

# Repetitive Transcranial Magnetic Stimulation (rTMS): The Neuromagnetic Linkage

<http://www.medscape.com/viewarticle/452988>

---

## Summary and Introduction

---

### *Summary*

Attention-deficit hyperactivity disorder (ADHD) is the most common developmental disorder that is associated with environmental and genetic factors. Neurobiological evidence suggests that fronto-striatum-cerebellum circuit abnormalities, mainly in the right hemisphere, are responsible for most of the disturbed sensorimotor integration; dopamine seems to be the main neurochemical alteration underlying these morphological abnormalities. Different conventional treatments have been employed on ADHD; however, repetitive transcranial magnetic stimulation (rTMS), a new and useful option for the clinical/research investigation of several neuropsychiatric disorders involving dopamine circuits, has yet to be considered as a therapeutic tool and possible drug-free option for ADHD. Here the authors explore the available evidence that makes this tool a rational therapeutic possibility for patients with ADHD, calling attention to safety issues, while highlighting the potentials of such an approach and the new hope it may bring for patients, parents, researchers and clinicians. The authors advocate carefully conducted clinical trials to investigate efficacy, safety, cost-effectiveness and clinical utility of rTMS for ADHD patients—in comparison to both placebo and standard treatments.

### *Introduction*

Attention-deficit hyperactivity disorder (ADHD) is the most common developmental disorder affecting at least 5% of school-aged children, with boys more frequently affected than girls.<sup>[1]</sup> It persists into adulthood in up to 60% of the cases.<sup>[2, 3]</sup> It is characterised by inattention, impulsiveness and hyperactivity that impair normal daily life function, especially at home and school. The long-term consequences of childhood ADHD include lower educational and vocational outcomes as well as an increased risk for antisocial behavioural disorders and drug abuse in adulthood, among other psychopathologies.<sup>[4, 5]</sup>

ADHD is a multifactorial disorder associated with environmental and genetic factors. Variations in brain size and morphology are present from early life, with fronto-striatum-cerebellum circuit abnormalities, mainly in the right hemisphere, considered responsible for most of the disturbed motor control and the abnormal sensory-motor programme;<sup>[3]</sup> dopamine seems to be the main neurochemical alteration underlying these morphological alterations. Based on these facts, stimulants of the nervous system are, to date, the most successful as well as the most controversial therapy employed.<sup>[6]</sup> Nevertheless, despite the enormous amount of research done, clinicians and parents are eagerly awaiting additional and better therapeutic options.

Magnetic stimulation is a recent and powerful non-invasive tool developed for studying the nervous system with promising findings on neural plasticity.<sup>[7-9]</sup> It is also currently being used to treat brain diseases, improving functional deficits and achieving noteworthy results in recent years.<sup>[9]</sup> This new tool has also been found useful in increasing the understanding of ADHD pathophysiology;<sup>[10,11]</sup> however, it has not been considered as a drug-free therapeutic option for treating ADHD. Therefore, we anticipate that if the rTMS effects on the dopaminergic system found in normals can be replicated in ADHD patients,<sup>[12]</sup> it could be the first step in offering new hope to patients, researchers and clinicians. Here we explore the available evidence that makes this option a viable possibility in the treatment of ADHD.

## Neurobiological Considerations

---

Anatomical studies have shown significant prefrontal asymmetry in ADHD, with smaller right-sided prefrontal brain regions.<sup>[13]</sup> A decrease in grey matter in the right frontal gyrus, the right posterior cingulate gyrus and the left central white matter have been reported.<sup>[3, 11]</sup> Left-to-right asymmetry of the caudate nucleus,<sup>[14, 15]</sup> or volume abnormalities of it,<sup>[13]</sup> as well as a significant decrease in the right globus pallidus size<sup>16</sup> or smaller posterior-inferior cerebellar vermis, are also common features of this disease.<sup>[3, 17, 18]</sup> The significance of these findings is still under debate;<sup>[13]</sup> however, they do support the involvement of a circuit in the above-mentioned areas that are certainly hypofunctional in ADHD.<sup>[3]</sup>

The pathophysiology of ADHD has been based on the catecholamine hypothesis<sup>[19, 20]</sup> since the 1970s. Unfortunately, after a quarter-century of research, its role still remains unclear. Dopaminergic dysfunction has been suspected in ADHD, among other neuro-transmitters, because symptoms respond favourably, albeit temporarily, to stimulant medications such as dextroamphetamine and methylphenidate (MPH).<sup>[21]</sup> These medications increase the release and inhibit the re-uptake of catecholamines, especially dopamine, whose modulatory influence is pervasive in frontalstriatal regions. This evidence suggests that the dysfunction in dopaminergic transmission is located in the frontal lobe and in striatal structures.<sup>[21, 22]</sup> Genetic studies have also reported an association between ADHD and dopaminergic gene dysfunction, including associations between ADHD and variability of the dopamine transporter as well as D4 and D2 receptor gene abnormalities.<sup>[23-25]</sup> Such receptors have an inhibitory effect on GABAergic synapses and are found in the relevant cortical, basal ganglia, thalamus and cerebellar vermis interneurons related to ADHD pathophysiology.<sup>[26]</sup>

From a neuropsychological perspective, ADHD has commonly been defined by sustained attention deficits, impulsiveness and a high level of activity.<sup>[27]</sup> More recently, the nature of the disorder has been examined and is undergoing further redefinition, being considered a disorder of executive functions. Although an extensive review of the correlation between executive function and its anatomical substrates is beyond the scope of this article, it can be said that the location of executive functions implies activation of pre-frontal lobes, basal ganglia structures and other cortical and subcortical areas, including cortico-striatal-thalamo-cortical circuits,<sup>[28]</sup> which select, initiate and execute complex motor and cognitive responses.<sup>[29]</sup> The cerebellum provides an on-line guidance of these functions.<sup>[13-15]</sup>

Using functional magnetic resonance imaging, Vaidya *et al.* found differences between children with ADHD and healthy controls in their fronto-striatal functioning during response inhibition tasks.<sup>[30]</sup> However, changes in caudate and putamen, as well as prefrontal and striatal activation, varied according to the task itself only in patients. Interestingly, MPH enhanced activation in prefrontal and striatal areas in both patients and normals and decreased the latter in normals.<sup>[31]</sup> These findings suggest an atypical functioning of the fronto-striatal circuit in ADHD probably making a significant contribution to striatal dysfunction. In fact, functional studies showed decreased blood flow in the striatum of ADHD subjects,<sup>[32]</sup> mostly in prefrontal regions, with a frontal-cerebral decreased metabolism in adults with ADHD demonstrated by positron-emission tomography with [<sup>18</sup>F]-fluoro-2-deoxy-D-glucose, <sup>133</sup>xenon inhalation and single-photon emission tomography.<sup>[33]</sup>

While neurophysiological studies have been difficult to integrate into the physiopathology of ADHD, P300 studies have shown smaller amplitude and longer latencies which correlated with attentional dysfunction.<sup>[34]</sup> Steady-state visually evoked potentials<sup>[35]</sup> were also strongly supportive of right prefrontal dysfunction in ADHD.<sup>[13, 36]</sup> The main findings with magnetic stimulation are discussed below.

## Current Therapies

---

Several pharmacological or non-pharmacological approaches have been considered in treating ADHD, but no important advances have been made since 1937 when Bradley first used stimulants to relieve ADHD symptoms.<sup>[21]</sup> Today, psychostimulant medications, in particular MPH, are the most commonly prescribed drug for treating ADHD in children and adults, offering clinical benefits in up to 80% of cases.<sup>[37, 38]</sup> It is known that MPH captures the dopamine transporter and is taken up primarily in the striatum of healthy adults,<sup>[23]</sup> increasing striatal and frontal activation.<sup>[30]</sup> Although there is a large amount of evidence available on the beneficial effects, safety and prognosis, with short-term stimulant treatment in children with ADHD, many questions remain unanswered. Parents and physicians still have concerns regarding safety issues with the long-term use of stimulants in children as well. Needless to say, new approaches to the treatment of this disease would be welcome.

A multimodal treatment study of children with ADHD<sup>[38]</sup> concluded that medication alone was superior to medication plus behavioural treatment or routine community care, or if given in combination with any of the latter therapies for ADHD symptoms. These authors concluded that modifications in neurotransmitters carried out through non-conventional pharmacological therapy would be an excellent alternative for treating ADHD.<sup>[38]</sup> All of these facts, therefore, make room for new therapies, including those with TMS.

## The Neuromagnetic Linkage

---

Transcranial magnetic stimulation (TMS) is a newly developed tool for assessing functionality of the central nervous system (CNS). After Baker *et al.* demonstrated its value in humans in 1985, single and paired-pulse TMS have proven useful in detecting clinical and subclinical abnormalities in a large array of neurological and neuropsychiatric disorders including Tourette's syndrome, obsessive compulsive disorder, depression, schizophrenia, bipolar disorders and ADHD among others.<sup>[39-43]</sup> Regarding ADHD specifically, TMS seems to be an ideal method for studying the maturational process of the motor pathways since it clearly excites the corticomotoneuronal system presumed to be involved in this disorder.<sup>[10]</sup>

Ucles *et al.*,<sup>[10]</sup> using single stimulation in children with ADHD, found a prolongation of central motor conduction time as well as some side-to-side stimulation differences compared with those found in age- and sex-matched controls. These findings demonstrated a delay in the maturation of the corticomotoneuronal system in patients with ADHD. Moll *et al.*<sup>[11]</sup> reported that children with ADHD had significantly reduced intracortical inhibition (ICI) with a normal intracortical facilitation compared to healthy controls and such ICI showed improvement after giving 10 mg of MPH. However, most of the morphophysiochemical hallmarks of ADHD involving prefrontal-caudate-cerebellar pathways with noteworthy dopaminergic abnormalities have not yet been taken into account. Therefore we consider that they should be the current focus if rTMS is to be employed as a therapeutic option.

rTMS has been found effective in Parkinson disease, depression, obsessive-compulsive disorder, Tourette's syndrome and some types of tic.<sup>[42-44]</sup> With regard to children, rTMS has been tried with a small number of patients with action myoclonus, progressive myoclonic epilepsy, bipolar disorder, major depression and schizophrenia<sup>45</sup> with some promising, albeit, short-lasting positive results. Some of these disorders are due to dopamine abnormalities and share some genetic, clinical, biochemical, neuroanatomical and neuro-behavioural similarities with ADHD. Even though a complete understanding of the mechanism of action of rTMS has not been developed,<sup>[42]</sup> it is now clear that rTMS at low frequencies could cause long-term depression of cortico-cortical transmission in normals<sup>43</sup> as well as improvement of symptoms of some neuropsychiatric disorders commented on above, including the modulation of several neurotransmitters such as dopamine and its metabolites (e.g. homovanilic acid) mainly after prefrontal cortex stimulation.<sup>[46]</sup>

It should also be noted that modulation of dopamine release could be due to GABAergic and glutamatergic corticostriatal projection, the latter being spared in ADHD. In fact, the recent reduced ICI found in patients with ADHD and demonstrated by TMS is known to be modulated by GABAergic synapsis,<sup>[47]</sup> suggesting that a cortical instability in the excitatory and inhibitory signals interexchange is present in this disease.<sup>[48]</sup> It is, therefore, likely that parasitic foci of autonomous electrical or magnetic neuronal activity modifying the input-output neural shortcuts and decreasing the appropriate integration and complex dynamics of the CNS, as suggested elsewhere,<sup>[48]</sup> seem also to be present in ADHD patients and, perhaps, associated conditions. Such cortical instability, with an imbalance between the so-called direct and indirect cortical pathways mediating sensory-motor integration, might be the most important target for applying the appropriate rTMS treatment in this disorder.<sup>[12, 34]</sup>

Because of this, the recent findings reported by Strafella *et al.*<sup>[12]</sup> may be significant in ADHD cases. These authors showed that rTMS applied to the left mid-dorsolateral prefrontal cortex (MDL-PFC) induced the release of endogenous dopamine from the left caudate as a consequence of direct corticostriatal axon stimulation, increasing the extracellular dopamine concentration measured by the [<sup>11</sup>C]raclopride binding method.<sup>[49]</sup> These findings are more than interesting because the clinical benefits of MPH seem to be due to an increase in the resting extracellular levels of dopamine, lowering the levels of pulsatile release of it as well. These pharmacological effects also produce a decreased activation of postsynaptic dopamine receptors involved in psychomotor activity modulation,<sup>[50]</sup> making it

possible to suggest that a similar mechanism of action leading to the improvement of clinical symptoms might be considered in ADHD after applying rTMS. The fact that in depressed patients some forms of rTMS also produce similar effects to those described with the use of conventional pharmacological antidepressants,<sup>[51]</sup> adds strength to the concepts expressed above and encourage us to apply it to ADHD patients.

We concede that rTMS can produce not only a release of amines, but also an increase in the production of growth or other trophic factors<sup>[43]</sup> leading to gene induction, modulation and expression<sup>[42]</sup> and even a release of nitric oxide due to blood flow changes produced by rTMS.<sup>[52]</sup> The actions of these co-factors could also play a role in leading to the expected clinical benefits of applying rTMS.

Some safety issues must be considered in some of patients since there is a limited experience of possible side-effects in children and adolescents using TMS particularly rTMS.<sup>[45]</sup> Even though muscle-tension headache that resolved promptly is the only side-effect found in children receiving rTMS, there is still concern in applying it with pulse frequencies of 50 Hz or more for periods of several seconds because of the possibility of seizures.<sup>[42]</sup> At present, there is no reason for applying rTMS at higher frequencies, intensities or with longer train durations than those employed in clinical or research studies. Thus, frequencies lower than 50 Hz might be used with some confidence in humans until new safety guidelines on rTMS applications can be published.<sup>[53]</sup> The use of other pharmacological treatment (e.g. neuroleptics, antidepressants, etc.) should also be borne in mind when using this tool, since such drugs may change cortical excitability and lower seizure thresholds, with further increase of the risk of seizures.<sup>[45]</sup>

Some technical considerations should be taken into account as well. For example, the recent study carried out by Strafella *et al.*,<sup>[12]</sup> demonstrating dopamine release after MDL-PFC stimulation, was performed with the subjects' eyes closed. This condition modulates the release of dopamine, modifies cortical excitability itself<sup>[54, 55]</sup> and could produce a 'natural' deafferentation that might modify final outcomes. Stimulation parameters such as frequency, intensity, train duration, coil size and sham conditions, among others, must also be considered.<sup>[42]</sup> The individual variations cited with blood flow and brain metabolism after applying TMS<sup>[56]</sup> should also be borne in mind when applying rTMS to patients with ADHD who have been found to have a decreased blood flow and metabolism in the frontal, prefrontal and striatum regions.<sup>[33, 57]</sup> Additionally, patients with decreased metabolism seem to respond better to higher frequency stimulation (10 or 20 Hz), with those possessing baseline hypermetabolism responding better to 1 Hz stimulation.

## Conclusion

---

If the evidence-based science and experimental effects of rTMS (mostly dopamine modulation) can be replicated in children with ADHD after systematic clinical research trials to investigate efficacy, safety, cost-effectiveness and clinical utility—in comparison to both placebo and standard treatments—we anticipate that this tool and the like might become an effective and secure treatment to be employed for this neuropsychiatric condition targeting the specific cortical systems affected. Since the available evidence suggests this is a safe and well-tolerated technique for children,<sup>[58]</sup> rTMS application on ADHD patients is worth trying and we advocate carefully conducted clinical trials, the results of which are awaited with much and obvious interest.