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Noninvasive Brain Stimulation in Pediatric ADHD: A Review

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Abstract

Attention-deficit hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders in the pediatric population. The clinical management of ADHD is currently limited by a lack of reliable diagnostic biomarkers and inadequate therapy for a minority of patients that do not respond to standard pharmacotherapy. There is optimism that noninvasive brain stimulation may help to address these limitations. Transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) are two methods of noninvasive brain stimulation that modulate cortical excitability and brain network activity. TMS can be used diagnostically to probe cortical neurophysiology, while daily use of repetitive TMS or tDCS can induce long-lasting and potentially therapeutic changes in targeted networks. In this review we highlight research showing the potential diagnostic and therapeutic applications of TMS and tDCS in pediatric ADHD. We also discuss the safety and ethics of using these tools in the pediatric population.

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B.R. conceived of the review, performed the literature review, and wrote the manuscript. A.D.B. also wrote the manuscript and reviewed the literature. S.L., A.R., D.J. and A.P.L. all contributed significantly to editing the manuscript and each contributed important ideas to the final product.

Declaration of conflicting interests

A.P.L serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Neuroelectrics, Neosync, and Novavision, and is listed as inventor in issued patents and patent applications on the real-time integration of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) and magnetic resonance imaging (MRI).

Keywords

ADHD; pediatric; neuromodulation; TMS; tDCS

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders, affecting 2 – 7.5% of school-aged children and often persisting into adulthood [1-4]. It is characterized by three core symptoms: inattention, hyperactivity, and impulsivity [3]. Despite intensive study, the pathophysiology of ADHD remains unclear [5]. The clinical management of ADHD is hindered by a lack of widely accepted biomarkers or diagnostic tests. As such, diagnosis is typically made using parent- and teacher-reported behavioural rating scales in combination with a physician's clinical impression, without regard to the neural correlates of the individual's symptoms. Pharmacological treatments for ADHD are generally effective and there is strong evidence that treatment improves long-term outcomes in several social and academic domains [6]. Despite the well-established clinical efficacy of available medications [7,8], a minority of patients do not respond to standard pharmacotherapy, and its use may be limited by side effects and concerns of abuse [9-11].

Noninvasive brain stimulation may help address some of the aforementioned diagnostic and therapeutic challenges associated with the clinical management of ADHD. Several noninvasive brain stimulation procedures are available to physicians and investigators, and all have in common the capacity to modulate cortical excitability via transcranial electrical stimulation. Of these, the two most common procedures are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), both of which are emerging as realistic clinical tools.

In this review we will briefly highlight leading theories regarding the neural basis of ADHD. We then discuss TMS and tDCS, focusing on their mechanism of neuromodulation, their safety profile in the pediatric population, and their application in ADHD. We also briefly discuss newer neuromodulation techniques and ethical considerations in applying noninvasive brain stimulation to the pediatric population.

Neural Correlates of ADHD

The exact pathophysiology of ADHD has been difficult to delineate due to complicating factors such as evolving diagnostic criteria, phenotypic heterogeneity, frequent comorbidities, and environmental variables that may exacerbate or mimic symptoms. The three hallmark symptoms of ADHD are each likely to have distinct neural substrates [12,13], which may obscure attempts to elucidate the pathophysiology from studies that incorporate a variety of clinical presentations. Even well designed neuroimaging studies in ADHD struggle with a variety of potentially confounding variables, such as maturational changes in the brain and motion artifacts from a population that has trouble complying with prolonged MRI studies [14]. Despite these challenges there has been some recent headway in understanding the neural correlates of ADHD.

One of the most influential theories for the neural basis of ADHD has focused on deficient inhibitory control leading to executive dysfunction [15,16], which is likely under genetic influence [17]. The neuroanatomical substrate of inhibitory control is believed to involve basal ganglia-thalamo-cortical circuits [18,19]. Specifically, this network links: the prefrontal cortex to the dorsal neostriatum via excitatory glutaminergic cells, the basal ganglia to the dorsomedial thalamus via inhibitory projections, and the thalamus back to the prefrontal cortex via excitatory projections [20,21]. Inhibitory control parallels the maturation of this circuit, and both structural and functional neuroimaging studies reveal differences in this circuit in association with ADHD [22-24].

A number of other large-scale networks have also been implicated in ADHD. Impulse control deficits have been linked to fronto-striatal circuits, specifically under-activity in the ventrolateral prefrontal cortex, dorsolateral prefrontal cortex and the anterior cingulate [25-27]. Anticipation of reward was shown to correspond with underactivity in the mesolimbic circuit, which includes the ventral striatum and orbitofrontal cortex [27,28]. Spatial working memory deficits are associated with a temporo-parietal circuit [29-31]. As noted, the involvement of these networks is likely to vary by ADHD subtype, which is taken into account with recent studies. [12,13]

To add a layer of complexity to the imaging findings in ADHD, abnormal patterns of brain activity may sometimes represent compensatory changes rather than the primary underlying deficits. For instance, there is a compensatory and likely adaptive increase in posterior parietal activity that accompanies under-activation in fronto-striatal regions during executive tasks [23,27,32-34].

There are also a large number of ADHD studies showing regional volumetric changes [23,24,35-39], abnormal trajectory of brain development, [37,40], abnormal functional connectivity [41] and abnormal EEG patterns [42,43] A detailed summary of this work is beyond the scope of this review, but several reviews are available: [12,37].

Structural and functional differences in the ADHD brain are accompanied by abnormalities of the catecholaminergic neurotransmitters, dopamine and norepinephrine, which are believed to be critical in the pathophysiology of ADHD [44,45]. Low levels of dopamine in prefrontal regions are associated with increased hyperactivity and irritability [46]. Stimulant drugs used in the treatment of ADHD increase dopamine and norepinephrine activity in frontostriatal networks with improvement in symptoms [47,48].

While acknowledging the complexity of ADHD and the significant limitations in our current understanding of the underlying neural processes, we now turn our attention to noninvasive brain stimulation and its potential utility in pediatric ADHD.

TMS Basics

Transcranial magnetic stimulation (TMS) is based on the principle of electromagnetic induction: an electric current in the stimulation coil produces a magnetic field, which induces an electric current in nearby conductors, in this case, in the cerebral cortex. The TMS device components include a charging mechanism, the storage capacitor, the thyrister,

and a discharging coil. The coil design impacts the focality of the resulting stimulation. A circular coil activates a broad area, a figure-8 coil provides relatively focal stimulation of approximately 5 mm^3, and an H-coil targets deeper structures, up to 6 cm below the stimulation site [49,50]. The induced electrical current triggers action potentials in the brain via current flowing parallel to the surface of the coil. The magnitude of the stimulation is inversely related to the distance from the coil [51].

Single-Pulse TMS

The simplest stimulation paradigm for TMS involves applying a single, brief electromagnetic pulse. When a TMS pulse is applied to the motor cortex it can elicit observable motor output, often in the contralateral hand [49]. The motor evoked potential resulting from the TMS pulse can be recorded using electromyography (EMG). When applied to the visual cortex a TMS pulse may induce a visual percept, or a phosphene. The effect of a single TMS pulse on other cortical areas outside the motor and visual cortices can be recorded by scalp EEG or other imaging modalities. The effects of a single TMS pulse are brief and its safety is well established [52].

Paired-Pulse TMS

Paired-pulse TMS stimulates the cortex with 2 pulses separated by a variable delay. The main application of this protocol is to measure cortical inhibitory-excitatory balance, which is described in more detail below.

Repetitive TMS

Repetitive TMS (rTMS) uses a rapid sequence of magnetic pulses to induce longer-lasting modulation of the underlying cortex. Low-frequency rTMS (1 Hz or less) generally has an inhibitory effect on the underlying cortex and high frequency stimulation will typically increase the excitability of the underlying cortex [53]. For example, when applied to the motor cortex, 1 Hz rTMS will depress the motor evoked potential while 20 Hz rTMS will increase it [54,55]. Theta-burst stimulation (TBS) is a patterned form of rTMS that requires less stimulation time relative to the duration of effect. For example, a single session with 3 minutes of theta-burst stimulation may modulate the underlying cortex for 30 minutes, and the duration of effect is extended with repeated application. Continuous theta-burst stimulation typically has an inhibitory effect on the underlying cortex, while intermittent theta-burst stimulation is excitatory [56]. Single sessions of TBS in children appear to be safe and well tolerated [57].

TMS Measures of Cortical Excitability

There are a few commonly used neurophysiological measures to study cortical excitability, which have relevance as potential diagnostic tests for ADHD. Motor threshold is a proxy of motor cortex excitability [58,59], and is defined as the minimum intensity of stimulation necessary to elicit a motor evoked potential (>50μV) in a target muscle 50% of the time [53].

Paired-pulse TMS protocols are used to assess the intracortical inhibitory-excitatory balance. Varying the interstimulus interval between two TMS pulses leads to reliable alterations in

the size of the motor evoked potential. The three most commonly used paired-pulse protocols include: short-interval intracortical inhibition (SICI), long-interval intracortical inhibition (LICI), and intracortical facilitation. SICI uses a subthreshold TMS pulse followed by a short interstimulus interval of 1-5msec, then a suprathreshold pulse [60]. The first pulse may activate inhibitory neurons that project to corticospinal neurons, thus lowering the excitability of these corticospinal neurons for the 2nd suprathrshold stimulus [60]. This effect appears to be mediated primarily by $GABA_A$, [61-63]. LICI uses two suprathreshold pulses at a longer interstimulus interval of 50-100ms. $GABA_B$ has a role in mediating the inhibitory effect of the first pulse on the second [63]. Intracortical facilitation uses a subthreshold pulse followed by a suprathreshold pulse, separated by an interstimulus interval of 7-20ms [60]. In this case the initial pulse facilitates the motor evoked potential of the second, possibly mediated by NMDA-receptor excitatory neurotransmission [60].

In addition to using motor output to assess cortical excitability of the motor cortex it is also possible to combine TMS with EEG to probe other cortical regions [64] .

TMS pulses can elicit a characteristic EEG response, termed a TMS-evoked potential. This consists of a set of peaks and volleys in the EEG that occurs along a defined temporal sequence. These tend to be consistent among subjects, and the amplitude can be correlated to other measures of cortical excitability, even at intensities below the motor threshold.

Interhemispheric Connectivity

Paired pulse stimulation can also be used to study interhemispheric interactions using two TMS coils. The effects of a conditioning stimulus applied to the motor cortex of one hemisphere can affect the motor evoked potential elicited by TMS in the contralateral hemisphere [65]. The motor evoked potential is reduced if the conditioning stimulus in the opposite hemisphere precedes the second stimulus by 7 msec or more [65]. This interhemispheric inhibition appears to occur at the level of motor cortex and it is mediated by transcallosal motor fibers. The ipsilateral cortical silent period is another protocol for assessing interhemispheric interaction. It involves a single TMS pulse to the motor cortex that induces a transient suppression of voluntary tonic muscle activity in the ipsilateral hand muscles, as assessed with EMG [65]. It may be mediated by excitatory transcallosal neurons projecting to contralateral inhibitory interneurons in the homologous region of the motor cortex, thus reflecting the functional integrity of the transcallosal projections between motor cortices [65,66].

Noninvasive Brain Stimulation in ADHD

Literature Review Method

The use of noninvasive brain stimulation in the ADHD pediatric population was searched systematically using MEDLINE. Search terms included [(ADHD) OR (comorbidities) OR (neuroplasticity) OR (child psychiatry) OR (child neurology) OR (adolescents)] AND [(transcranial magnetic stimulation) OR (transcranial direct current stimulation) OR (alternating current stimulation) OR (transcranial random noise stimulation)]. Searches were

limited to humans under age 18. References of the articles obtained were cross-referenced. The literature review was performed in January of 2015.

TMS as a Diagnostic Tool in ADHD

Behavioral ratings of hyperactivity in ADHD patients have neurophysiological correlates in the motor cortex, which can be probed with single-pulse and paired-pulse TMS protocols (Table 1). These studies have shown an inverse correlation between SICI and hyperactivity, such that low levels of intracortical inhibition are associated with greater hyperactivity. This suggests that SICI may serve as a biomarker of symptom severity [16,67-69]. Moreover, these abnormalities in SICI improve with administration of methylphenidate [67]. It is not clear if these deficits in cortical inhibition are due to differences at a microscopic scale or from large-scale network properties, or some combination. It is similarly unclear if differences in cortical excitability in ADHD are present throughout the cortex or limited to the motor cortex.

In addition to differences in SICI, transcallosal-mediated inhibition is also deficient in ADHD [70-72]. Both the latency and duration of the ipsilateral silent period is prolonged in children with ADHD [70-72], with the duration being correlated with hyperactivity and restlessness [73]. The cause of abnormal transcallosal-mediated inhibition in pediatric ADHD is not clear. The ipsilateral silent period normalizes with a single dose of methylphenidate, suggesting that abnormal motor cortex excitability may have a more important role than structural differences in the corpus callosum. This view is also supported by the inverse correlation of ipsilateral silent period duration and magnitude of the SICI [54,74].

Interestingly, early results of cortical excitability from adults differ from those reported in the pediatric population. Adults with ADHD have less hyperactivity and relatively normal inhibitory motor circuits [73]. Unlike children with ADHD, adults have a shortened ipsilateral silent period with normal latency [73]. These differences between adults and children may relate to developmental differences in the inhibitory intracortical pathways [75], but additional study is needed. A neurophysiologic correlate of inattentive symptoms in ADHD has not been identified.

TMS-evoked EEG potentials have also been used to assess neurophysiology in ADHD cohorts. The negative deflection of EEG at 100 milliseconds after a TMS pulse, termed the N100, is a proxy of cortical inhibitory processes [76-80]. Recent studies have shown N100 abnormalities in association with ADHD [808182].

Most of the research to date relevant to TMS-derived neurophysiological measures in ADHD has focused on the motor cortex. TMS-evoked potentials, as described above, will allow future studies to incorporate physiological measures of sites beyond the motor cortex. As methodologies improve and become easier to integrate, future studies may use TMS-EEG to probe the neurophysiology of individual networks [83,8483]. The ultimate diagnostic utility of TMS-derived measures may require an integration of multiple parameters to elucidate a neurophysiological profile to which machine learning algorithms could be applied to identify common profiles among patients with ADHD or even subgroups within ADHD cohorts, a technique currently being explored in neuroimaging research [13].

TMS in Guiding Pharmacotherapy in ADHD

To date, the selection of specific medications for ADHD treatment is done empirically, often using trial and error to identify the optimal medication for an individual patient. Current pharmacotherapy is not reliably guided by any disease-specific biomarkers or diagnostic tests, though advances in pharmacognetics may prove useful with further study [85]. It is possible that neurophysiological abnormalities assessed by TMS could also be used for this purpose [86]. Methylphenidate enhances SICI, which has also been reported with other medications that enhance dopaminergic neurotransmission [67,87-91]. Given that SICI is correlated to hyperactivity, and methylphenidate normalizes SICI and improves hyperactivity, it is possible that SICI could be used as an objective and quantitative proxy of the therapeutic effectiveness of methylphenidate. There are a variety of potential uses for this information, such as identifying whether an individual has a greater change in SICI with methylphenidate versus other ADHD medications, or as a way to identify methylphenidate non-responders without the need for a prolonged medication trial. SICI could also be monitored as a way to optimize dosing to adjust for increased weight or increased tolerance over time. SICI could also be tracked when investigating new medications for ADHD. Each of these possibilities would require careful investigation prior to any clinical use. As advances are made in the study of TMS-evoked potentials, it may be possible to assess neurophysiological responses to medications outside of the motor cortex as well [83].

Therapeutic TMS in ADHD

An ideal therapy for ADHD should address the underlying nervous system dysfunction, be associated with minimal or no adverse effects, and be financially and practically feasible for use in clinical practice. Pharmacological treatments for ADHD generally meet these goals. However, standard pharmacotherapy is not effective for manyADHD patients, stimulants are sometimes contraindicated, and some patients experience untoward side effects, including cardiovascular, hepatic, growth or suicidal events [92,93]. New interventions are needed to augment or provide alternatives to pharmacotherapy.

Repetitive TMS, when used on a daily basis, can induce long-lasting changes in the excitability of the stimulated site. These functional changes can be leveraged for therapeutic effect, as has been shown for medication-refractory depression in adults [94]. Although there are no current FDA-approved therapeutic uses of TMS in the pediatric population, a multi-center trial is currently underway investigating its role in treating medication-refractory depression [95,96]. With regards to ADHD, there have only been a small number of pilot trials exploring the use of therapeutic TMS in the pediatric population.

In 2012, Weaver et al. performed a pilot trial of 9 adolescents and young adults, age 15-20, using 10 Hz rTMS to the right dorsolateral prefrontal cortex [97]. Subjects underwent 10 sessions over two weeks and each subject was crossed-over to receive sham. The objective of the study was to assess safety and the conclusion was that this was that rTMS was safe in this cohort, but the study was underpowered to show efficacy. Although the authors reported an improvement in core ADHD symptoms in the treatment group the effect did not differ significantly from the sham condition.

There have been a few studies of therapeutic rTMS in adults with ADHD, reviewed in Zaman, 2013 [98]. In 2010, Bloch et al. performed a double blind, randomized, sham controlled crossover pilot study with positive effects in 13 patients [99]. Niederhofer reported improved ADHD symptoms in a case study that involved motor cortex stimulation using 1 Hz rTMS at 1200 pulses per day for 5 days [100].

To date, however, there are no published large, randomized, sham-controlled trials of therapeutic rTMS in ADHD, though several trials are ongoing (see clinicaltrials.gov for details). Moreover, the optimal target, frequency, and duration are all unknown. It is likely that the target will vary depending on the symptom being treated, as studies have shown distinct neural substrates for distinct ADHD subtypes [12,13].

Safety in Pediatric TMS—The majority of the safety data in TMS is derived from adults. Common side effects of TMS include headache and scalp discomfort, which is experienced by up to 40% of participants [101]. Rare, but more concerning effects include hearing loss [102,103] or the induction of a seizure with rTMS [52]. The risk of hearing loss can be minimized by using earplugs, and the risk of seizure is estimated at less than 1 in 10,000 when appropriate safety guidelines are adhered to [52,104].

TMS has been used in over 800 normal children and over 300 neurologically abnormal children, with a good tolerability and safety profile [105,106]. No change in auditory function has been reported in the pediatric population to date [105]. Single- or paired-pulse TMS has not been shown to cause seizures in children, including those with epilepsy or with conditions like cerebral palsy that are associated with increased risk of seizures [101,107-113]. One case of rTMS-induced seizure was reported in an adolescent patient being treated for depression [114], though other risk factors for seizure were also present, including alcohol use the night before the induced seizure [95]. In 2009, a consensus conference issued recommendations for the safe use TMS in the pediatric population. They concluded that single-pulse and paired-pulse TMS was safe for children two years and older. In the absence of an appreciable volume of data on the potential for adverse effects with rTMS, they recommended that children should not be used as subjects for rTMS without compelling clinical reasons, such as the treatment of particular psychiatric conditions [52].

tDCS in ADHD

Transcranial DCS is a noninvasive brain stimulation technique that has received a surge of interest in the last decade. With tDCS, a low-amplitude direct current (0.5 −2 mA) is applied to the scalp via electrodes. Electric current flows from the negatively charged cathode to the positively charged anode, penetrating the skull and modifying neuronal transmembrane potentials in the current path. The effect is to modulate the excitability of a given region, but unlike TMS, tDCS does not deliver suprathreshold currents to induce action potentials [115-118]. The cortex underlying the anode typically becomes more excitable while the cathode site has decreased excitability. The efficacy of tDCS depends on the location, intensity, and duration of the current applied to the brain, which is affected by electrode size and the orientation of the electric field [118-120]. TDCS is a much more diffuse form of

stimulation than TMS, though smaller electrodes and multi-electrode arrays can be used to improve the spatial resolution.

Enduring changes in brain function after tDCS are documented in the same manner as TMS. When several sessions are applied, the effects can last for several weeks [121,122]. Because tDCS is subthreshold for inducing action potentials the greatest therapeutic benefit may be realized by coupling tDCS sessions with cognitive training. This effect has been leveraged to induce therapeutic effects in disorders such as depression and pain [123-126].

An ongoing study is investigating the use of tDCS in adult patients with ADHD, which uses anodal tDCS stimulation over the left dorsolateral preftonal cortex at 1 mA[127]. The aim of this parallel, randomized, double-blind, sham-controlled trial is to study the modulation of inhibitory control in this population. While the results of tDCS in ADHD are not yet available there is a burgeoning literature suggesting that tDCS may be used to improve cognitive performance. These studies have shown that tDCS can improve behavioural inhibition, memory, and attention in healthy subjects [128,129], and these findings extend to clinical populations [127,130]. There is reason to be optimistic that similar stimulation paradigms may have a beneficial effect for ADHD patients, though it will be critical that future studies be sufficiently powered and include a sham-controlled experimental design.

If tDCS is effective for certain symptoms of ADHD it may offer many advantages over rTMS as a therapy. For example, the stimulators are relatively inexpensive compared to TMS equipment and application requires less cooperation from the patient relative to rTMS, which may be important for hyperactive children. Moreover, the safety profile of tDCS is excellent and the main recognized side effects include an itching sensation and skin redness under the electrode [106,119].

Newer Noninvasive Brain Stimulation Tools

Two new promising neuromodulation techniques include transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS). TACS is similar to tDCS but the current alternates at a specific frequency. This can alter the oscillatory frequencies in regions being stimulated. A recent study of 12 children with ADHD showed that 0.75 Hz tACS during slow wave sleep improved declarative memory consolidation to normal levels [130]. Given prior research highlighting abnormal oscillatory activity in the ADHD brain, such as an elevated theta-to-beta ratio in fronto-central leads [131], it is possible that normalizing these patterns via tACS may be therapeutic. TRNS is similar to tACS except instead of a defined frequency the alternating current is random, resembling noise [132]. It may act by introducing noise into a system to increase the signal- to-noise ratio [133]. Although tRNS has not been used in ADHD to date, it has improved cognitive parameters for healthy controls [134].

Ethics of Noninvasive Brain Stimulation in Pediatric ADHD

There are major questions raised by the prospect of inducing functional changes in a child's brain through exogenous stimulation. This includes, but is not limited to: possible long-term effects, access to this technology and cognitive domain performance trade-offs. In fact, there is evidence that while therapeutic brain stimulation can result in benefits in certain domains,

others can become impaired [135,136]. Given the availability of transcranial electrical stimulation devices and direct-to-consumer marketing, one major ethical concern is the proliferation of non-medical use. If a company markets tDCS equipment using non-medical terms (e.g. to enhance focus) it may bypass the regulatory processes in place for medical devices, potentially making transcranial stimulation available to consumers prior to carefully monitored clinical trials that are needed to rigorously establish the optimal parameters of use, efficacy and side effect profile. In addition, there is no guarantee that safety data derived from adult trials will carry-over to the pediatric population. As such, we must proceed forward with great caution and foresight. For excellent discussions of the ethics of pediatric brain stimulation see [137,138].

Conclusion

This review highlights studies that build early support for the cautious extension of research into the diagnostic and therapeutic use of noninvasive brain stimulation in pediatric ADHD. While the current evidence is admittedly limited, there is reason to be optimistic. With respect to therapy, the developing brain is believed to be more plastic than its adult counterpart, and thus is likely to be more easily influenced by neuromodulation. Supportive of this concept, one of the predictors of better response to rTMS therapy in adult depression is younger age [139,140], and early results of therapeutic neuromodulation in the pediatric population are encouraging. However, increased plasticity in the pediatric brain may also correspond to increased vulnerability to unintended changes induced by neuromodulation. Researchers must proceed cautiously with a high level of vigilance for side effects. Exactly how noninvasive brain stimulation can be optimally integrated with current clinical management of ADHD will require years of intensive study, but the pervasiveness of ADHD and the need for improved management should make this endeavour a high priority.

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Table 1

Neurophysiological TMS-Measurements in Children with ADHD, ADHD with comorbid Tourette syndrom or Tics, or Tourette syndrome and methylphenidate and atomoxetine effects

	Sample (Mean age/range)	MT	CMCT	CSP	ICI	SICI	LICI	iSP-L	iSP-D	ICF	MPH	ATX	Study Design
ADHD													
Moll et al. 2000 [141]	18 (8-12)	⊘			↓				⊘	⊘	↑ICI		Open, non-controlled study
Moll et al. 2001 [142]	16 (12±1.6)	⊘			↓					⊘			
Ucles et al. 2000 [143]	27 (4-18)		↑										
Garvey et al. 2005 [72]	12 (10.7±1.6)	⊘						↓	⊘				
Buchmann et al. 2003 [70]	13 (10.8±1.7)	⊘						↑	↓				
Buchmann et al. 2006 [71]	23 (11±2.6)	⊘	⊘					↑	↓		↓iSP-L ↑↑ iSP-D		Open, non-controlled study
Buchmann et al. 2007 [67]	18 (11±2)	⊘	⊘			↓	↓			↓	↑SICI ↑LICI ↑ICF		Open, non-controlled study
Hoeppner et al. 2008 [73]	21 (28.9±9.2)	⊘	⊘					⊘	↓		⊘ iPS-L ↑iPS-D		Open, non-controlled study
Richter et al. 2007 [144]	10 (29±3.4)	⊘				↓				⊘			
Gilbert et al 2011 [16]	49 (10.5)					↓							Case-control study
ADHD/TS/Tics													
Moll et al. 2001 [142]	16 (12.5±1.1)	⊘		↓	↓					⊘			
Gilbert et al. 2004 [68]	36 (13-18)	⊘		⊘		↓				⊘	⊘		Open, non-controlled study *
Gilbert et al. 2005 [69]	28 (9-48)	⊘				↓							
Gilbert et al. 2007	14 (8-16)											↓SICI ⊘ ICF	Open, non-controlled study

	Sample (Mean age/range)	MT	CMCT	CSP	ICI	SICI	LICI	iSP-L	iSP-D	ICF	MPH	ATX	Study Design
[145]													
Orth et al. 2009 [146]	6 (18-68)	↑				↓				↑			
HEALTHY													
Kratz et al. 2009 [91]	14 (20-40)										⊘ MT ↑SICI		Double-blind, placebo controlled, crossover study
Moll et al. 2003 [147]	12 (20-40)										⊘SICI ↑ICF		Open, non-controlled study
Kirschner et al. 2003 [148]	12										↑SICI ↑ICF		Placebo controlled, crossover study
Ilic et al. 2003 [149]	8										⊘ MT ⊘ CSP ↓SICI ↑ICF		Open, non-controlled
Gilbert et al. 2006 [150]	9 (19-35)										↓SICI ↑ICF	↓SICI ↑ICF	Randomized, double-blinded crossover trial

Note: MT= rest motor threshold; CMCT= central motor conduction time; CSP= cortical silent period, ICI=intracortical inhibition; SICI= short-interval intracortical inhibition; LICI= long-interval intracortical inhibition; ICF= intracortical facilitation; iSP-L= ipsilateral silent period, latency; iSP-D= ipsilateral silent period, duration; MPH= methylphenidate; ATX= atomoxetine

Symbols: ⊘= no differences between clinical versus normal group; ↓= decreased parameter value between clinical versus normal group; ↑= increased parameter value between clinical versus normal group. In MPH and ATX columns: ↑: enhanced parameter value after the drug intake; ↓: diminished parameter value after the drug intake.

*Small drug samples to reliability;

**Three patients had Tourette syndrom and ADHD