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Chapter 15

Repetitive Transcranial Magnetic Stimulation in ADHD

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Additional information is available at the end of the chapter

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Abstract

Although there are very effective treatment approaches for ADHD available, the clinical management has its limits and a search for new treatment modalities is useful. rTMS found its use in neurology and is widely applied in psychiatric research and although its effect seems mild, it can be specific to some extend. The text reviews current knowledge on the neurobiology of ADHD symptoms with regard to a possible rTMS treatment. The basics of the rTMS method are described. The use of rTMS is summarized both generally in psychiatric disorders and specifically in ADHD. The safety issues are discussed both in adults and children. The text also brings a case study where rTMS was applied in an adult patient with ADHD.

Keywords: ADHD, rTMS, neurobiology

1. Introduction

1.1. Limits of current treatments for ADHD

Although the current treatment approaches in ADHD are highly supported by research and are very effective, they are not suitable for all patients in need for treatment. Medications used in clinical practice are generally well tolerated; however, they have some safety issues. Cardiovascular effects are the most important of them. Both stimulants and atomoxetine increase heart rate and blood pressure and for some patients it prevents their use. Treatment with stimulants belongs to the most effective within psychiatry. Almost all guidelines recommend stimulants as first-line treatment. However, 20–35% of children and adolescents in clinical trials may have an inadequate response to initial stimulant treatment either due to insufficient efficacy or non-adherence [1]. The response rate in atomoxetine is even lower, with 40% of patients without significant improvement [2]. In adults, the response rates for methyl-

phenidate are around 50% [3]. The long-time studies in adults with ADHD show high rates of non-adherence to medications. Only about half of the patients remain in treatment after two years [4]. As for the psychosocial treatment, the evidence-based efficacy remains unclear, although psychosocial treatments can have some positive impact for children with ADHD beyond the impact of pharmacologic treatment alone. The quality of studies aimed at psychosocial interventions is insufficient, although it improves continuously [5].

Therefore, although specific pharmacotherapies for ADHD exist, they are not always available or suitable for all individuals. Moreover, as for the effect on specific symptom clusters, such as impulsivity, inconsistent data exist with both positive and negative effect of stimulants [6]. Even more, there are other issues, such as parents' non-acceptance of pharmacological treatment, that limit the benefit from pharmacological treatment. The need for novel treatment approaches is clear. Repetitive transcranial magnetic stimulation (rTMS), one of the most recent treatment approaches in psychiatry, allows selective neuromodulation of regions involved in the functional neuroanatomy of individual symptomatic profiles.

1.2. Functional neuroanatomy of ADHD symptoms

Although there exist unifying theories on the nature of symptom clusters in ADHD, the evidence on unequal expression of individual symptoms across clinical samples suggests that at least some symptom clusters are based on distinct neurobiology. This notion is demonstrated by a multivariate analysis of the results of testing of a large sample of ADHD subjects using cognitive battery that focused on cognitive control, reward- and time-processing that showed that these domains form distinct components, and that 80 % of subjects who had a deficit were deficient on only one component [7]. Dysfunctions in these cognitive domains may manifest in distinct symptom profiles in ADHD, i.e. inattention, impulsivity, and hyperactivity. Below, we summarize their functional neuroanatomy to evaluate the potential targets for rTMS treatment.

1.2.1. Impulsivity

Impulsivity is a clinically important feature that accompanies many neuropsychiatric disorders, including ADHD, and constitutes a significant risk for their development, and complicates their course and treatment. In contrast to its frequent manifestation and significant impact, relatively little is known about its neurobiology, and, more importantly, there is no effective specific treatment available at present, except for behavioral modification. This situation may result from inadequate definition of impulsive behaviour with insufficient discrimination between phenomenologically similar, but neurobiologically different, processes.

Indeed, impulsivity is a heterogeneous concept which manifests in many ways, such as personality traits, behavioral features and particular way of behavioural and cognitive task performance. Moreover, in clinical populations, there is rather variable phenomenology of behaviour that is generally labeled as impulsive and a considerable inconsistency of impulsivity concepts in neuropsychiatric disorders exists. It is not clear if there is a single psycho-

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logical process linked to a distinct neurobiology or if discrete patterns of impulsive behaviour could be found with specific functional neuroanatomy in various clinical contexts.

Impulsive behaviour is the execution of an immediate urge to act, bypassing consideration of possible means and outcomes of available alternatives. In a closer look, there may be several sources of such behaviour. Moreover, behaviours like compulsions or hyperactivity may resemble impulsivity on the phenomenological level while they result from different neurobiological and psychological processes [8]. Contemporary neuroscience opens new possibilities for objective analysis of neurophysiological sources of behavior. Moreover, it brings new ways of treatment that are guided by detailed knowledge of neurobiology of individual signs and symptoms.

Impulsivity may be expressed in personality traits, cognitive and emotional processes or behaviour control [9]. **Impulsive personality traits** include impulsivity proper, i.e. tendency to act rashly without evaluation of consequences (most frequently measured using the Barrat Impulsivity Scale); furthermore, it is reflected in the concept of *sensation seeking* (search of novel intense experiences without consideration of associated risks), *lack of perseverance*, *positive and negative urgency* (a tendency to act rashly during intense positive or negative affects) or high *reward sensitivity*.

Cognitive manifestation of impulsivity includes a concept of **behavioural disinhibition**, i.e. inability to suppress irrelevant or unfavourable behaviour ("stop impulsivity" – Go-No go task, Stop signal task), and a concept of **risky decision-making** and **reward processing** with preference of immediate, but in a long run, disadvantageous gains, and inability to postpone reward ("wait impulsivity" – various modifications of Delayed Discounting paradigm, Iowa Gambling task). Compulsion is a repetitive urge to act that leads to a stereotyped behavior; impulsivity, on the other hand, is not stereotypic.

The forms of impulsivity associated with ADHD involve the inadequate control of behaviour, poor sustained inhibition, the inability to delay a response or defer gratification, or the inability to inhibit dominant or prepotent responses. An equal or perhaps greater problem is the delay aversion – children and adults find waiting aversive, and therefore they act impulsively to terminate the delay more quickly. There is a reduction of symptoms of impulsivity with age, but adults still describe some symptoms of it. The clinical manifestations of impulsivity are described as "acts before thinking", "does not learn from mistakes", "says things without thinking" and "does not think about risks or effects of actions" [10, 11]. Impulsivity in individuals with ADHD is associated with greater emotional and behavioral impairments in all stages of life. The consequences of impulsivity often include poor academic and occupational performance, problems in interpersonal relationships. Impulsivity is also associated with an elevated risk for substance abuse, cigarette smoking, driving problems or antisocial behaviors. [12]

1.2.1.1. Functional neuroanatomy of impulsivity

Functional neuroanatomy of symptoms is based on imaging of brain activity during execution of a specific behavioral paradigm. Therefore, there are no studies of impulsivity, hyperactivity,

nor any other clinical symptom. Rather, the neuroanatomy is based on associations between a particular pattern of responses during behavioral paradigm that engage specific cognitive processes and clinical manifestation of an illness. Impulsivity is associated with changes in reward processing, behavioral inhibition, and, perhaps, time processing. Failures in any of these processes can manifest as impulsivity. Although it might be difficult sometimes to differentiate what process causes a specific pattern of behavioral responses, for the sake of clarity the functional neuroanatomy of reward, behavioral inhibition, and time processing will be elaborated individually. The evidence suggests that they represent distinct patterns of brain circuit dysfunctions, and, therefore, they may form distinct phenotypes of impulsivity (i.e. "stopping" – "inhibition-dependent" and "waiting" – "reward-dependent" impulsivity).

Test features that require **inhibition** of inappropriate behaviour activate right inferior frontal gyrus, orbitofrontal gyrus, anterior cingulate, motor and premotor regions (motor cortex M1, supplementary motor area, dorsal premotor cortex), striatum, thalamus, and nucleus subthalamicus. It seems that behavioural inhibition itself consists of several subprocesses: inhibition of interference, response delay, and response cancellation. All of them are linked to the activation of the right inferior frontal gyrus, supplementary motor cortex, and parietal cortex. Inhibition of interference activates to a greater degree premotor and parietal cortex; cancellation of response represents a late phase of response inhibition and is linked with higher activation of fronto-striatal circuits. Meta-analysis of fMRI studies revealed strong evidence for decreased activation of the right inferior frontal gyrus, right supplementary motor area (BA6) and anterior cingulate (BA 32), right fusiform gyrus (BA 19), left caudate head, and right thalamus during motor inhibition tasks (Go-NoGo or Stop signal tasks) in ADHD [13].

Impulsivity linked with inadequate **reward processing** that involves decision-making and reward evaluation activates medial prefrontal cortex, medial orbitofrontal cortex, anterior cingulate, hippocampus, insula, amygdala, and ventral striatum or nucleus accumbens [9, 14]. Subjects with ADHD show decreased activation within this network, with a replicated finding of hypoactivation of ventral striatum during reward anticipation [15]. Edel et al. [16] showed that there might be dissociation of the neuronal deficit during reward processing between ADHD subtypes: predominantly inattentive subtype was linked with hypoactivation of ventral striatum, combined subtype with hypoactivation of orbitofrontal cortex.

1.2.2. Attention deficit

Deficits of sustained attention belong to very common findings in ADHD. A meta-analysis of fMRI studies (that used Continuous performance, Odd-ball, or Mental rotation tasks) detected significant decrease of brain activity in the right dorsolateral prefrontal cortex (BA 8, 46), right inferior parietal cortex (BA 40), right precuneus (BA 7), right superior temporal gyrus (BA 42), left putamen, and right thalamus; on the other hand, increased activity in cerebellum was found too [13]. However, individual studies show also involvement of the left hemisphere dysfunctions – using fMRI during vigilance task in boys with ADHD found decreased activation of the left dorsolateral prefrontal cortex (middle frontal gyrus, BA 46, 9, 8), superior parietal cortex (postcentral gyrus, BA 6, 4, 2, 1, 7), and subcortical structures involved in fronto-striatal loops [17]. DLPFC activation was related to the test performance, i.e. the reduced

DLPFC activation corresponded to deficits in sustained attention. Findings of abnormal functional connectivity within fronto-striatal loop during Continuous performance task in children with ADHD [18] demonstrates that the abnormal pattern of activity affects whole networks – which might be advantageous for the TMS applications, where only selected parts of the network are accessible, and still the influence of a part of a network may affect interconnected areas as well.

Arnsten describes a comprehensible model of attention, with two systems. The "bottom-up" system represents stimuli from the environment processed in association areas (posterior parts of the brain – the occipital, parietal, and temporal lobes) and projected to the PFC according to their salience. The "top-down" system represents the actions of the PFC which chooses which stimuli will be enhanced (relevant) and which will be suppressed (distracting) according to their relevance for long-time goals processed by the PFC. The PFC uses its extensive projections back to the sensory association cortices. [19]

In addition to the disorders of attention, dysfunction of several other cognitive functions, such as working memory and executive functions can be found in ADHD [20], albeit only in a subgroup of patients [21]. They are linked to reduced DLPFC activity [22].

1.2.3. Time processing

There exists growing evidence on impairment of various time-processing mechanisms in ADHD that form an independent domain of ADHD manifestation: perceptual timing, temporal foresight, and motor timing reflected in abnormalities of interval duration estimation and discrimination, delay discounting, and sensorimotor synchronization [23], i.e. processing of both interval estimation and fine-grained millisecond timing of brain events is affected. Since there is a relationship between time-processing deficits and measures of impulsivity and attention deficit [23], it seems that this neurocognitive abnormality may be another source of core behavioral manifestations of ADHD.

Functional neuroanatomy of time-processing deficits in ADHD converges on the pattern of reduced activation of bilateral inferior frontal gyrus, orbitofrontal cortex (in particular, in time foresight paradigms – delayed discounting task), SMA, precentral gyrus, insula, and cerebellum [24–27].

1.2.4. Emotion dysregulation

Emotion dysregulation is an important component of ADHD and according to many it should be considered in diagnostic conceptualizations of ADHD [28, 29]. It was found to be linked to some ADHD variables such as greater ADHD functional impairment, lower quality of life, ADHD persistence, and higher ADHD severity in childhood [30]. Shaw et al. [31] describes emotion dysregulation as emotional expressions and experiences that are excessive in relation to social norms and context-inappropriate; rapid, poorly controlled shifts in emotion ("lability"); and the anomalous allocation of attention to emotional stimuli. In the study of Vidal et al., adults with ADHD presented higher levels of emotional lability when compared to clinical control subjects and community subjects [30].

Similarly to attention, there are different systems that regulate emotions. The "bottom-up" system is represented by emotional responses of the amygdala and ventral striatum to external stimuli. Their projections to prefrontal cortex (PFC) draw attention to emotionally loaded processes and similarly to attention, this bottom-up system stresses salience of emotions and not their current relevance. Subcortical structures, the amygdala, and the ventral striatum play a key role in generation of emotions. These areas project to ventrolateral prefrontal cortex (VLPFC), which is not a centre for emotion regulation, rather it decides if regulation is necessary. The need for regulation is signalized to the dorsolateral PFC (DLPFC), either via the anterior middle cingulate cortex or directly. The DLPFC processes the information from VLPFC and relays it to other brain structures involved in emotomotor control [32], which represents the “top-down” regulation based on relevance of the emotion for tasks and goals currently processed by the DLPFC. This ability is included in the broader concept of "executive functions", i.e. the processes that are focused on attaining long-term goals through organizing and planning.

Emotion dysregulation in ADHD may arise from deficits at multiple levels. These range from abnormal early orienting to emotional stimuli, particularly with regard to negative stimuli and reward valuation through an inability to recruit top-down regulatory effort in response to emotional stimuli. Meantime, deficits in cognitive processes, including working memory and response inhibition, may contribute to emotion dysregulation, but they do not seem to be alone to explain its presence in ADHD [31]. In children with ADHD and emotional lability, deficits in emotion regulation were associated with altered amygdala–cortical intrinsic functional connectivity (iFC). The cortical structures involved were rostral anterior cingulate cortex (positive iFC in individuals with high emotional lability). Emotional lability scores were also negatively associated with iFC between bilateral amygdala and posterior insula/superior temporal gyrus [33].

1.2.5. Motor symptoms and hyperactivity

Hyperactivity is a non-specifically increased tendency to act. The question is if it is a consequence of inadequate motor inhibition or if there are other sources for hyperactivity. Although there are no functional imaging studies of hyperactivity per se, there are reports of motor system changes in ADHD. During simple motor tasks, reduced activity of primary motor (BA4) and sensor cortex in ADHD subjects was observed [34]. Moreover, abnormal co-operation of motor system was seen as well – McLeod et al. (2014) [35] described reductions in functional connectivity at rest between the primary motor cortex and the bilateral inferior frontal gyri, right supramarginal gyrus, angular gyri, insular cortices, amygdala, putamen, and pallidum. It seems that increased lateral prefrontal cortex activity is involved in compensation of inadequate motor system performance in ADHD subjects [36].

1.3. Potential targets for rTMS treatment

From the network point of view, there seems to be an involvement of at least three distinct circuits – lateral attentional network, medial reward-related network, and fronto-cerebellar time-processing network. At present, the state-of-the-art rTMS technology enables modulation

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of regions that lay close to the surface of the brain, i.e. lateral parts. Based on the above reviewed functional neuroanatomy, potential accessible candidate targets are represented by dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, inferior frontal gyrus, dorsal parts of supplementary motor cortex, and cerebellum. Modulation of dorsolateral prefrontal cortex may lead to changes of attention, working memory, and executive functions, but through the top-down regulations it may exert effects on emotional dysregulation symptoms, and impulsivity. Inferior frontal gyrus stimulation may lead to changes in behavioral inhibition and time estimation. Cerebellar stimulation may influence time processing, cognitive functioning, and, perhaps, even the affective symptoms of ADHD. rTMS of cerebellum is technically possible; however, the tolerability due to the neck muscle stimulation might limit its clinical use. Quite recently, rTMS approaches that use a double-cone or HAUT coils demonstrated their ability to modulate activity of medial cortical regions [37, 38]. This technological advancement would enable direct targeting of medial cortical nodes related to reward processing, which may bring increased efficacy in the treatment of impulsivity in ADHD.

2. Repetitive transcranial magnetic stimulation

2.1. General description and current use in psychiatry

Transcranial magnetic stimulation (TMS) is a diagnostic and therapeutical technique based on the principle of electromagnetic induction of electric current in the brain. It uses high-density magnetic field (approximately 2T lasting 0.1 ms) to induce electric field inside cortex, which is able to depolarize neurons [39]. Repetitive transcranial magnetic stimulation (rTMS) depolarizes neurons repetitively with either high (HF) or low frequency (LF) in order to change neuronal excitability for a longer period of time. The excitability can be lowered by using a low-frequency stimulation [40], and vice versa, high-frequency stimulation is able to render the neuron more sensible to stimuli, thus more excitable [41]. Findings from the neuroimaging studies that have localized dysfunctional parts of cortex in particular diseases can be transformed into new treatment approaches. However, recent findings suggest that the effect of rTMS is more complex and the excitatory/inhibitory paradigm is not fully satisfying as some works suggest mixed excitatory and inhibitory effects of either HF or LF-rTMS [42] and the excitatory effect of HF-rTMS on motor-evoked potentials might be caused by the decrease of gamma-amminobutyric acid-mediated inhibition [43]. The method is non-invasive and few side effects have been reported so far. The complete mechanism of changes remains unclear, but it is believed that rTMS affects gene expression [44], synaptic plasticity, dopamine release [45, 46], and release of endogenous opioids [47]. The ability of rTMS to affect not only the particular area it is aimed at but also the whole functional site is crucial as it is able to modulate function in more distant parts of brain [48, 49].

Each rTMS protocol is characterized by its focus of stimulation, frequency of stimuli, intensity, frequency of sessions, total number of pulses, train and intertrain time, a total time of session, and the shape of the coil. Taking this into account, many variables which can modify the effect of stimulation are present and researchers need to consider each of them when designing a

protocol. The choice of the region of the brain cortex used for stimulation is based on lesion studies or imaging data that suggest an approximate localization of the studied cortical function, e.g. dorsolateral prefrontal cortex, supplementary motor area, etc. The choice of a particular place on subject's scalp to put on the coil is based on anatomy or imaging data of the particular subject. The intensity of each stimulation is usually standardized according to a percent of RMT (resting motor threshold), determined in each individual. 1 Hz stimulation is typically used for LF-rTMS, and 5–20 Hz stimulation in HF-rTMS. Multiple imaging techniques are used for online monitoring of rTMS effect in studies (EEG, PET, fMRI).

Another form of rTMS – the Theta-Burst stimulation (TBS) – consists of 3 pulses at 50 Hz repeated at 200 ms interval (hence 5 Hz frequency). This stimulation, when applied continuously (cTBS), is considered to mimic long-term depression effect on cortical excitability, while when applied intermittently (iTBS), long-term potentiation-like (LTP-like) effect is observed [50]. However, Gamboa showed that doubling the duration of the stimulation leads to conversion of its effect [51].

Largest body of evidence supporting the efficacy of rTMS was reached in trials with patients suffering of drug-resistant major depression and this success of rTMS led to approval of this technique in this indication by Food and Drug Administration in the USA in 2008. The method is also used in neuropsychiatry for the treatment of anxiety disorders [52], child autism [53, 54], Parkinson's disease [55], and positive symptoms of schizophrenia such as auditory hallucinations [56, 57]. And for number of other diseases, this technique is in various states of research (neuropathic pain, Tourette's syndrome, stroke, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, Alzheimer's disease, tinnitus, obsessive compulsive disorder, negative symptoms of schizophrenia, substance abuse, addiction, and craving) [55].

2.1.1. Safety issues

Although rTMS is believed to be a very safe technique, several side effects were described in previous studies. Of the major concern is the possibility of seizure induction, mostly during excitatory rTMS (HF), considered the most serious TMS-related acute side effect. However, the incidence of seizures was extremely rare (0.1–0.5%) and was mostly connected to receiving rTMS exceeding previous guideline recommendations, often in patients under a medication potentially lowering the seizure threshold. A short intertrain time is considered to be one of the potential triggers of seizures during rTMS [58]. Further research and analysis should be performed to identify protocol aspects and indication criteria lowering the risk of seizures.

As rTMS produces rather intensive noise (over 120 dB) [59], considerations about its effect on patient's hearing should be taken into account. The amplitude of rTMS sound depends on the coil design and the absolute stimulation intensity. Thus, sound intensity experienced by the patient during stimulation depends directly on the subject's motor threshold which is individually variable across the population [60]. According to safety guidelines [58], hearing protection is highly recommended as some subjects with no hearing protection experienced a hearing loss or threshold shifts in past studies [61, 62].

Headache is a relatively frequent adverse effect of rTMS, but this discomfort usually vanishes within minutes with either no need for medications or it responds to common analgesics. A scalp pain or discomfort is a common adverse effect of rTMS as well and an ideal method to decrease this discomfort is still in research (e.g. local application of lidocaine) [63, 64]. However, the scalp pain and discomfort typically vanish straight after the application of pulses and eventually it seems there is a kind of accommodation as the first session is usually refered as the most painful.

Repetitive transcranial magnetic stimulation is contraindicated in patients with metallic (conductive, ferromagnetic, or other magnetic-sensitive) objects in or near the head (within 30 cm of the treatment coil), e.g. implanted electrodes, bullet fragments, aneurysm clips, stents and similar, or implanted stimulator devices in or near the head, e.g. deep brain stimulators and vagus nerve stimulators.

2.2. Repetitive transcranial magnetic stimulation in the treatment of ADHD

2.2.1. Children and adolescents

Several limitations exist for the use of any therapy in children regarding their developing brain. Every novel therapy in neuropsychiatry needs to be evaluated carefully in children, especially in the terms of long-term safety. According to the theory of "sensitive periods" (a time period within brain development when an intervention has a strong effect on the brain [65]) in childhood, neuromodulation methods might be able to affect the brain function in a more stable and effective way during these periods. Although there is no evidence of any serious side effects of rTMS in children, it has to be kept in mind that the risk of inducing maladaptive neuroplasticity during sensitive periods of development of the child brain is still present and there is great need to clearly describe the neurophysiology of the impact of rTMS on a developing brain [54].

Dorsolateral prefrontal cortex (DLPFC), and especially right DLPFC, is believed to be highly involved in the pathophysiology of ADHD – see above. Two studies reported an application of rTMS over DLPFC in children and adolescents with ADHD. Weaver and colleagues (2012) applied HF-rTMS (10 Hz, 100% of the observed motor threshold) over the right DLPFC in 9 young patients (4 of them between 15 and 17). Their sham-controlled crossover safety study revealed an overall improvement in ADHD symptoms, but no difference between the sham and the active rTMS sessions [66]. Isenberg et al. showed that LF-rTMS on the left DLPFC has similar effect in patients with depression as HF-rTMS on the right DLPFC [67]. Gomez et al. based their protocol on these findings and applied 1 Hz rTMS of 90% of the rest motor threshold over the left DLPFC in ten school-aged boys (ages 7–12) suffering from ADHD. Although this study was performed to establish tolerability and safety of this protocol in children, their preliminary results have been promising because of significant clinical improvement of ADHD symptoms (mainly inattentiveness in school and hyperactivity/impulsivity at home) as referred by teachers, parents, and partly confirmed by the attending physician [68].

Two other studies applied the rTMS in children with ADHD for different purposes. One of them successfully evaluated TMS-evoked N100 measuring by EEG as a suitable marker for

online monitoring of rTMS effects in children with ADHD as they found significant reduction of the amplitude of TMS-evoked N100 in comparison to the sham stimulation [69]. Loo et al. (2006) used 10 Hz rTMS on two 16-years-old girls suffering from depression and ADHD and described improvement in depression but no change in ADHD symptoms [70]. Nevertheless, all these studies revealed no serious adverse effects in children with ADHD undergoing rTMS.

Considering the wide comorbidity of ADHD and Tourette's syndrome (60–80% according to hospital studies) [71], it is worth noticing some promising results of rTMS treatment. Two studies [72, 73] applied LF-rTMS of 100/110% of motor threshold over the supplementary motor area and showed significant improvement in tics; these improvements lasted for a minimum of 6 months [73]. However, three participants with ADHD reported no change in ADHD symptoms. Nevertheless, improving the tic symptoms can increase the compliance of ADHD patients and give the therapist possibility to better address the therapy of ADHD symptoms.

2.2.2. Adults

As the recent findings have revealed, in over 50% of children with ADHD the symptoms persist to adulthood. Adult ADHD has become a large point of interest for research. Considering the fact that attention deficit symptoms tend to persist into adulthood more often than hyperactivity symptoms, a pilot study was performed using HF-rTMS on the right DLPFC. This stimulation resulted in improvements in attention but with small clinical significance [74]. One patient in a case study reported particular dysphoria, inability to respond emotionally, hypobulia, tension, and impaired attention after the same stimulation protocol [75]. Applying inhibitory protocol on the contralateral DLPFC might be worth trying as well.

On the other hand, two studies with inhibitory protocol with LF-rTMS over the supplementary motor area (SMA) reported significant clinical improvement in hyperactivity in two women with the hyperactive/impulsive subtype of ADHD [76, 77].

Some studies focused on other functions typically impaired in ADHD (e.g. attention, impulsivity) trying to influence them by non-invasive brain stimulation in healthy population. The DLPFC was stimulated in studies measuring the effect of stimulation on sustained attention or impulsivity or inhibition. HF-rTMS over the left DLPFC led to better performance in the Conners Continuous Performance task [78]. Continuous Theta-burst stimulation over the DLPFC resulted in choosing larger delayed rewards rather than smaller immediate ones in the Delay Discounting test [79]. Similar results were reached after stimulation of the medial prefrontal cortex by HF-rTMS [80]. Interestingly, anodal transcranial direct current stimulation (tDCS) applied over either the left or the right DLPFC resulted in more careful driving on a driving simulator [81].

The performance in the Stop Signal task, which is also used for the diagnosis of impulsivity, was affected by anodal tDCS over the pre-SMA and participants performed greater number of correctly inhibited responses in comparison with the active stimulation over M1 [82].

2.3. Why are the results of studies so variable?

The differences between individual studies result from their methodology. There are great many parameters in rTMS that can be adjusted differently. The parameters are described above and studies use unequal designs. The reason for such differences is the practical absence of standard rTMS protocols for ADHD, the firm knowledge of the right technical setting is absent.

There is a possibility to use parameters that have been successful in the treatment of depressive disorder or negative symptoms of schizophrenia where the stimulation of the DLPFC is applied as well – high frequency, ideally 10Hz, above-threshold intensity (above 100% of the individual's resting motor threshold), higher number of treatment sessions (15 at least), higher number of pulses per session and totally during the treatment, and possibly the use of structural and functional brain imaging techniques for more accurate targeting of the best place of stimulation. This protocol has to be tested in trials (double-blind and placebo-controlled ideally) that could prove whether these parameters are really optimal for patients with ADHD. It is worth noting that in patients with obsessive-compulsive disorder this assumption was wrong and there is a search for a different target instead of the DLPFC. Even the protocols for much more studied disorders like depression or negative symptoms of schizophrenia differ, however, in different studies. In ADHD studies, the inter-individual variability is an important factor as extensive studies are lacking. The same protocol may lead to different outcomes in individual patients and in small sample studies the inter-individual variability can overweight the inter-group variability.

The measures of outcome can also differ in different studies. ADHD is defined by its diagnostic criteria and a lot of questionnaires are used to measure the changes in symptomatology. The functioning in individuals with ADHD varies considerably and the results in neuropsychological tests correspond to this variability. Changes induced by rTMS may be small and only detectable in testing, but patients' expectations may be higher with such a "hi-tech treatment" so patients can subjectively overestimate or underestimate the results. More studies examining patients' subjective feelings as well as objective measures of attention and hyperactivity before and after rTMS are needed.

3. Case study

An adult female patient 25-years-old with ADHD, a university student, was enrolled to the pilot study which examined the efficacy and safety of repetitive transcranial magnetic stimulation (rTMS) in adult ADHD. Although she described having had the symptoms of ADHD before starting school education at the age of 6 years, she was never diagnosed by a psychiatrist and was never treated. She was assessed by only a school psychologist who communicated to her parents that she would not be able to study at university. She, however, did not give up, and this motivated her to work harder. She had good results at basic and secondary schools even though she suffered from inattention. The results at university were considerably poorer, but with a high level of motivation she was able to finish her bachelor's degree. Nonetheless, she had to consult a psychiatrist for the first time during the studies and

she was diagnosed with adjustment disorder with prevailing depressive mood and suspected ADHD. She was medicated with paroxetine 20 mg daily and also with valproate 500 mg daily for emotional instability. Her mood improved with the medication, but she still had disturbing symptoms of inattention. A year later she found our experimental rTMS study and agreed willingly to participate.

Before the procedure, she was assessed by two psychiatrists experienced in diagnosing ADHD and the diagnosis was confirmed. Consecutively, she had a neuropsychological evaluation aimed at attention. She did not meet any contraindication for rTMS (epilepsy, pathological EEG, metal object in skull, cardiostimulator, or drug pump) and thus she could start rTMS. The high-frequency stimulation of the left dorsolateral prefrontal cortex (DLPFC) was used; this alternative had been previously used in another patient with ADHD (see [74]) and seemed effective and well-tolerated.

Before the initiation of stimulation, we first localized the spot whose stimulation triggered a motor-evoked potential (MEP) in the abductor pollicis brevis muscle. Then, we determined in a standard way the resting motor threshold (RMT) as the lowest stimulation intensity that is able to trigger a MEP of at least 50 μV in the above mentioned muscle five times out of ten consecutive trials [83]. The exact stimulation localization was determined according to the "5 cms rule" – that is, a localization 5 cm more rostral from the RTM spot. The patient had ten sessions during her treatment with high-frequency (10Hz) rTMS; the intensity was 110% of the RTM; and the pulse count was 1500 in a session with the stimulation train invariably 10 seconds long with an inter-train pause of 30 seconds. The treatment was well tolerated and no adverse effects were seen during the whole course of treatment. After treatment, she did not feel any subjective improvement in attention, but the control neuropsychological evaluation showed improvements in almost all tests focused on attention. A few weeks after rTMS, she was informed she was in the second trimester of pregnancy which meant she had been pregnant in the course of the rTMS treatment. In a year, she contacted us again and reported her pregnancy without complications as well as the delivery of a healthy child. She even managed to finish successfully her university studies.

This case study supports with evidence the hypothesis that rTMS may be an effective and safe treatment option for adult ADHD. It seems safe even in pregnant female subjects; the evidence is however insufficient.

4. Summary

rTMS treatment of ADHD is in its infancy. The best treatment regimen, duration of acute treatment, neurostimulation target, and symptoms modulated by rTMS are to be determined. Although the method proved to be effective in several psychiatric indications (schizophrenia, major depression), the efficacy in ADHD needs to be studied in detail before any final conclusions. The neurobiology of ADHD is linked with dysfunctions of cortical regions that are accessible to rTMS modulation. The many regulatory functions of DLPFC enable TMS stimulation trials for many disorders. Majority of neurobiologic findings in ADHD involve

this cortical area, thus giving sense to the use of rTMS in ADHD. Since frequent limitation of rTMS studies is only approximate localization of stimulation targets, when trying to target specific regions linked with ADHD, fMRI-guided neuronavigation may be of crucial importance for the success of treatment regimens.

5. Abbreviations

This chapter tries to provide with current knowledge about the neurobiology of ADHD for the purpose of explaining the role of a novel treatment approach in psychiatry – repetitive transcranial magnetic stimulation. The structures of brain have usually long and complicated names. We use some abbreviations to shorten the text. All abbreviations are written in full words as they occur for the first time. Here are some of the most common for your reference.

ADHD – attention-deficit hyperactivity disorder

BA – Brodmann area

DCS – direct current stimulation

DLPFC – dorsolateral prefrontal cortex

fMRI – functional magnetic resonance imaging

HF – high frequency

LF – low frequency

PFC – prefrontal cortex

SMA – supplementary motor area

rTMS – repetitive transcranial magnetic stimulation

TMS – transcranial magnetic stimulation

VLPFC – ventrolateral prefrontal cortex

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