9 Neuromodulation in Attention-Deficit/Hyperactivity Disorder: Toward a Precision Psychiatry Approach

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9.1 Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a childhood onset, characterized by developmentally inadequate levels of inattention, hyperactivity, and impulsivity [1]. Epidemiological studies show a prevalence rate of ADHD in children of 5–6% [2, 3] and of 2.8% in adults [4]. ADHD persists in most cases from childhood to adulthood, and even if ADHD is considered "in partial remission," it still causes interference with the individual functioning and psychosocial impairment [5–7]. Apart from the widely recognized impairment associated with untreated ADHD, including academic failure, self-esteem problems, and interpersonal relationship difficulties, people with ADHD have an increased risk for being involved in criminal situations, for facing unplanned pregnancies, for suffering from sexually transmitted diseases and several health problems due to their maladaptive lifestyle habits, such as excessive cigarette consumption, impulsive and dysregulated eating leading to obesity, hypertension, and type 2 diabetes mellitus [8]. Also, a high prevalence of fibromyalgia syndrome (FMS) has been reported in patients with ADHD [9].

A hallmark of ADHD is its high heterogeneity, which can manifest not only between individuals who received the diagnosis but also within the same individuals across the lifespan. The classification of ADHD in the three presentations of predominantly hyperactive-impulsive, predominantly inattentive, or combined ADHD

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is only an attempt to deal with its heterogeneity, but even in this way two subjects with the same ADHD clinical presentation share no more than three symptoms [10]. Moreover, the ADHD presentation is not stable during the lifespan, as a child who received a diagnosis of predominantly inattentive ADHD can become an adult with a combined ADHD. The ADHD heterogeneity affects not only symptom profiles, but even neuropsychological impairments. In fact, although the evidence indicating that people with ADHD, as a group, are more impaired in some neuropsychological domains compared to healthy controls, and particularly in executive functioning and motivational processes [11–15], not all individuals with ADHD present this kind of deficits [11, 16, 17]. Furthmore, 50–75% of adults with ADHD have at least one comorbid learning, neurodevelopmental, or psychiatric disorder [18–22] complicating the current clinical presentation, and it is possible that some comorbid conditions, such as anxiety or depression, are not simple coexistent disorders, but rather the direct consequence of the lifelong impairment caused by untreated ADHD.

At present, the diagnosis of ADHD does not take into account etiological sources or biological markers, but it is established on the presence of a certain number of symptoms, presenting in more than one context and with an onset before age 12. However, even though the current manuals for diagnosing psychiatric disorders have been of value in facilitating communication between clinicians and researchers, they did not keep the promise of a heightened focus on neurobiological markers and on the use of a dimensional system, and failed in establishing the validity of their diagnostic categories beyond the clinical level. The relationship between ADHD clinical definition and its neurobiological substrates constitutes an important issue, as its etiological heterogeneity can be the result of diverse neural correlates, which in turn can explain the treatment response to different therapeutic agents, to different doses, and to a combination of them. In this context, the approach proposed by the National Institute of Mental Health (NIMH) called Research Domain Criteria (RDoC) emerged as a useful framework, as a project aiming to transform diagnosis by incorporating genetics, imaging, cognitive science, and other information levels in order to establish the starting point for a new classification system [23]. It assumes that mental disorders are biological conditions involving brain circuits that implicate specific domains of cognition, emotion, and behavior, and therefore symptoms cannot be constrained by the categories of current diagnostic manuals. Its ultimate goal is “precision medicine” for psychiatry, and therefore a diagnostic refinement based on a deeper understanding of the circuitries and networks of psychiatric disorders considered to be responsible for brain diseases [24].

Even though the treatment with psychostimulants is a mainstay of ADHD treatment, it is still challenged by stigma and fear regarding potential side effects. Moreover, it is estimated that at least 30% of individuals do not appropriately respond to, or are not able to tolerate them [25]. Last but not least, there are some concerns about the risk for stimulant misuse and diversion in ADHD patients [26]. Noninvasive brain stimulation (NIBS) techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), have been increasingly used in different contexts to improve cognitive performance

and ameliorate depressive symptoms [27]. Their use can be of value also for the treatment of the dysfunctional networks underpinning the clinical manifestation of ADHD.

9.2 The Rationale for the Use of NIBS in ADHD: Main Dysfunctional Networks

ADHD in children and adults is associated with several cognitive deficits and brain alterations. Studies on children with ADHD found impairments related to inhibitory control, sustained attention, visuospatial and verbal working memory, timing, vigilance, planning, and reward processing [11, 28–30]. Recently, great attention was focused on the finding regarding the association of ADHD with reaction time variability (RTV), which is thought to represent attentional lapses [28, 31, 32]. Similar impairments have been found in adults with ADHD [31–35]. There is consistent evidence indicating a disruption in several brain networks explaining the variety of cognitive deficits and behavioral symptoms characterizing people with ADHD. Impairments in the anterior cingulate cortico-striato-thalamo-cortical (ACCSTC) circuit, known as the selective attention circuit [36], are considered responsible for the lack of attention to details and distractibility characterizing people with ADHD. Deficient response inhibition appears related to impaired circuitry, including inferior frontal gyrus, anterior insula cortex, dorsomedial frontal cortex with the presupplementary motor area or pre-SMA and caudate [37–40]. Timing-related dysfunction is associated with functional hypoactivation of inferior frontal cortex, dorsolateral prefrontal cortex, supplementary motor area, anterior cingulate cortex, basal ganglia, parietal regions, and cerebellum [41, 42]. Impulsive decision making has been associated with disrupted connectivity between the nucleus accumbens and the anterior prefrontal cortex (PFC) and ventromedial PFC [43], ventro–striatal hypo-responsiveness during reward anticipation [44] and hyper-responsiveness in the ventral striatum/nucleus accumbens upon receipt of reward [45]. Alterations in the cortico-striatal network have been considered as underlying the deficits in motor control characterizing ADHD, causing excessive moving or talking in subjects affected by the disorder [46, 47]. Moreover, hypofunctionality in basal ganglia showed to predict poor movement preparations as well as cognitive planning deficits [48]. Emotional dysregulation seemed to be associated with an impaired emotion regulation network, including circuitry implicated in the emotional impulsivity (EI) and therefore mesolimbic circuitry, involving the orbitofrontal cortex, the amygdala, and the ventral striatum [49–51] as well as that of deficient emotional self-control (DESR) mediated by the ventrolateral prefrontal cortex, the medial prefrontal cortex, and the anterior cingulate cortical region [52–55]. Finally, ADHD is associated with reduced activation in neuroanatomical regions involved in working memory such as occipital, inferior parietal cortex, caudate nucleus, cerebellar regions [56] during working memory tasks, and in left and right prefrontal brain regions in both children and adults [57, 58].

Besides the rationale provided by the brain circuits alterations reported here, important insights for the use of NIBS for the treatment of ADHD symptomatology derive from studies indicating that the most used pharmacological agents for treating ADHD work by altering cortical excitability [59]. Indeed, methylphenidate influences motor cortex excitability in both inhibitory and excitatory neuronal circuitry in healthy subjects [59, 60].

On the basis of such evidence, NIBS techniques represent potential alternative tools with respect to ADHD medications for influencing cortical excitability. NIBS techniques offer the opportunity to develop a tailored intervention targeting a specific cognitive domain or other symptomatological dimension and, therefore, to the specific disrupted brain networks. Up until now, the NIBS brain targets in ADHD have been the dorsolateral prefrontal cortex (DLPFC) for inhibitory deficits, and the orbitofrontal cortex (OFC), which is more closely involved in motivational dysfunction [61].

The most used NIBS in ADHD are Transcranial Magnetic Stimulation or TMS and transcranial Direct Current Stimulation or tDCS. Both TMS and tDCS permit to modulate cortical and brain regions through electromagnetic fields or direct electrical currents over the scalp, which can either increase or decrease cortical excitability in relatively focal areas according to different stimulation parameters [62].

rTMS consists of repetitive trains of magnetic pulses, inducing temporary electrical currents in localized cortical tissue. Recently, two new rTMS protocols have been introduced, using theta burst stimulation or TBS. TBS consists of bursts of three pulses of stimulation with a frequency of 50 Hz repeated every 200 ms, provided through an intermittent bursting frequency (iTBS) with a facilitatory effect, or through a continuous bursting frequency (cTBS) with an inhibitory effect, inducing transient long-term depression of behavior [63, 64].

tDCS uses low-intensity direct current (up to 2.0 mA) through two or more electrodes placed on the scalp and modulates the resting membrane potential according to the type of electrode application.

9.3 TMS as a Therapeutic Tool: rTMS Studies in ADHD

To date, there are still few rTMS studies in people with ADHD, and the vast majority has been performed in children and adolescents. Helfrich and colleagues [65], in a randomized, sham-controlled study, investigated the effects of inhibitory rTMS in modifying the inhibitory/excitatory (I/E) unbalance in the motor system of children with ADHD ($N = 25$), by using as neurophysiological measures the TMS-evoked potentials (TEPs) and the motor-evoked potentials (MEPs). TEPs and MEPs in response to single-pulse TMS (110% resting motor threshold, RMT) were measured before and after active 1-Hz rTMS (900 pulses, 80% RMT) or sham stimulation (achieved through a deactivated coil) over the left M1, with the stimulation conditions delivered in counterbalanced order 30 minutes apart. rTMS showed to be safe and well tolerated, but the study results showed a decrease in N100 after inhibitory low frequency-rTMS (LF-rTMS) rather than an increase [66], not supporting

the use of rTMS to increase intracortical inhibition in ADHD [61]. However, findings from this study indicated that the N100 amplitude may be useful as an indicator to maximize the functional effects of rTMS on the cortex [65].

In a randomized, sham-controlled crossover study, nine adolescents and young adults with ADHD received either active or sham high frequency-rTMS (HF-rTMS) over the right DLPFC. The protocol was implemented in a counterbalanced order in two phases, each lasting 2 weeks, with 1-week interval of no treatment between phases. Ten-Hertz rTMS was delivered at 100% of the MT (2000 pulses per session, 5 sessions per week), with informant ratings regarding functional impairment and ADHD symptoms obtained at baseline, midpoint, and end of the study. Results by the comparison of rating scales scores showed that, despite a significant improvement in ADHD symptoms and impairment, there were no differences between active and sham rTMS [67]. Instead, a tolerability and safety pilot study performed by the group of Gómez and colleagues [68] using LF-rTMS in ten children with ADHD classified as nonresponders to conventional treatment showed interesting results. This study investigated the effects of 5 consecutive daily sessions of 1-Hz rTMS (90% RMT) over the left DLPFC, with a total of 1500 stimuli per session, by comparing informant reports (parents and teachers) collected before and 1 week after completing the rTMS sessions. For what concerns tolerability, all children completed treatment, reporting a slight headache or local discomfort in 70% of cases, neck pain in 20%, and one patient reporting brief dizziness (only in two sessions). Results from informant ratings showed a significant improvement in inattentive symptoms at school and hyperactive/impulsive behavior at home. However, several limitations of the study, such as the open-label design, the small sample, and the lack of a sham arm, could not allow testing its clinical efficacy [61].

Studies on the effectiveness of rTMS in adults with ADHD are very scarce. Bloch and co-workers [69], in their crossover double-blind, randomized, sham-controlled pilot study, investigated the effect of either a single session of HF-rTMS directed to the right prefrontal cortex (active rTMS) or a single session of sham rTMS on adults with an ADHD diagnosis according to DSM-IV ($N = 13$). The stimulation protocol consisted of a 20-Hz stimulation over the right DLPFC at a 100% MT for a total of 1680 stimuli per session. They found a specific beneficial effect on attention 10 minutes after active rTMS, with a subsequent improvement in attention, according to Positive and Negative Affect Schedule (PANAS) scores. Any significant effect on measures of mood and anxiety was detected and the sham rTMS showed no effect at all.

Niederhofer [70] reported improved ADHD symptoms in a case study that consisted of motor cortex stimulation using 1 Hz rTMS at 1200 pulses per day for 5 days.

Even though there are no published large, randomized, sham-controlled trials of therapeutic rTMS in ADHD so far, several clinical trials are ongoing, as documented on the website https://clinicaltrials.gov/.

Recently, also a trial with deep-TMS (dTMS), which uses special coils for reaching up to 4 cm beneath the surface of the skull, and that has been recently approved for both treatment-resistant major depressive disorder and treatment-resistant obsessive-compulsive disorder, has been performed in subjects with ADHD. Specifically, 26 adults with ADHD were included in a double-blind

sham-controlled study exploring the safety and effectiveness of bilateral prefrontal deep rTMS [71]. Subjects underwent 20 daily sessions targeting the prefrontal cortex with a bilateral coil at 120% of MT at high frequency, and behavioral and cognitive ADHD symptoms were evaluated through an ADHD-rating scale and a continuous performance test. At the end of the trial, results showed no differences in clinical outcomes between the active dTMS and sham groups, providing no support to the utility of such a bilateral prefrontal stimulation to treat adult ADHD.

Despite mixed results, the potential application of rTMS as an alternative or add-on treatment in ADHD seems supported by evidence emerging from positron emission tomography (PET) studies of rTMS, which revealed changes in striatal dopamine receptor occupancy following rTMS, being the changes localized to the specific region of the striatum serving the cortical target (dorsomedial prefrontal cortex, DMPFC, and dorsolateral prefrontal cortex, DLPFC) of stimulation [72, 73]. Moreover, dopamine agonists and antagonists appeared to potentiate or block the effects of rTMS [74]. Furthermore, there is growing evidence indicating the utility of rTMS in enhancing cognitive control, such as the excitatory dorsomedial rTMS protocol, which resulted effective in reducing impulsivity on a delay-discounting task [75, 76]. In relation to tolerability, TMS treatment is generally well tolerated, and among adverse reactions, the most frequently reported are mild and self-limited headache, scalp pain at the stimulation site, and potential transient hearing alterations caused by the clicking sound of the machine. The most serious adverse event is the seizure induction, which, however, is rare [77].

9.4 TMS as an Investigative Tool in ADHD

Since it permits us to evaluate motor pathways excitability, TMS represents a very useful investigative tool helping us to improve our understanding of the neurobiology of ADHD. TMS pulses are delivered to the primary motor cortex, and single- and paired-pulse TMS can capture the neurophysiological correlates of behavioral symptoms of ADHD in the motor cortex. For example, evidence from TMS studies as an investigative tool showed an inverse correlation between the Short-Interval Cortical Inhibition (SICI) and hyperactivity. As low levels of intracortical inhibition appeared associated with greater hyperactivity, and these abnormalities normalized after methylphenidate (MPH) administration [78], it has been suggested that SICI may represent a putative biomarker of ADHD symptom severity [78–82]. Interestingly, another TMS study, investigating motor cortex excitability and its modulation by attention in healthy adults, showed that SICI decreases under task conditions requiring attentional focus on an internal or external locus, compared to a resting condition [83]. Authors suggested that altered SICI characterizing other conditions, such as Tourette's syndrome [84] and ADHD [82, 85], may not be only the reflections of impaired intracortical GABA circuits per se, but the result of disorder-specific (and therefore different) attentional states [83].

Other TMS studies showed impaired transcallosal-mediated inhibition in ADHD [86–88], and that both latency and duration of the ipsilateral silent period (iSP) are prolonged in children with ADHD [86–88], with the duration being correlated with

hyperactivity and restlessness [89]. Instead, adults with ADHD showed a shortened iSP but a normal latency [89]. The increased iSP latencies in children with ADHD have been explained as a defective myelination of fast-conducting fibers in corpus callosum [86], indicating a callosal maturation deficit in ADHD approximating normality with increased age [86, 87]. Therefore, it is likely that the different iSP latencies found between children and adults with ADHD are due to developmental differences in the inhibitory intracortical pathways [90].

TMS can be a useful tool for guiding ADHD pharmacotherapy. ADHD children under medication with methylphenidate showed a significant prolongation of iSP duration and a latency shortening [88], indicating that methylphenidate, as an indirect dopamine agonist, might improve the imbalance between excitatory and inhibitory interneuronal activities of this neuronal network, via dopaminergic modulatory effects on the striato-thalamo-cortical loop [89]. As TMS studies showed SICI to be correlated with hyperactivity, and MPH administration showed a normalizing effect on SICI and hyperactivity, SICI has been suggested as an objective and quantitative proxy of the therapeutic effectiveness of MPH [81]. By identifying ADHD individuals showing a greater SICI change after MPH administration, it would be possible to identify potential responders from nonresponders. Moreover, by monitoring SICI changes, clinicians could optimize drug titration [81]. However, these hypotheses require more research and may benefit from the advances of TMS-evoked potentials. The combination of TMS with electroencephalography (TMS-EEG) appears as a powerful technology for characterizing and modulating brain networks. Indeed, TMS-EEG allows us to assess in vivo neural excitation, inhibition, connectivity as well as plasticity across brain regions providing useful information regarding brain function-behavior relationship in health and disease [91]. In this context, future research should take into account findings related to the utility of TEP monitoring, together with clinical EEG, for assessing the immediate online effects of rTMS on cortical excitability (N100 amplitude changed during 1 Hz stimulation) that may serve as a safety measure and to maximize the functional effects of rTMS on the cortex [65]. Moreover, TMS-EEG use may allow the assessment of neurophysiological responses to medications outside of the motor cortex [81, 92].

9.5 tDCS Studies in ADHD

In respect to the evidence of TMS as a therapeutic tool for both behavioral and cognitive symptoms in ADHD, which requires more research for establishing its efficacy, promising results come from the studies investigating the tDCS use on people with the disorder. Studies performed in children and adolescents with ADHD investigated the acute effects of a single session of tDCS on working memory dysfunction and inhibitory control deficits. A double-blind, sham-controlled experimental design investigated the effect of a single session of anodal active electrode (1 mA) over the left DLPFC and cathodal active electrode over the Cz during an N-back working memory (WM) task. Interestingly, tDCS demonstrated to improve significantly WM performance, but also the activation and connectivity of the WM network. Compared to sham condition, tDCS led to a greater activation of the left

DLPFC, left premotor cortex, left supplementary motor cortex, and precuneus, and its effect was long lasting. In fact, tDCS influenced the resting-state functional connectivity even 20 minutes after the stimulation [93].

In a sham-controlled experiment performed on 25 children with ADHD, anodal stimulation over the left DLPFC and cathodal stimulation over the right DLPFC showed a significant effect of tDCS on WM and interference inhibition. By changing parameters, using therefore cathodal stimulation of the left DLPFC and anodal stimulation of the right orbitofrontal cortex (OFC), a positive tDCS effect on response inhibition and improvement of attentional shifting have been also found [94].

Both anodal and cathodal tDCS on the left DLPFC improved performance accuracy during a Go/NoGo task in a sham-controlled trial performed on students with ADHD, indicating that both types of stimulation could improve executive functions in people with the disorder [95].

As the right inferior frontal gyrus has been recognized as an important region in the inhibitory control network, the effects of tDCS applied over this area in 21 male adolescents with ADHD and matched controls were explored. Subjects underwent three separate sessions of tDCS (anodal, cathodal, and sham) while completing a Flanker task. The overall analysis did not show a significant effect of tDCS, but in consideration of the learning effect from the first to the second session, the performance in the first session was therefore separately analyzed. This second analysis revealed that while ADHD patients receiving sham stimulation in the first session showed impaired interference control compared to controls, ADHD subjects who received anodal stimulation showed comparable performance levels (commission errors, reaction time variability) to the control group. According to these results, the authors concluded that anodal tDCS over the right inferior frontal gyrus could improve interference control in patients with ADHD [96].

A study exploring the effect of repeated sessions of tDCS (30 minutes for 5 days) with 2 mA anodal stimulation of the left DLPFC and cathode positioned over the right supraorbital area in a small group of children and adolescents with ADHD ($N = 9$) showed that tDCS induced a more efficient processing speed, improved detection of stimuli, and improved ability in switching between an ongoing activity and a new one [97].

In a randomized, double-blinded, sham-controlled crossover study performed on adolescents with ADHD ($N = 15$), 1 session a day for 5 consecutive days of anodal tDCS (active stimulation: 1 mA) over the left DLPC and cathodal active electrode over the Cz (vertex), during which patients performed a working memory task, anodal tDCS showed to significantly reduce clinical symptoms of inattention and impulsivity compared to sham stimulation. Noteworthy, tDCS effects appeared more pronounced 7 days after the end of stimulation, supporting the putative long-lasting clinical and neuropsychological changes of tDCS [98].

For what concerns adults with ADHD, tDCS studies performed on this kind of population showed promising results. A recent double-blind sham-controlled study investigated the effects of tDCS (2 mA) daily sessions of 20 minutes for 5 days with the anode over the right DLPFC and cathode over the left DLPFC in adults with ADHD ($N = 17$), through self-report measures for both ADHD symptoms and

impairment (Adult ADHD Report Scale and Sheehan Disability Scale). Results showed that subjects treated with active vs. sham tDCS with ADHD displayed a symptom reduction and a decreased impairment. Follow-up data analysis revealed a positive interaction between time and treatment in both self-rated inattention, impairment, and total ADHD score [99]. As the study of Cachoeira et al. [99] showed a clinical positive effect on ADHD symptomatology, which was driven primarily by attentional improvement rather than impulsivity/hyperactivity reduction, another group of researchers explored the effectiveness of 2 mA anodal stimulation (tDCS) applied over the left DLPFC versus sham stimulation in improving impulse control. Overall, 37 adults with ADHD completed two periods of three tDCS (or sham) sessions 2 weeks apart in a within-subject, double-blind, counterbalanced order and performed a fractal *N*-back training task concurrent with tDCS (or sham) stimulation. For this aim, participants also performed the Conners Continuous Performance Test (CPT) and the Stop Signal Task (SST), and the CPT and the SST reaction time (SSRT) were analyzed. A comparison between the CPT and SST scores performed at baseline, at the end of the treatment, and at a 3-day post-stimulation follow-up showed no significant change in SSRT but rather a decrease in CPT false-positive errors from baseline to end of treatment in the tDCS group, reflecting a reduction in impulsive response. Such positive effect did not persist at the follow-up conducted 3 days after the final stimulation session, but authors concluded that repeated tDCS may be a novel treatment for impulsivity in ADHD, although additional research was necessary to determine whether an optimized treatment approach could induce persistent effects [100].

A parallel, randomized, double-blind, sham-controlled trial performed on 30 adults with ADHD explored the efficacy of a single session of tDCS (1 mA anode over the left DLPFC and cathode over the right DLPFC) on the modulation of inhibitory control, as measured by a go/no-go task before and after the active/sham stimulation [101]. Results did not show any significant differences between active and sham tDCS, and it is not clear whether this lack of effect was due to the use of 1 mA current stimulation rather than 2 mA (the most used tDCS intensity in psychiatric disorders), or to the fact that, unlike many tDCS trials, in this study people were not required to simultaneously perform a cognitive task (online tDCS). The latter hypothesis has been considered as very likely, as the application of tDCS when subjects are actively involved in a cognitive task may activate more specific brain networks, resulting in better performance than when they are at rest. This is in line with evidence from studies coupling tDCS with cognitive training showing greater effects compared to tDCS intervention at rest [102, 103]. Furthermore, evidence from neuroimaging studies showed that people with ADHD are characterized by reduced brain activation in the prefrontal regions, and therefore one single session of tDCS may not be strong enough to improve their cognitive performance, even though it may enhance cortical excitability [104].

In consideration of the high frequency of comorbid disorders in people with ADHD, such as sleep-wake disorders, the recent findings from a study performed by Munz et al. [105] using slow-oscillating tDCS (so-tDCS) on children with ADHD ($N = 14$), aged 10–14 years, are noteworthy. They used so-tDCS, 0.75 Hz,

over the right and left DLPFC during non-REM sleep and evaluated its effect on inhibition using a Go/no-go Task. They found an enhancement of endogenous oscillatory activity as a result of their intervention, with an improvement of behavioral inhibition performance, which is typically impaired in ADHD. Previously, so-tDCS applied to 12 children with ADHD over the bilateral DLPFC in a double-blind crossover design showed an enhancement of declarative memory [106]. Therefore, Slow Oscillation (SO) has been considered as a promising somatic marker in the pathophysiology of ADHD [106–108] and a future potential therapeutic target [105].

In conclusion, tDCS is a low-cost, easily accessible, and pain-free stimulation method that is generally well tolerated, having limited side effects, such as itchiness or scalp irritation. It is easily applicable to children as well as adults with ADHD, notwithstanding the presence of a high level of hyperactivity. tDCS has been successfully used in the treatment of several neurological and psychiatric disorders, including Parkinson's disease and major depression [109]. Even though its mechanism of action is not fully understood, tDCS demonstrated the potential to induce some neurochemical modifications in targeted brain tissues, which last longer than the period of active stimulation [110], therefore allowing maintenance of results.

9.6 Summary of NIBS in ADHD

Collectively, evidence up to date provides support to the use of NIBS as a treatment tool for neurodevelopmental disorders such as ADHD, as these interventions showed to produce positive effects and particularly when combined with functional cognitive training. However, the studies conducted hitherto are characterized by some methodological issues, such as small sample sizes and lack or inconsistent use of sham protocols. Moreover, despite the high heterogeneity characterizing the ADHD phenotype, the vast majority of studies have focused mainly on the DLPFC stimulation. It should be underscored that, in spite of being NIBS protocols divided into excitatory and inhibitory, many subjects show opposite effects or even no effect at all. In fact, about 50% of subjects who receive 1-Hz rTMS show a pattern of excitation instead of inhibition, and similarly, a consistent proportion of people who receive 10-Hz rTMS display an inhibitory rather than excitatory pattern [76]. Variability appeared to characterize also 1-Hz parietal rTMS on resting-state functional connectivity, according to findings from fMRI studies [111]. As for TMS, also in studies using tDCS it has been reported that only the 36% show an excitatory effect after anodal stimulation and inhibitory effect after cathodal stimulation, while the opposite has been reported in 21% of cases [112].

In conclusion, NIBS techniques offer a promising new approach to reduce some ADHD dimensions of pathology. Although research in the use of NIBS in ADHD is still in its infancy, data deriving from protocols for strengthening cognitive control [76] may help to personalize the treatment plan of people with this neurodevelopmental disorder, and may be particularly well suited for comorbid cases. The use of combined TMS-EEG appears as particularly useful for the goal of "precision

medicine" for psychiatry, as interindividual differences in TMS-EEG markers of brain health seem to have a genetic basis [113]. Finally, the utility of Transcranial Near-Infrared Light Therapy, a noninvasive intervention in which near-infrared light (830 nm) is applied to forebrain, should be explored in ADHD, considering the recent evidence indicating some positive effects on core symptoms of autism spectrum disorders [114].

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