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

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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

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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.

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