication [85, 87]. A transoral technique has been described with a remote powering system that avoids extension leads and the need to replace the batteries [86], where patients switch-on the stimulation with a handheld remote controller when the pain attack starts [85]. This markedly reduces the incidence of AEs [86]. Some patients use the stimulation continuously to reduce the attack incidence [85]. Bilateral stimulation is more effective than unilateral [39], but it is not so effective in the chronic variant of this disease [85]. AEs are uncommon and mild, including sensory loss in the maxillary region (81%) [87], that may last over 1 year (2–28%), epistaxis (13%), facial numbness (25%), and local pain (4%) [86]. SPGS has also been used successfully in CM [44].

4.2.2. Occipital nerve stimulation (ONS)

ONS is the stimulation of the distal branches of C_2 and C_3 nerve roots (greater and lesser occipital nerves). The electrodes (one at each side) can be inserted either through a 2 cm midline skin incision at C_1 level and tunnelled subcutaneously through a bent Touhy needle inserted laterally from the mastoid area or alternatively from a lateral approach with a bilateral mastoid area skin incision and the electrodes inserted from a lateral to medial direction with the Touhy needle [14, 60, 88]. As ONS only covers 85% of the head leaving the forehead uncovered, some have combined it with SONS [15, 89, 90]. Percutaneous ONS is recommended to foresee the results of a permanent implantation [91]. In any case, a temporary external stimulation must be performed before definitive implantation [35]. Those with no positive response are referred to other treatment modalities.

ONS has been used in chronic CH [5, 24–26, 28, 29, 32–35, 40], CM [29, 32, 33], TACs [5], hypnic headache (happening regularly sleep) [92], SUNCT/SUNA [93, 94], and occipital neuralgia [32]. In chronic CH, it reduces the attack incidence in over 50% in 70% of patients [5, 24, 25, 28, 33, 40]. In CM, its average success rate is 65.4% in 67.9–80% of the cases [29, 95]. In SUNCT/SUNA, bilateral ONS induced a 69% pain improvement in 77% of the patients [93, 94]. In idiopathic intracranial hypertension, it has been used to treat the associated headache and the residual headache once the intracranial hypertension is resolved, with higher than 75% pain improvement [89], but it requires bilateral stimulation [89].

AEs plague 33–70% of the cases [24, 25, 29, 33, 96]. Among them are lead erosion [19, 89], local infection [29, 33], electrode emigration [96, 97], lead breakage [28, 30, 33], hardware-related discomfort [98], hardware/stimulation dysfunction [25], and early battery depletion related to high energy consumption [25, 33]. Some technical modifications have been devised to reduce the chance of lead migration [97] that in some series reaches 24% [99]. These include using silicone glue with silicone anchors [100], 2-point anchoring stimulator leads with a tension-relief loop [26], narrow paddle electrodes [101] and to insert the impulse generator as close as possible to the leads (i.e., supraclavicular area) [96]. Unfortunately, solving the AE entails additional surgical procedures in 26–40.7% of the cases [25, 29].

Simultaneous ONS and SONS in CH provide more than 50% pain reduction in over 70% of patients [14]. This dual stimulation has also been successful in HM [15] and TACs [19]. Although the results are promising, the number of cases is too small to draw any statistically significant conclusions.

4.2.3. Great auricular nerve stimulation (GANS)

Pain relief was reported using this technique in a single case of persistent MTHI-Ha 90% [37]. Further studies are needed.

4.2.4. Supraorbital nerve stimulation (SONS)

The first case was reported in 2009 in the treatment of CH [36]. In this disorder, SONS produced more than 50% pain reduction in 71% of the patients [19, 36, 90]. In a series of five patients with TACs, it improved the pain in all of them, but the series is too short to draw any conclusions [19]. It can be used alone or associated with ONS [14, 15, 19, 90].

4.2.5. Cervical spinal cord stimulation (SCS)

The electrode is introduced in the epidural space at the upper thoracic level and advanced to the cervical spinal cord until its distal tip is at the C_2 level. One or two electrodes are inserted. The leads are connected to a subcutaneous impulse generator inserted at the infraclavicular area [46].

SCS has been used in CM [46, 47], SUNA [54], CH [45, 64], and MTBI-HA [48], reducing the headache frequency and/or intensity by ≥50% in 71% of the patients [45–47]. In CM, it improves the headache by >30% in 50% of the cases [46, 47, 102]. The AEs are frequent (71%) and usually require system explant and replacement in a second surgery [102]. Among these AEs are infections (13%) and lead rupture or migration (17%) [45–47, 89].

4.2.6. Hypothalamic deep brain stimulation (hDBS)

hDBS was introduced in 2000 to treat drug-resistant CH [61]. It is useful in many types of chronic headache disorders like HC, CH, SUNCT/SUNA, and in TACs [4, 50]. In chronic CH, it results in reduction of ≥50% of the attacks in 60% of the patients [5, 40, 50, 52]. The response rate in HC and SUNA is 82% [49]. In TACSs, the improvement rate is >50% in 69.9% of patients [50].

AEs include incision site pain, subcutaneous dislodgement of the impulse generator, transient gaze disturbance (oscillopsia, diplopia), autonomic disturbances, myosis, dizziness, wound infection, cervical dystonia, intracranial haemorrhage, and lead disconnection or rupture [40, 49, 52]. Many of these complications require system explant [49]. hDBS is reserved for those very few cases, in which everything else has failed as death has been reported [50].

The target was initially in the posterior hypothalamus [103, 104], but other areas have also been used like the mesencephalic grey substance, the red nucleus, the fasciculus retroflexus, the dorsal longitudinal fasciculus, the ansa lenticularis, the medial longitudinal fasciculus or the medial thalamus superficialis [104]. In the latest years, the ventral tegmental area is used to decrease the chance of haemorrhages [49, 52].

http://dx.doi.org/10.5772/intechopen.72150

5. Indications and results for specific chronic headache disorders

5.1. Cluster headache (CH)

CH consists of bouts of unilateral periorbital pain lasting between 15 minutes and 3 hours that follow an annual pattern [105]. It is considered as the most painful headache type, with 0.12% prevalence. About 10% of the cases cannot be controlled with medical treatment [34]. CH has two variants: chronic and episodic [106]. In the episodic, headache periods alternate with others of remission, and the attacks last between 7 days and 1 year with a pain free period lasting at least 1 month [105]. The chronic variant represents 10–15% of the cases [34, 86] and has free pain periods shorter than 1 month or attacks that are present nonstop through at least 1 year [105].

Percutaneous VNS has been used in the acute treatment of the chronic variant of CH with a higher than 50% pain reduction in 40% of the patients [33, 42, 81, 107]. Although not universally effective, it is minimally invasive and with very minor and reversible AEs.

Both ONS [25, 26, 34] and SPGS [40–43, 73] are the first options among the invasive techniques [5, 86]. About 70% of patients respond to these treatments with 48% of excellent responders [25, 34]. ONS together with SONS has been applied with >50% pain reduction in 71% of the patients [90]. Cervical SCS has also been used with some success [102]. hDBS should be left as the very last resource as its complications are more severe and potentially life threatening [5, 52].

5.2. Hemicrania continua (HC)

It is a continuous and unilateral headache (it only affects one side of the head), associated autonomic symptoms and episodes of increased headache intensity [105]. Indomethacin is the drug of choice, but some patients do not tolerate it due to side effects like hypertension, gastrointestinal problems (particularly when combined with aspirin), vascular events, or bronchial spasms [83]. In a single case, it was found to respond to noninvasive percutaneous VNS [83]. Others tried repetitive sphenopalatine ganglion block [108]. The data are not statistically significant, and no definite conclusions can be drawn.

5.3. Chronic migraine (CM)

CM is described as having migraine headaches 15 or more days in every month [99]. Worldwide, it is the seventh cause of disability [109]. It affects 2–5% of the adult population [3, 105, 110].

The transcranial stimulation has contradictory results, so no recommendations can be offered [9]. The cervical percutaneous VNS shows promising but moderate results, better in the episodic than in chronic variant [20, 111]. Transcutaneous SONS reduces the number of attacks but not its intensity [18, 111]. Much more efficient is the ONS via implanted electrodes [5, 24, 29, 46], with a success rate of 65.4% in 67.9–80% of the cases [29, 95].

Unfortunately, 70% of the patients suffer AEs, 40.7% of which require a new surgical procedure [29]. Some have combined the ONS with the SONS with ≥50% pain reduction in >70% of the patients [14]. The SCS has also been applied with 30% pain reduction in 50% of the cases [46].

5.4. Hemiplegic migraine

It is a very severe migraine variant, refractory to most known therapies and that often evolves to a very debilitating state. It has been treated with combined SONS and ONS with a 92% average decrease in the number of attacks [15]. The number of cases is limited, so further studies are needed.

5.5. Trigeminal autonomic cephalalgias (TACs)

TAC is a group of headache disorders characterised by unilateral headache accompanied by cranial autonomic symptoms. Although SONS has been attempted [19], ONS is the first option [27], reserving the hDBS to the most recalcitrant cases [49, 50, 52].

5.6. Short-lasting unilateral Neuralgiform headache attacks with autonomic symptoms (SUNA) and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)

These consist of primary headache attacks associated with cranial autonomic dysfunction. In refractory cases, bilateral ONS induced a 69% pain improvement in 77% of the patients [93, 94]. Deep brain ventral tegmental area stimulation achieved a 78% headache rate improvement in almost all patients but with frequent AEs that at times required to explant the system [49].

5.7. Mild traumatic head injury-related headache (MTHI-H)

MTHI-H represents about 4% of the chronic headaches [112]. Transcranial magnetic stimulation has shown a 57% improvement in the intensity and frequency in this disorder [11–13]. SCS or GANS [37] stimulation has been used, stimulating the left prefrontal cortex [11]. In both cases, there was a 90% headache frequency reduction. Unfortunately, only two case reports exist, and no conclusions can be drawn.

6. Availability and usefulness of ambulatory techniques that can be practiced at home

All noninvasive procedures can be safely practiced at home. Their only drawback is low effectiveness, but they induce no harm in those in whom no beneficial results are obtained. Further studies are necessary. The AEs are minor and completely reversible once the device is no longer used. The biggest problem may arise from the economical point of view, as health providers could choose not to pay for treatments that show moderate response.

7. Conclusions

Although the immense majority of chronic headache disorders can be controlled with pharmacological means, there is a subset of patients that are refractory to all of them. A thorough diagnosis of the specific headache subtype is essential to provide an effective treatment. For those few refractory patients to the current available drugs, there are other treatment possibilities. We have now a wide array of noninvasive techniques that can be tried as a first attempt. In case of failure, surgically implanted stimulating systems can be of help. We should choose the more suitable option to the specific headache variant, keeping in mind the effectivity possible incidence of AEs of each treatment. hDBS should be considered the very last resource, as it is associated with some serious AEs and potentially to death.

Appendices and nomenclatures

AE	Adverse event
CH	Cluster headache
CM	Chronic migraine
GANS	Great auricular nerve stimulation
HC	Hemicrania continua
hDBS	Hypothalamic deep brain stimulation
HM	Hemiplegic migraine
MTHI-H	Mild traumatic head injury-related headache
ONS	Occipital nerve stimulation
SCS	Spinal cord stimulation
SONS	Supraorbital nerve stimulation
SPGS	Sphenopalatine ganglion stimulation
SUNA	Short-lasting unilateral neuralgiform headache attacks with autonomic symptoms
SUNCT	Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
TACs	Trigeminal autonomic cephalagias
TMS	Transcranial magnetic stimulation
tSNS	Noninvasive transcutaneous supraorbital neurostimulation
VNS	Vagus nerve stimulation

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References

[1] Leone M, Cecchini AP. Central and peripheral neural targets for Neurostimulation of chronic headaches. Current Pain and Headache Reports. 2017 Mar;**21**(3):16

[2] Schuster NM, Rapoport AM. New strategies for the treatment and prevention of primary headache disorders. Nature Reviews. Neurology. 2016 Oct 27;**12**(11):635-650

[3] Lipton RB. Chronic migraine, classification, differential diagnosis, and epidemiology. Headache. 2011 Aug;**51**(Suppl 2):77-83

[4] Altinay M, Estemalik E, Malone DA. A comprehensive review of the use of deep brain stimulation (DBS) in treatment of psychiatric and headache disorders. Headache. 2015 Feb;**55**(2):345-350

[5] Láinez MJ, Guillamón E. Cluster headache and other TACs: Pathophysiology and neurostimulation options. Headache. 2017 Feb;**57**(2):327-335

[6] Hsu ES. Medication overuse in chronic pain. Current Pain and Headache Reports. 2017 Jan;**21**(1):2

[7] Puledda F, Goadsby PJ. An update on non-pharmacological Neuromodulation for the acute and preventive treatment of migraine. Headache. 2017 Apr;**57**(4):685-691

[8] Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, Cohen LG, Dowthwaite G, Ellrich J, Flöel A, Fregni F, George MS, Hamilton R, Haueisen J, Herrmann CS, Hummel FC, Lefaucheur JP, Liebetanz D, Loo CK, McCaig CD, Miniussi C, Miranda PC, Moliadze V, Nitsche MA, Nowak R, Padberg F, Pascual-Leone A, Poppendieck W, Priori A, Rossi S, Rossini PM, Rothwell J, Rueger MA, Ruffini G, Schellhorn K, Siebner HR, Ugawa Y, Wexler A, Ziemann U, Hallett M, Paulus W. Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology. 2017 Jun 19

[9] Schoenen J, Roberta B, Magis D, Coppola G. Noninvasive neurostimulation methods for migraine therapy: The available evidence. Cephalalgia: An International Journal of Headache. 2016 Mar 29

[10] DaSilva AF, Truong DQ, DosSantos MF, Toback RL, Datta A, Bikson M. State-of-art neuroanatomical target analysis of high-definition and conventional tDCS montages used for migraine and pain control. Frontiers in Neuroanatomy. 2015;**9**:89

[11] Leung A, Metzger-Smith V, He Y, Cordero J, Ehlert B, Song D, Lin L, Shahrokh G, Tsai A, Vaninetti M, Rutledge T, Polston G, Sheu R, Lee R. Left dorsolateral prefrontal cortex rTMS in alleviating MTBI related headaches and depressive symptoms. Neuromodulation Journal of International Neuromodulation Society. 2017 May 30

[12] Leung A, Fallah A, Shukla S, Lin L, Tsia A, Song D, Polston G, Lee R. rTMS in alleviating mild TBI related headaches–a case series. Pain Physician. 2016 Feb;**19**(2):E347-E354

[13] Leung A, Shukla S, Fallah A, Song D, Lin L, Golshan S, Tsai A, Jak A, Polston G, Lee R. Repetitive Transcranial magnetic stimulation in managing mild traumatic brain injury-related headaches. Neuromodulation Journal of International Neuromodulation Society. 2016 Feb;**19**(2):133-141

[14] Clark SW, Wu C, Boorman DW, Chalouhi N, Zanaty M, Oshinsky M, Young WB, Silberstein SD, Sharan AD. Long-term pain reduction does not imply improved functional outcome in patients treated with combined supraorbital and occipital nerve stimulation for chronic migraine. Neuromodulation Journal of International Neuromodulation Society. 2016 Jul;**19**(5):507-514

[15] Reed KL, Will KR, Conidi F, Bulger R. Concordant occipital and supraorbital neurostimulation therapy for hemiplegic migraine; initial experience; a case series. Neuromodulation Journal of International Neuromodulation Society. 2015 Jun;**18**(4):297-303; discussion 304

[16] Przeklasa-Muszyńska A, Skrzypiec K, Kocot-Kępska M, Dobrogowski J, Wiatr M, Mika J. Non-invasive transcutaneous supraorbital Neurostimulation (tSNS) using Cefaly(®) device in prevention of primary headaches. Neurologia i Neurochirurgia Polska. 2017 Apr;**51**(2):127-134

[17] Robbins MS, Lipton RB. Transcutaneous and Percutaneous Neurostimulation for headache disorders. Headache. 2017 Apr;**57**(Suppl 1):4-13

[18] Riederer F, Penning S, Schoenen J. Transcutaneous Supraorbital Nerve stimulation (t-SNS) with the Cefaly(®) device for migraine prevention: A review of the available data. Pain Theraphy. 2015 Oct 14

[19] Vaisman J, Lopez E, Muraoka NK. Supraorbital and supratrochlear stimulation for trigeminal autonomic cephalalgias. Current Pain and Headache Reports. 2014 Apr;**18**(4):409

[20] Kinfe TM, Pintea B, Muhammad S, Zaremba S, Roeske S, Simon BJ, Vatter H. Cervical non-invasive vagus nerve stimulation (nVNS) for preventive and acute treatment of episodic and chronic migraine and migraine-associated sleep disturbance: A prospective observational cohort study. The Journal of Headache and Pain. 2015;**16**:101

[21] Yuan H, Silberstein SD. Vagus nerve stimulation and headache. Headache. 2017 Apr; **57**(Suppl 1):29-33

[22] Barbanti P, Grazzi L, Egeo G, Padovan AM, Liebler E, Bussone G. Non-invasive vagus nerve stimulation for acute treatment of high-frequency and chronic migraine: An open-label study. The Journal of Headache and Pain. 2015;**16**:61

[23] Goadsby PJ, Grosberg BM, Mauskop A, Cady R, Simmons KA. Effect of noninvasive vagus nerve stimulation on acute migraine: An open-label pilot study. Cephalalgia: An International Journal of Headache. 2014 Oct;**34**(12):986-993

[24] Mekhail NA, Estemalik E, Azer G, Davis K, Tepper SJ. Safety and efficacy of occipital nerves stimulation for the treatment of chronic migraines: Randomized, double-blind, controlled single-center experience. Pain Practice : the Official Journal of World Institute of Pain World Institute of Pain. 2017 Jun;**17**(5):669-677

[25] Fontaine D, Blond S, Lucas C, Regis J, Donnet A, Derrey S, Guegan-Massardier E, Jarraya B, Dang-Vu B, Bourdain F, Valade D, Roos C, Creach C, Chabardes S, Giraud P, Voirin J, Bloch J, Rocca A, Colnat-Coulbois S, Caire F, Roger C, Romettino S, Lanteri-Minet M. Occipital nerve stimulation improves the quality of life in medically-intractable chronic cluster headache: Results of an observational prospective study. Cephalalgia: An International Journal of Headache. 2016 Oct 3

[26] Pittelkow TP, Pagani-Estevez GL, Landry B, Pingree MJ, Eldrige JS. Occipital Neuromodulation: A surgical technique with reduced complications. Pain Physician. 2016 Oct;**19**(7):E1005-E1012

[27] Lambru G, Giakoumakis E, Al-Kaisy A. Advanced technologies and novel neurostimulation targets in trigeminal autonomic cephalalgias. Neurological sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology. 2015 May;**36**(Suppl 1):125-129

[28] Bermejo PE, Torres CV, Sola RG. Occipital nerve stimulation for refractory chronic migraine. Revista de Neurologia. 2015 Jun 1;**60**(11):509-516

[29] Dodick DW, Silberstein SD, Reed KL, Deer TR, Slavin KV, Huh B, Sharan AD, Narouze S, Mogilner AY, Trentman TL, Ordia J, Vaisman J, Goldstein J, Mekhail N. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: Long-term results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia: An International Journal of Headache. 2015 Apr;**35**(4):344-358

[30] Freeman JA, Trentman TL. Clinical utility of implantable neurostimulation devices in the treatment of chronic migraine. Medical Devices (Auckland, N.Z.). 2013 Nov 20;**6**:195-201

[31] Verrills P, Rose R, Mitchell B, Vivian D, Barnard A. Peripheral nerve field stimulation for chronic headache: 60 cases and long-term follow-up. Neuromodulation Journal of International Neuromodulation Society. 2014 Jan;**17**(1):54-59

[32] Palmisani S, Al-Kaisy A, Arcioni R, Smith T, Negro A, Lambru G, Bandikatla V, Carson E, Martelletti P. A six year retrospective review of occipital nerve stimulation practice–controversies and challenges of an emerging technique for treating refractory headache syndromes. The Journal of Headache and Pain. 2013 Aug 6;**14**:67

[33] Mueller O, Diener H-C, Dammann P, Rabe K, Hagel V, Sure U, Gaul C. Occipital nerve stimulation for intractable chronic cluster headache or migraine: A critical analysis of direct treatment costs and complications. Cephalalgia: An International Journal of Headache. 2013 Dec;**33**(16):1283-1291

[34] Wilbrink LA, Teernstra OPM, Haan J, van Zwet EW, Evers SMAA, Spincemaille GH, Veltink PH, Mulleners W, Brand R, Huygen FJPM, Jensen RH, Paemeleire K, Goadsby PJ, Visser-Vandewalle V, Ferrari MD. Occipital nerve stimulation in medically intractable, chronic cluster headache. The ICON study: Rationale and protocol of a randomised trial. Cephalalgia: An International Journal of Headache. 2013 Nov;**33**(15):1238-1247

[35] Brewer AC, Trentman TL, Ivancic MG, Vargas BB, Rebecca AM, Zimmerman RS, Rosenfeld DM, Dodick DW. Long-term outcome in occipital nerve stimulation patients with medically intractable primary headache disorders. Neuromodulation Journal of International Neuromodulation Society. 2013 Dec;**16**(6):557-562-564

[36] Narouze SN, Kapural L. Supraorbital nerve electric stimulation for the treatment of intractable chronic cluster headache: A case report. Headache. 2007 Aug;**47**(7):1100-1102

[37] Elahi F, Reddy C. Neuromodulation of the great auricular nerve for persistent post-traumatic headache. Pain Physician. 2014 Aug;**17**(4):E531-E536

[38] Tepper SJ, Caparso A. Sphenopalatine ganglion (SPG): Stimulation mechanism, safety, and efficacy. Headache. 2017 Apr;**57**(Suppl 1):14-28

[39] Meng D-W, Zhang J-G, Zheng Z, Wang X, Luo F, Chronic Bilateral ZK. Sphenopalatine ganglion stimulation for intractable bilateral chronic cluster headache: A case report. Pain Physician. 2016;**19**(4):E637-E642

[40] Fontaine D, Vandersteen C, Magis D, Lanteri-Minet M. Neuromodulation in cluster headache. Advances and Technical Standards in Neurosurgery. 2015;**42**:3-21

[41] Narouze S. Neurostimulation at pterygopalatine fossa for cluster headaches and cerebrovascular disorders. Current Pain and Headache Reports. 2014 Jul;**18**(7):432

[42] Jürgens TP, Schoenen J, Rostgaard J, Hillerup S, Láinez MJA, Assaf AT, May A, Jensen RH. Stimulation of the sphenopalatine ganglion in intractable cluster headache: Expert consensus on patient selection and standards of care. Cephalalgia: An International Journal of Headache. 2014 Nov;**34**(13):1100-1110

[43] Jürgens TP, Barloese M, May A, Láinez JM, Schoenen J, Gaul C, Goodman AM, Caparso A, Jensen RH. Long-term effectiveness of sphenopalatine ganglion stimulation for cluster headache. Cephalalgia: An International Journal of Headache. 2017 Apr;**37**(5):423-434

[44] Khan S, Schoenen J, Ashina M. Sphenopalatine ganglion neuromodulation in migraine: What is the rationale? Cephalalgia: An International Journal of Headache. 2014 Apr;**34**(5): 382-391

[45] Lambru G, Trimboli M, Palmisani S, Smith T, Al-Kaisy A. Safety and efficacy of cervical 10 kHz spinal cord stimulation in chronic refractory primary headaches: A retrospective case series. The Journal of Headache and Pain. 2016 Dec;**17**(1):66

[46] Arcioni R, Palmisani S, Mercieri M, Vano V, Tigano S, Smith T, Fiore MRD, Al-Kaisy A, Martelletti P. Cervical 10 kHz spinal cord stimulation in the management of chronic, medically refractory migraine: A prospective, open-label, exploratory study. European Journal of Pain London England. 2016 Jan;**20**(1):70-78

[47] De Agostino R, Federspiel B, Cesnulis E, Sandor PS. High-cervical spinal cord stimulation for medically intractable chronic migraine. Neuromodulation Journal of International Neuromodulation Society. 2015 Jun;**18**(4):289-296 discussion 296

[48] Elahi F, Reddy C. High cervical epidural neurostimulation for post-traumatic headache management. Pain Physician. 2014 Aug;**17**(4):E537-E541

[49] Miller S, Akram H, Lagrata S, Hariz M, Zrinzo L, Matharu M. Ventral tegmental area deep brain stimulation in refractory short-lasting unilateral neuralgiform headache attacks. Brain: A Journal of Neurology. 2016 Oct;**139**(Pt 10):2631-2640

[50] Leone M, Proietti Cecchini A. Deep brain stimulation in headache. Cephalalgia: An International Journal of Headache. 2015 Dec 7

[51] Avecillas-Chasin JM, Alonso-Frech F, Parras O, Del Prado N, Barcia JA. Assessment of a method to determine deep brain stimulation targets using deterministic tractography in a navigation system. Neurosurgical Review. 2015 Oct;**38**(4):739-750; discussion 751

[52] Seijo F, Saiz A, Lozano B, Santamarta E, Alvarez-Vega M, Seijo E, Fernández de León R, Fernández-González F, Pascual J. Neuromodulation of the posterolateral hypothalamus for the treatment of chronic refractory cluster headache: Experience in five patients with a modified anatomical target. Cephalalgia: An International Journal of Headache. 2011 Dec;**31**(16):1634-1641

[53] Farber SH, Hatef J, Han JL, Marky AH, Xie J, Huang K, Verla T, Lokhnygina Y, Collins TA, Lad SP. Implantable Neurostimulation for headache disorders: Effect on healthcare utilization and expenditures. Neuromodulation Journal of International Neuromodulation Society. 2016 Apr;**19**(3):319-328

[54] Barolat G, Ketcik B, He J. Long-term outcome of spinal cord stimulation for chronic pain management. Neuromodulation Journal of International Neuromodulation Society. 1998 Jan;**1**(1):19-29

[55] Leone M. Deep brain stimulation in headache. Lancet Neurology. 2006 Oct;**5**(10):873-877

[56] Schwalb JM, Hamani C. The history and future of deep brain stimulation. Neurother: Journal of the American Society for Experimental Neurotherapeutics. 2008 Jan;**5**(1):3-13

[57] Mazars G, Pull H. Neurosurgical treatment of headaches. Minerva Medica. 1976 Jun 23;**67**(31):2020-2022

[58] Picaza JA, Hunter SE, Cannon BW. Pain suppression by peripheral nerve stimulation. Chronic effects of implanted devices. Applied Neurophysiology. 1977-1978;**40**(2-4):223-234

[59] Wichmann T, Delong MR. Deep brain stimulation for neurologic and neuropsychiatric disorders. Neuron. 2006 Oct 5;**52**(1):197-204

[60] Weiner RL, Reed KL. Peripheral neurostimulation for control of intractable occipital neuralgia. Neuromodulation Journal of International Neuromodulation Society. 1999 Jul;**2**(3):217-221

[61] Franzini A, Ferroli P, Leone M, Broggi G. Stimulation of the posterior hypothalamus for treatment of chronic intractable cluster headaches: First reported series. Neurosurgery. 2003 May;**52**(5):1095-1099-1101

[62] Dunteman E. Peripheral nerve stimulation for unremitting ophthalmic postherpetic neuralgia. Neuromodulation Journal of International Neuromodulation Society. 2002 Jan;**5**(1):32-37

[63] Matharu MS, Bartsch T, Ward N, Frackowiak RSJ, Weiner R, Goadsby PJ. Central neuromodulation in chronic migraine patients with suboccipital stimulators: A PET study. Brain: A Journal of Neurology. 2004 Jan;**127**(Pt 1):220-230

[64] Wolter T, Kaube H, Mohadjer M. High cervical epidural neurostimulation for cluster headache: Case report and review of the literature. Cephalalgia: An International Journal of Headache. 2008 Oct;**28**(10):1091-1094

[65] Barker AT, Shields K. Transcranial magnetic stimulation: Basic principles and clinical applications in migraine. Headache. 2017 Mar;**57**(3):517-524

[66] McComas AJ, Upton ARM. Transcranial magnetic stimulation in migraine: A new therapy and new insights into pathogenesis. Critical Reviews in Biomedical Engineering. 2016;**44**(5):319-326

[67] Kalita J, Bhoi SK, Misra UK. Effect of high rate rTMS on somatosensory evoked potential in migraine. Cephalalgia: An International Journal of Headache. 2017 Nov;**37**(13):1222-1230

[68] Conforto AB, Amaro E, Gonçalves AL, Mercante JP, Guendler VZ, Ferreira JR, Kirschner CC, Peres MF. Randomized, proof-of-principle clinical trial of active transcranial magnetic stimulation in chronic migraine. Cephalalgia: An International Journal of Headache. 2014 May;**34**(6):464-472

[69] Bhola R, Kinsella E, Giffin N, Lipscombe S, Ahmed F, Weatherall M, Goadsby PJ. Single-pulse transcranial magnetic stimulation (sTMS) for the acute treatment of migraine: Evaluation of outcome data for the UK post market pilot program. The Journal of Headache and Pain. 2015;**16**:535

[70] Zardouz S, Shi L, Leung A. A feasible repetitive transcranial magnetic stimulation clinical protocol in migraine prevention. SAGE Open Medical Case Report. 2016;**4** 20503 13X16675257

[71] Lan L, Zhang X, Li X, Rong X, Peng Y. The efficacy of transcranial magnetic stimulation on migraine: A meta-analysis of randomized controlled trails. The Journal of Headache and Pain. 2017 Aug 22;**18**(1):86

[72] Andreou AP, Holland PR, Akerman S, Summ O, Fredrick J, Goadsby PJ. Transcranial magnetic stimulation and potential cortical and trigeminothalamic mechanisms in migraine. Brain: A Journal of Neurology. 2016 Jul;**139**(Pt 7):2002-2014

[73] Rapinesi C, Del Casale A, Scatena P, Kotzalidis GD, Di Pietro S, Ferri VR, Bersani FS, Brugnoli R, Raccah RN, Zangen A, Ferracuti S, Orzi F, Girardi P, Sette G. Add-on deep Transcranial magnetic stimulation (dTMS) for the treatment of chronic migraine: A preliminary study. Neuroscience Letters. 2016 Jun 3;**623**:7-12

[74] Cosentino G, Fierro B, Vigneri S, Talamanca S, Paladino P, Baschi R, Indovino S, Maccora S, Valentino F, Fileccia E, Giglia G, Brighina F. Cyclical changes of cortical excitability and metaplasticity in migraine: Evidence from a repetitive transcranial magnetic stimulation study. Pain. 2014 Jun;**155**(6):1070-1078

[75] Misra UK, Kalita J, Bhoi SK. High-rate repetitive transcranial magnetic stimulation in migraine prophylaxis: A randomized, placebo-controlled study. Journal of Neurology. 2013 Nov;**260**(11):2793-2801

[76] Shehata HS, Esmail EH, Abdelalim A, El-Jaafary S, Elmazny A, Sabbah A, Shalaby NM. Repetitive transcranial magnetic stimulation versus botulinum toxin injection in chronic migraine prophylaxis: A pilot randomized trial. Journal of Pain Research. 2016;**9**:771-777

[77] Hodaj H, Alibeu J-P, Payen J-F, Lefaucheur J-P. Treatment of chronic facial pain including cluster headache by repetitive Transcranial magnetic stimulation of the motor cortex with maintenance sessions: A naturalistic study. Brain Stimulation. 2015 Aug;**8**(4):801-807

[78] Durmaz O, Ateş MA, Şenol MG. Repetitive Transcranial magnetic stimulation (rTMS)-induced trigeminal autonomic Cephalalgia. Noro Psikiyatri Arsivi. 2015 Sep;**52**(3):309-311

[79] Sadler RM, Purdy RA, Rahey S. Vagal nerve stimulation aborts migraine in patient with intractable epilepsy. Cephalalgia: An International Journal of Headache. 2002 Jul;**22**(6):482-484

[80] Silberstein SD, Mechtler LL, Kudrow DB, Calhoun AH, McClure C, Saper JR, Liebler EJ, Rubenstein Engel E, Tepper SJ. ACT1 study group. Non-invasive vagus nerve stimulation for the acute treatment of cluster headache: Findings from the randomized, double-blind, sham-controlled ACT1 study. Headache. 2016 Sep;**56**(8):1317-1332

[81] Gaul C, Diener H-C, Silver N, Magis D, Reuter U, Andersson A, Liebler EJ, Straube A, PREVA Study Group. Non-invasive vagus nerve stimulation for prevention and acute treatment of chronic cluster headache (PREVA): A randomised controlled study. Cephalalgia: An International Journal of Headache. 2016 May;**36**(6):534-546

[82] Straube A, Ellrich J, Eren O, Blum B, Ruscheweyh R. Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): A randomized, monocentric clinical trial. The Journal of Headache and Pain. 2015;**16**:543

[83] Eren O, Straube A, Schöberl F, Schankin C. Hemicrania continua: Beneficial effect of non-invasive Vagus nerve stimulation in a patient with a contraindication for indomethacin. Headache. 2017 Feb;**57**(2):298-301

[84] Akbas M, Gunduz E, Sanli S, Yegin A. Sphenopalatine ganglion pulsed radiofrequency treatment in patients suffering from chronic face and head pain. Brazilian Journal of Anesthesiology Elsevier. 2016 Feb;**66**(1):50-54

[85] Barloese MCJ, Jürgens TP, May A, Lainez JM, Schoenen J, Gaul C, Goodman AM, Caparso A, Jensen RH. Cluster headache attack remission with sphenopalatine ganglion stimulation: Experiences in chronic cluster headache patients through 24 months. The Journal of Headache and Pain. 2016 Dec;**17**(1):67

[86] Assaf AT, Hillerup S, Rostgaard J, Puche M, Blessmann M, Kohlmeier C, Pohlenz P, Klatt JC, Heiland M, Caparso A, Papay F. Technical and surgical aspects of the sphenopalatine ganglion (SPG) microstimulator insertion procedure. International Journal of Oral and Maxillofacial Surgery. 2016 Feb;**45**(2):245-254

[87] Schoenen J, Jensen RH, Lantéri-Minet M, Láinez MJA, Gaul C, Goodman AM, Caparso A, May A. Stimulation of the sphenopalatine ganglion (SPG) for cluster headache treatment. Pathway CH-1: A randomized, sham-controlled study. Cephalalgia: An International Journal of Headache. 2013 Jul;**33**(10):816-830

[88] Magis D, Allena M, Bolla M, De Pasqua V, Remacle J-M, Schoenen J. Occipital nerve stimulation for drug-resistant chronic cluster headache: A prospective pilot study. Lancet Neurology. 2007 Apr;**6**(4):314-321

[89] Shaw AB, Sharma M, Shaikhouni A, Marlin ES, Ikeda DS, McGregor JM, Deogaonkar M. Neuromodulation as a last resort option in the treatment of chronic daily headaches in patients with idiopathic intracranial hypertension. Neurology India. 2015 Oct;**63**(5):707-711

[90] Hann S, Sharan A. Dual occipital and supraorbital nerve stimulation for chronic migraine: A single-center experience, review of literature, and surgical considerations. Neurosurgical Focus. 2013 Sep;**35**(3):E9

[91] Kinfe TM, Pintea B, Roeske S, Güresir Á, Güresir E, Vatter H. Percutaneous nerve field stimulation (PENS) of the occipital region as a possible predictor for occipital nerve stimulation (ONS) responsiveness in refractory headache disorders? A feasibility study. Cephalalgia: An International Journal of Headache. 2016 Jul;**36**(8):779-789

[92] Son B-C, Yang S-H, Hong J-T, Lee S-W. Occipital nerve stimulation for medically refractory hypnic headache. Neuromodulation Journal of International Neuromodulation Society. 2012 Jul;**15**(4):381-386

[93] Lambru G, Shanahan P, Watkins L, Matharu MS. Occipital nerve stimulation in the treatment of medically intractable SUNCT and SUNA. Pain Physician. 2014 Feb;**17**(1):29-41

[94] Miller S, Watkins L, Matharu M. Long-term follow up of intractable chronic short lasting unilateral neuralgiform headache disorders treated with occipital nerve stimulation. Cephalalgia: An International Journal of Headache. 2017 Jan 1 333102417721716

[95] Tavanaiepour D, Levy RM. Peripheral neuromodulation for treatment of chronic migraine headache. Neurosurgery Clinics of North America. 2014 Jan;**25**(1):11-14

[96] Sharan A, Huh B, Narouze S, Trentman T, Mogilner A, Vaisman J, Ordia J, Deer T, Venkatesan L, Slavin K. Analysis of adverse events in the management of chronic migraine by peripheral nerve stimulation. Neuromodulation Journal of International Neuromodulation Society. 2015 Jun;**18**(4):305-312 discussion 312

[97] Zimmerman RS, Rosenfeld DM, Freeman JA, Rebecca AM, Trentman TL. Revision of occipital nerve stimulator leads: Technical note of two techniques. Neuromodulation Journal of International Neuromodulation Society. 2012 Jul;**15**(4):387-391

[98] Magis D, Schoenen J. Advances and challenges in neurostimulation for headaches. Lancet Neurology. 2012 Aug;**11**(8):708-719

[99] Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M, Goadsby PJ, ONSTIM Investigators. Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study. Cephalalgia: An International Journal of Headache. 2011 Feb;**31**(3):271-285

[100] Rogers LL, Swidan S. Stimulation of the occipital nerve for the treatment of migraine: Current state and future prospects. Acta Neurochirurgica. Supplement. 2007;**97**(Pt 1): 121-128

[101] Abhinav K, Park ND, Prakash SK, Love-Jones S, Patel NK. Novel use of narrow paddle electrodes for occipital nerve stimulation--technical note. Neuromodulation Journal of International Neuromodulation Society. 2013 Dec;**16**(6):607-609

[102] Wolter T, Kiemen A, Kaube H. High cervical spinal cord stimulation for chronic cluster headache. Cephalalgia: An International Journal of Headache. 2011 Aug;**31**(11):1170-1180

[103] Fontaine D, Lanteri-Minet M, Ouchchane L, Lazorthes Y, Mertens P, Blond S, Geraud G, Fabre N, Navez M, Lucas C, Dubois F, Sol JC, Paquis P, Lemaire JJ. Anatomical location of effective deep brain stimulation electrodes in chronic cluster headache. Brain: A Journal of Neurology. 2010 Apr;**133**(Pt 4):1214-1223

[104] Matharu MS, Zrinzo L. Deep brain stimulation in cluster headache: Hypothalamus or midbrain tegmentum? Current Pain and Headache Reports. 2010 Apr;**14**(2):151-159

[105] Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition (beta version). Cephalalgia: An International Journal of Headache. 2013 Jul;**33**(9):629-808

[106] Fischera M, Marziniak M, Gralow I, Evers S. The incidence and prevalence of cluster headache: A meta-analysis of population-based studies. Cephalalgia: An International Journal of Headache. 2008 Jun;**28**(6):614-618

[107] Nesbitt AD, Marin JCA, Tompkins E, Ruttledge MH, Goadsby PJ. Initial use of a novel noninvasive vagus nerve stimulator for cluster headache treatment. Neurology. 2015 Mar 24;**84**(12):1249-1253

[108] Androulakis XM, Krebs KA, Ashkenazi A. Hemicrania continua may respond to repetitive sphenopalatine ganglion block: A case report. Headache. 2016 Mar;**56**(3):573-579

[109] Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basáñez M-G, Baxter A, Bell ML,

Benjamin EJ, Bennett D, Bernabé E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brugha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT-A, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet London England. 2012 Dec 15; **380**(9859):2163-96.

[110] Irimia P, Palma J-A, Fernandez-Torron R, Martinez-Vila E. Refractory migraine in a headache clinic population. BMC Neurology. 2011 Aug;**11**(1):94

[111] Magis D. Neuromodulation in migraine: State of the art and perspectives. Expert Review of Medical Devices. 2015 May;**12**(3):329-339

[112] Seifert TD, Evans RW. Posttraumatic headache: A review. Current Pain and Headache Reports. 2010 Aug;**14**(4):292-298

Chapter 9

Occupational Exposure to Magnetic Field in Transcranial Magnetic Stimulation Treatment

Kjell Hansson Mild and Ole Jacob Møllerløkken

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.73224

Abstract

Transcranial magnetic stimulation (TMS) is used both as a diagnostic instrument and for therapy, available only at some psychiatric clinics for treatment of depression and at clinical neurophysiology where TMS is used for diagnosis of nerve damage. The Swedish National Board of Health and Welfare issued a referral edition about the use of repetitive TMS as an alternative treatment for depression. This may lead to a major increase in the application of TMS to treat depression. TMS is based on induction of an electric (E) field inside the brain by application of an external magnetic field with rapid rise and fall time. The E field in the brain has been calculated when different coils were used for the treatment. The reported E fields are of the order of tens to hundreds of volts per meter and the induced current density is estimated at tens of A/m^2. This field can depolarize neurons or modulate cortical excitability by selecting the appropriate parameters for stimulation and the duration of the treatment session. The mechanisms of action of neurostimulation still remain incompletely understood.

Keywords: staff, EU directive, health risk, precautionary principle

1. Introduction

Transcranial magnetic stimulation (TMS) is used primarily in research and treatments of central nervous diseases, such as recurrent depressions, and has been used for several years. The non-invasive stimulation of the cortical cortex is accomplished through the application of pulsed magnetic fields generated by coils in different arrangements. The effects on major depressive disorder in adults have been reviewed by Perera et al. [1] and the Clinical TMS society, and they state that following the clinical recommendations given in their document it should result in continued safe and effective use of the TMS.

However, it is not yet so widespread, and today in Sweden and Norway, TMS equipment is available only at some psychiatric clinics for treatment of depression and at clinical neurophysiology where TMS is used for diagnosis of nerve damage. The Swedish National Board of Health and Welfare has issued a referral edition about the use of repetitive TMS as an alternative treatment for depression. The method is new, but it has been used with positive effects on persons with medium-to-severe depression. This may lead to a major increase in the application of TMS to treat depression.

However, although TMS have been reviewed several times, the potential exposure to the therapeutic staff has been neglected. The magnetic pulses can be targeted to selected cortical areas through the design and placement of the different coils used.

Occupational exposure limits have been recently revised in Europe and are given in the new EU directive [2] and the ICNIRP guidelines [3]. For the exposure experienced during TMS treatment, the limits are set to avoid stimulation of nerves. Studies by Karlström et al. [4] and Möllerlökken et al. [5] investigated the therapeutic staff exposure to pulsed magnetic fields during TMS/rTMS treatments in relation to the occupational exposure limits given and found that these limits may be exceeded close to the coil and safety measures are needed. In this paper, we will look closer into this exposure.

2. Different coil design

The magnetic pulses can be targeted to selected cortical areas through the design and placement of the different coils used. Lu and Ueno [6] have recently reviewed different coil configurations and how the induced electric field in the brain is distributed. **Figure 1** from their publication shows some of the most common designs. Most commonly used is a pair of coils arranged in the form of the figure-8. The pulsed magnetic field will induce electric currents in the cerebral tissue, and the effect will be strongest in the areas close to the coil. The treatment is non-invasive and therefore to prefer compared to electro-convulsion therapy.

2.1. Measurement

Figure 2 shows a typical position of a patient receiving treatment with a figure-8 coil positioned with a fixed position on the head.

The current in the coils can reach some kA in strength and the waveform is sinusoidal with frequency around some kHz. The magnetic flux density generated by TMS equipment can reach the order of 1 Tesla. Since the duration is only about 0.05–0.4 ms, this give rise to a time derivative of the field of the order of tens of kT/s. This then induce an electric field in the tissue that can reach the threshold for localized axonal depolarization of more than 100 V/m. For further information on this, we refer the reader to Deng et al. [7], Bottauscio et al. [8] and Lu and Ueno [6]. Since the limit for occupational exposure for the frequencies used in TMS is around

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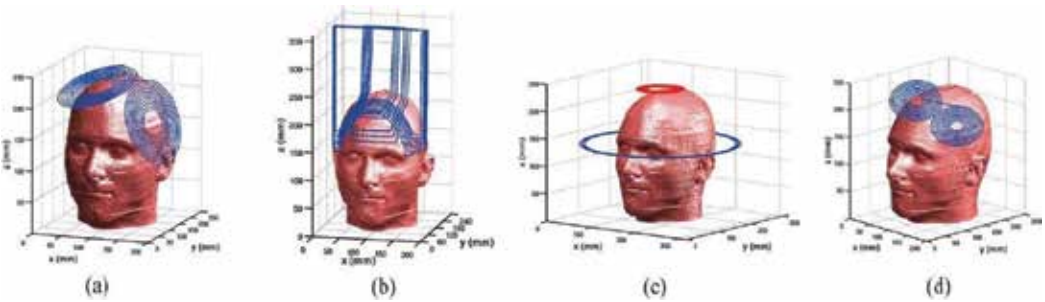

Figure 1. Realistic head model with coils. (a) Double cone coil, (b) H-coil, (c) HCA coil, and (d) Figure-8 coil. Reproduced from Lu and Ueno [6] with permission.

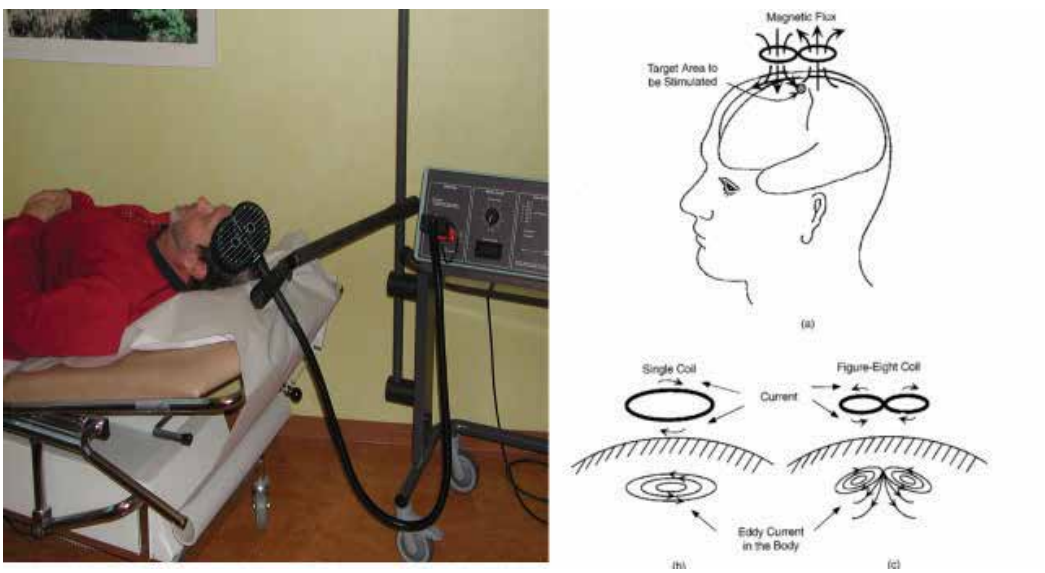

Figure 2. Position of a "patient" received TMS treatment with a figure-8 coil. The schematic drawing shows the induced electric field in tissue. Photo: Kjell Hansson Mild, drawing courtesy of Shoogo Ueno, Tokyo.

1 V/m, it is not surprising that staff can be at risk for overexposure if working too close to the coil when in use. This is something they often need to be because either the coil moves out of position or the patient needs assistance. In addition, many of the coils are designed so that the trigger-button for the pulse is placed on the coil itself. This button is used in the beginning of the treatment sequence to establish what power is needed to place the coil in the correct position. Such work makes it impossible for the operator to not be in close contact with the coil and therefore in risk of overexposure.

We have measured the magnetic field from some TMS machines. We used a system with an electrically shielded circular coil with 2.5 cm radius, calibrated. The induced voltage was

registered with a Tektronix TDS 1012 digital storage oscilloscope. With this equipment, we pick up the time derivate of the magnetic field, dB/dt. An example of the single pulse can be seen in **Figure 3**. **Figure 4** gives an example of the series of pulses delivered in treatment sessions.

The system we have looked at is: MagVenture rTMS system with a magnetic coil type Cool-B65 (MagVenture A/S, Inc., USA). The Cool-B65 coil is a figure-8 coil with partially overlapping coils, and a MegPro unit with a magnetic coil transducer model, and MC-B70 (Medtronic Synectics AB, P.O. Box 265, SE-177 25 Järfälla, Sweden; http://www.synectics.se).

At some distance, depending on power setting and coil design, the distance from the coil where the action levels of the EU directive are exceeded is from some decimeter to almost a full meter. For the MagVenture system, the limit distance was 0.4 m and for the MegPro 0.7 m.

In the EU guideline [9] for how to implement the new EU directive measurements and discussion about the TMS exposure to staff are given. They found that at a typical hand position

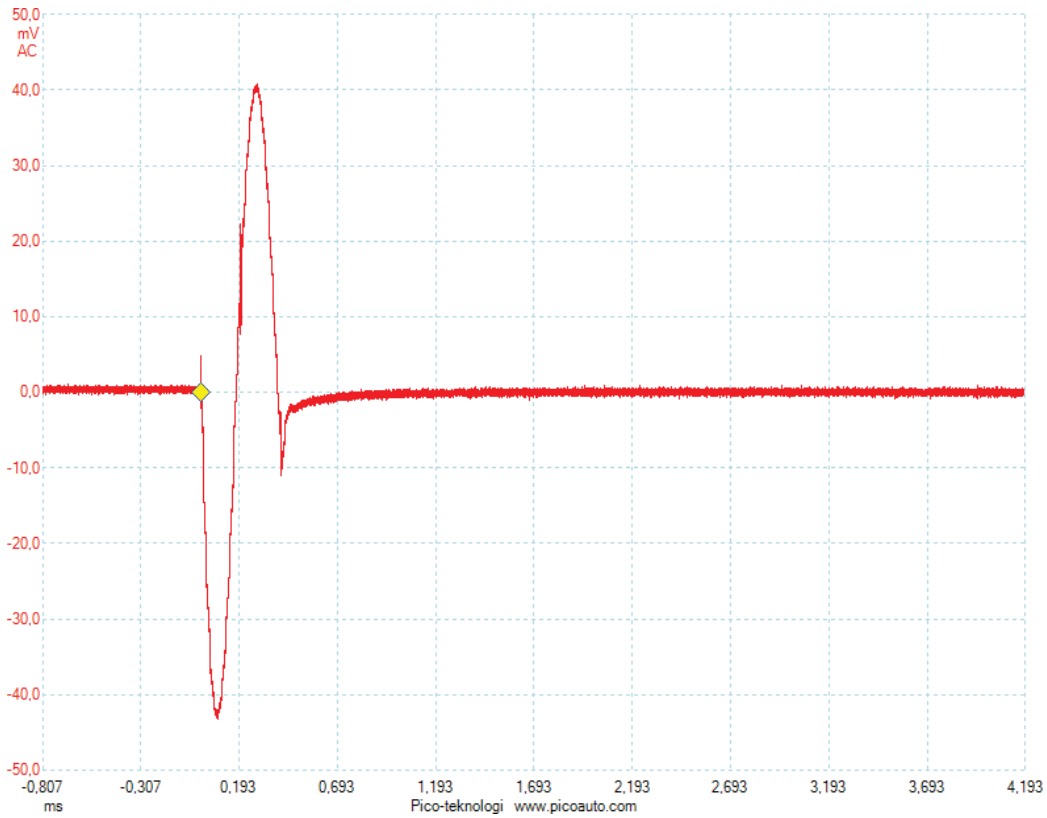

Figure 3. Recording of dB/dt in a single pulse from the MagVenture system. The frequency of the pulse was found to be about 2.5 kHz and practically sinusoidal.

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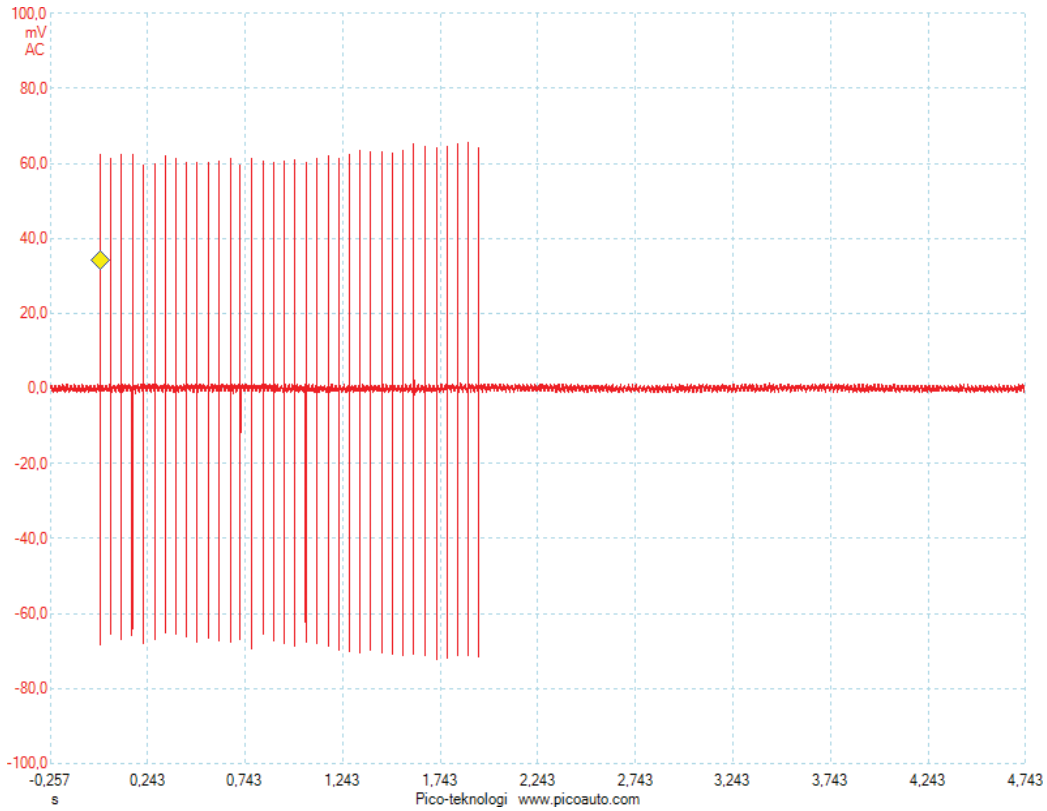

Figure 4. The system can be set to deliver a single pulse or a series pulses. In the rTMS, a pulse train with 20 pulses within some second is repeated with a frequency of some Hz. This is then applied for up to 15 min per session.

holding the hand piece with the coil the magnetic flux density exceed by 5,600% the limit for the limb. The team realized that the clinician was highly likely to exceed the action levels, and therefore a computer model was applied. From the computer calculation of the induced electric field, they found that the exposure limits could be exceeded up to 35,700% with the coil 15 cm from the torso.

2.2. Implants

The magnetic field pulses can exert attractive forces on ferromagnetic objects and repulsive forces on non-ferromagnetic objects. Therefore, it is of importance to screen the patients before treatment for metallic objects, such as cochlear implants, and other implanted objects in the scalp, such as deep brain stimulators and epidural electrode arrays for cortical stimulation. According to a review by Rossi et al. [10], it appears that TMS can be safely applied to patients with implanted stimulators of CNS and PNS when the coil is not in close proximity to the internal pulse generator. However, the information about the safe use in these cases is sparse, and therefore Rossi et al. [10] state that TMS should only be done in patients with implanted stimulators if there are scientifically or medically compelling reasons justifying this.

2.3. Discussion

It was clear from the measurements that the worker's exposure limits for the magnetic field pulses are transgressed at distances of about 0.7 m from the surface of the transducer's coils during normal patient treatment conditions. The coil handle, which is located in the plane of the figure-8 coils, is about 20 cm long, and this results in a short distance between the source of the field and the hand and forearm of the operator. The TMS transducer can in this case be seen as a single dipole with decay as the inverse of the cube of the distance, $1/r^3$. The head and trunk of the operator is at most an arm-length apart from the source, and since the basic restrictions are based on induced current in the head and the trunk for frequencies up to 10 MHz [2, 3], limiting exposures to the head and trunk are necessary. Different designs of TMS devices should be further studied to bring deeper insight in the issue of at what distance the limits in terms of induced electric field on the staff are exceeded from the surface of the transducer's coils during normal patient treatment conditions.

To avoid risks of overexposure to magnetic pulses, a recommendation that is valid for both single coil and figure-8 transducers, the equipment should be used with a mechanical arm holding the transducer in the right position for the patient. The staff operating the TMS equipment need to be educated and trained to operate the equipment in a safe way. EU guideline also states [9] that it is necessary to prohibit pregnant workers and workers with active implanted medical devices (AIMD) from operating the equipment or remaining in the room during treatment. Treatment should not be given to patients fitted with AIMD.

Unnecessary over-exposure to pulsed magnetic fields of this magnitude may cause negative health effects for the therapeutic staff. From the exposure guidelines, it is known that the rationale for limiting exposure is the well-defined biological responses ranging from perception of the fields to annoyance and stimulation of central and peripheral nervous tissue. Our studies were not designed to investigate health effects among the therapeutic staff, this is needed in the future, and neither did we investigate other possible risk factors for health complaints in this working environment, such as indoor climate, noise, and treatment lengths.

In conclusion, staff working with patient treatment with TMS/rTMS can become exposed to magnetic field levels exceeding both EU directive and ICNIRP guidelines; therefore, it is recommended that procedures are developed to avoid unnecessary exposure of staff. Information about the risks associated with the application of the strong magnetic pulses is necessary, and a training programme for the staff would be advisable.

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References

[1] Perera T, George MS, Grammer G, Janicak PG, Pascual-Leone A, Wirecki TS. The clinical TMS society consensus review and treatment recommendations for TMS therapy for major depressive disorder. Brain Stimulation. May–Jun, 2016;**9**(3):336-346. DOI: 10.1016/j.brs.2016.03.010. Epub 2016 Mar 16. Review.

[2] Directive 2013/35/EU of the European Parliament and of the Council of 26 June 2013 on the minimum health and safety requirements regarding the exposure of workers to the risks arising from physical agents (electromagnetic fields) (20th individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) and repealing Directive 2004/40/EC, Official Journal of the European Communities, L 179/1. Available from: http://www.ismrm.org/smrt/files/LexUriServ.do.pdf accessed 8 January 2018

[3] ICNIRP. ICNIRP guidelines for limiting exposure to time-varying electric and magnetic fields (1 Hz–100 kHz). Health Physics. 2010;**99**(6):818-836

[4] Figueroa Karlström E, Lundström R, Stensson O, Hansson Mild K. Therapeutic staff exposure to magnetic field pulses during TMS/rTMS treatments. Bioelectromagnetics. 2006;**27**:156-158

[5] Møllerløkken OJ, Stavang H, Hansson Mild K. Staff exposure to pulsed magnetic fields during depression treatment with transcranial magnetic stimulation. International Journal of Occupational Safety and Ergonomics. 2017 Mar;**23**(1):139-142. DOI: 10.1080/10803548.2016.1223193 Epub Sep 8, 2016

[6] Lu M, Ueno S. Comparison of the induced fields using different coil configurations during deep transcranial magnetic stimulation. PLoS One. 2017;**12**(6):e0178422. DOI: 10.1371/journal.pone.0178422

[7] Deng ZD, Lisanby SH, Peterchev AV. Coil design considerations for deep transcranial magnetic stimulation. Clinical Neurophysiology. Jun, 2014;**125**(6):1202-1212. DOI: 10.1016/j.clinph.2013.11.038 Epub Dec 22, 2013

[8] Bottauscio O, Zucca M, Chiampi M, and Zilberti L. Evaluation of the electric field induced in transcranial magnetic stimulation operators. IEEE Transactions on Magnetics. March 2016;**52**(3):5000204

[9] EU. Non-binding Guide to Good Practice for Implementing Directive 2013/35/EU Electromagnetic Fields Volume 2: Case Studies. 2013. Available from: https://osha.europa.eu/sv/legislation/guidelines/non-binding-guide-good-practice-implementing-directive-201335eu [Accessed: Sep 1, 2017]

[10] Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety of TMS consensus group. Clinical Neurophysiology Dec, 2009;**120**(12):2008-2039. DOI: 10.1016/j.clinph.2009.08.016. Epub Oct 14, 2009. Review

Edited by Libor Ustohal

This book describes several aspects of transcranial magnetic stimulation (TMS) in neuropsychiatry: inhibitory and excitatory mechanisms of the human brain, the use of TMS in the research and treatment of cognitive disorders, various aspects of TMS application aimed at the cerebellum, its effects on impulsivity in attention deficit hyperactivity disorder and borderline personality disorder, its effects in the treatment of tinnitus and obsessive–compulsive disorder, pain and chronic headache, and finally the safety of TMS for staff. Hopefully this book will help to expand the knowledge of TMS.

Published in London, UK

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ISBN 978-1-83881-385-7
9 781838 813857