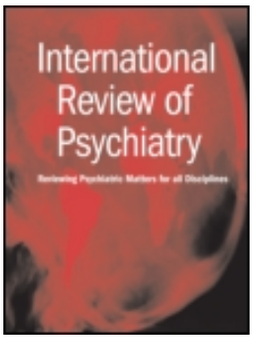

International Review of Psychiatry

ISSN: 0954-0261 (Print) 1369-1627 (Online) Journal homepage: www.tandfonline.com/journals/iirp20

Applications of transcranial magnetic stimulation (TMS) in child and adolescent psychiatry

Paul E. Croarkin, Christopher A. Wall & Jon Lee

To cite this article: Paul E. Croarkin, Christopher A. Wall & Jon Lee (2011) Applications of transcranial magnetic stimulation (TMS) in child and adolescent psychiatry, International Review of Psychiatry, 23:5, 445-453, DOI: 10.3109/09540261.2011.623688

To link to this article: https://doi.org/10.3109/09540261.2011.623688

International Review of Psychiatry, October 2011; 23(5): 445–453

informa
healthcare

Applications of transcranial magnetic stimulation (TMS) in child and adolescent psychiatry

PAUL E. CROARKIN[1], CHRISTOPHER A. WALL[1] & JON LEE[2]

[1]*Mayo Clinic, Rochester, Minnesota, USA and* [2]*University of Toronto, Toronto, Ontario, Canada*

Abstract
Transcranial magnetic stimulation (TMS) is emerging as a new treatment and neurophysiological research tool for psychiatric disorders. Recent publications suggest that this modality will also serve as a treatment and research tool in child and adolescent psychiatry. Current reports on therapeutic trials of repetitive transcranial magnetic stimulation (rTMS) in adolescents have primarily focused on depression. However, other pilot work involves the treatment of attention-deficit/hyperactivity disorder (ADHD), autism and schizophrenia. Neurophysiological studies typically utilize single and paired-pulse TMS paradigms which index cortical excitability and inhibition. Initial studies have focused on ADHD, autism, and depression. General knowledge regarding TMS among child and adolescent psychiatrists is lacking. The aim of this review is to provide an overview of TMS in the context of child and adolescent psychiatry, discuss recent therapeutic and neurophysiological studies, and examine relevant ethical considerations.

Introduction

Transcranial magnetic stimulation (TMS) is an emerging neuropsychiatric tool with therapeutic and research applications. This involves the non-invasive stimulation of cortical neurons by means of a rapidly changing magnetic field which induces weak electric currents in the brain (Daskalakis et al., 2002a). Stimulation results in specific or general activity changes in the brain with minimal discomfort. One readily observed example of this involves evoking a motor response in a human subject when the coil is placed over the primary motor cortex (Frye et al., 2008). The three most common types of TMS delivery include single-pulse, paired-pulse, and repetitive transcranial magnetic stimulation (rTMS). TMS devices consist of storage capacitors, a stimulating coil, and timing systems. Overall, TMS is considered safe with the most serious risk involving the accidental induction of seizures (Ridding & Rothwell, 2007). With proper safety precautions the risk of seizure from rTMS and TMS is low (0.1–0.6%). Other potential risks include syncope, scalp discomfort, and changes in auditory thresholds. The TMS coil expands rapidly during stimulation producing a loud click. This is more significant at higher intensities and with rTMS. Thus, hearing protection is worn during TMS sessions. Prior electroencephalographic, cognitive, and endocrine research has demonstrated the safety of TMS in adults. Recently, safety guidelines based on international expert consensus review have been developed and published (Rossi et al., 2009).

Frequently, rTMS protocols in adults involve the clinical treatment of neuropsychiatric disorders such as migraines, strokes, Parkinson's disease, mood disorders, and psychotic disorders. There are more than 30 controlled trials of rTMS and six meta-analysis studies that support the use of prefrontal rTMS for the treatment of major depressive disorder (MDD) in adults. The majority of these studies involve the use of high-frequency rTMS (>1 Hz) over the left dorsolatarel prefrontal cortex (LDLPFC) based on the supposition that this will increase cortical excitability in this brain region (Croarkin et al., 2010; Lisanby et al., 2002). Other trials have involved stimulation of the right DLPFC with low frequency stimulation (<1 Hz) working on the assumption that this will decrease excessive cortical activity in this hemisphere. Another novel approach involves sequenced, low and high frequency treatments delivered bilaterally. (Blumberger et al., 2011; Croarkin et al., 2010; Daskalakis et al., 2008a). The largest trial to date was a multicenter, double-blind, sham-controlled trial of 301 subjects with MDD which involved high frequency stimulation

Correspondence: Paul E. Croarkin, DO, MSCS, Department of Psychiatry and Psychology, Mayo Clinic, 200 First Street SW, Rochester, MN, 55905. Tel: (507) 284-1538, Fax: (507) 284-3933. E-mail: Croarkin.paul@mayo.edu.

(Received 5 August 2011; accepted 9 September 2011)

ISSN 0954–0261 print/ISSN 1369–1627 online
DOI: 10.3109/09540261.2011.623688

of the LDLPFC, five times per week at 120% motor threshold for 4 to 6 weeks. In 2008, this culminated in US Food and Drug Administration (FDA) clearance for rTMS treatment of adults with MDD who have failed one previous medication trial of an adequate dose and duration (Lisanby et al., 2009; O'Reardon et al., 2007). Previously, rTMS has been approved for treatment refractory depression in other countries such as Israel and Canada (Daskalakis et al., 2008a).

In neurophysiological studies of adult psychiatric disorders, TMS is typically coupled with electromyography to examine motor evoked potentials as single or paired-pulse TMS is delivered to the contralateral motor cortex. These paradigms assess cortical excitability and inhibition and include the motor threshold (MT), intracortical facilitation (ICF), short-interval intracortical inhibition (SICI), long-interval cortical inhibition (LICI) and the cortical silent period (CSP) (Bajbouj et al., 2006; Daskalakis et al., 2007, 2008b). It has been postulated that SICI indexes $GABA_A$ activity, CSP and LICI index $GABA_B$ activity, and that the MT and ICF are non-specific measures of glutamatergic functioning (Croarkin et al., 2011a; Daskalakis et al., 2002b; Ziemann, 2004). Recent studies have interleaved TMS with EEG to examine cortical activity beyond the motor cortex (Farzan et al., 2010a). For example, it has been demonstrated that adult subjects with schizophrenia have reduced evoked gamma oscillations in the prefrontal cortex (Farzan et al., 2010b). Studies in adult subjects have also combined TMS with other functional imaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI) and functional near infrared spectroscopy (fNIRS). These studies have produced valuable data but also present challenges with unique safety concerns and induced artifact (Kozel et al., 2009; McClintock et al., 2011).

Despite promising potential in the diagnosis, examination, and treatment of psychiatric disorders in adults, this technology has had somewhat limited use in children and adolescents thus far (D'Agati et al., 2010; Garvey & Gilbert, 2004). The purpose of this paper is to present an overview of TMS research in child and adolescent psychiatry. Literature was reviewed and collected with Ovid SP MEDLINE (1950–present) and PubMed (1948–present) searches. Search terms included adolescent (including psychiatry and psychology), anxiety disorder, attention deficit hyperactivity disorder, autism spectrum disorder, bipolar disorder, child (including psychiatry and psychology) major depressive disorder, mood disorder, schizophrenia, Tourette's syndrome, transcranial magnetic stimulation. Articles describing the delivery of TMS in subjects under the age of 21 were included as well as concept papers discussing the ethics, safety, and utility of this area of research in child and adolescent psychiatry.

Therapeutic rTMS in child and adolescent psychiatry

Treatment options for child and adolescent psychiatric disorders are often very limited. In many cases this population is suboptimally treated with consequent polypharmacy, repeated psychiatric hospitalizations, and adverse developmental consequences (Croarkin et al., 2010). Hence, new therapeutic modalities are essential. At this stage, the majority of child and adolescent rTMS research reports are comprised of case reports and open-label trials. Safety, ethical issues, and a thoughtful approach to this area of research are all paramount given neurodevelopmental concerns (D'Agati et al., 2010; Quintana, 2005). However, future research with rTMS should focus on optimal stimulation sites, treatment parameters, and its role in evidence-based algorithms. Findings will likely diverge from that of adults. Early intervention with neurostimulation modalities such as rTMS may one day address the developmental course of pathological neurocircuitry and spare patients from chronic treatment and a lifetime of disability (Croarkin et al., 2010).

The following is a brief summary of the extant literature regarding the therapeutic application of rTMS in child and adolescent psychiatric disorders.

Attention deficit hyperactivity disorder (ADHD)

Previously, Weaver and colleagues reported on initial findings from a double-blind, sham-controlled trial of 10 Hz rTMS at 100% MT. Subjects received 2000 pulses per session applied to the RDLPFC over 10 sessions for 2 weeks. These patients were between the ages of 17 and 21 with the diagnosis of ADHD. Seven of these individuals completed the study with no adverse effects. The mean Clinical Global Impression-Improvement (CGI-I) (Guy, 1976) and the ADHD-IV (Dupaul et al, 1998) scales improved over the course of this trial (Weaver et al., 2008). More recently, Bloch and colleagues described the results of a single session, double-blind, sham-controlled study of seven male and six female adult subjects with ADHD. In this investigation, subjects received one session of high frequency rTMS applied to the right prefrontal cortex or a single session of sham rTMS. Subjects who received active rTMS had an improvement in attention (based on an rTMS attention score) 10 min after the session. Sham rTMS showed no effects (Bloch et al., 2010). Given the high prevalence and public

health burden of ADHD further work in this area is essential.

Autism spectrum disorder (ASD)

Baruth and colleagues (2010) have noted clinical changes in subjects with ASD during the course of rTMS neurophysiological studies. Specifically, they reported on the electrophysiological effects of low frequency rTMS on 25 subjects (ages 9 to 26) with ASD and 20 age-matched controls. Early (pre-TMS), relative evoked (100 ms) gamma power was examined using Kanizsa illusory figures along with the impact of 12 sessions of bilateral, low frequency rTMS applied to the DLPFC. After rTMS, subjects with ASD demonstrated improvements in discriminatory gamma activity when presented with relevant and irrelevant stimuli. Clinical measures included the Aberrant Behavior Checklist (ABC) (Aman et al., 1985), a clinician-rated scale assessing difficulties with irritability, lethargy, social withdrawal, stereotypy, hyperactivity, and inappropriate speech. In this study, the irritability and hyperactivity scales were chosen as outcome measures. Further measures included the Social Responsiveness Scale (SRS) (Constantino et al., 2003), a caregiver-reported scale assessing social interest and interaction and the Repetitive Behavior Scale-Revised (RBS) (Lam & Aman, 2007), and a caregiver completed scale measuring repetitive and restricted behaviour patterns. After twelve sessions of bilateral rTMS, subjects displayed reduced repetitive and restricted behaviour patterns as assessed by the RBS. Subjects also had a statistically significant decrease in irritability on the ABC scale. There were no significant changes in social awareness or hyperactivity (Baruth et al., 2010). Other work by this group examined the impact of six low frequency rTMS treatments over 3 weeks in 13 subjects, ages 9–27 with ASD. After rTMS, these subjects had decreased repetitive-ritualistic behaviour based on the RBS. In this group there were no changes in social awareness, irritability, or hyperactivity. The authors did note that this sample was composed of relatively high functioning individuals with no significant behavioural problems (Sokhadze et al., 2010).

Enticott and colleagues recently described the treatment of a 20-year-old woman with Asperger's disorder. This case report described treatment with new coil technology – deep rTMS, which permits the stimulation of deep cortical structures. The research team postulated that the medial prefrontal cortex (mPFC) would be an optimum treatment target, as imaging studies of high-functioning ASD have suggested that portions of the mPFC are hypoactive in these individuals. This 20-year-old woman received 9 sessions of deep rTMS which consisted of 15 min of 5 Hz rTMS at 100% resting motor threshold. The coil was positioned over the bilateral mPFC. She tolerated these treatments, denied side effects, and had no missed sessions. Self-report measures were collected at baseline, immediately after the last treatment, and 1 month after the last treatment. This included the Interpersonal Reactivity Index (IRI) (Davis, 1980), the Autism Spectrum Quotient (Baron-Cohen et al., 2001), and the Ritvo Autism Asperger Diagnostic Scale (Ritvo et al., 2008). All of these measures improved after rTMS treatment and at one month follow up. Family members noted marked improvement in her social functioning as well (Enticott et al., 2011).

Mood disorders

At present there are published descriptions of 23 adolescents receiving rTMS treatment for major depressive episodes (D'Agati et al., 2010; Wall et al., 2011; Walter et al., 2001). In one case this was the depressive phase of bipolar disorder (Walter et al., 2001). Reported results are varied and this limited data should be viewed with scepticism. However, most depressed adolescents have tolerated rTMS with no serious adverse events (Croarkin et al., 2010).

In 2001, Walter and colleagues reviewed the treatment of four adolescents with depression. One 17-year-old adolescent male received 2 weeks of 10-Hz rTMS over the LDLPFC at 90% MT. He had clinical improvement but did complain of a tension headache during two of the treatment sessions. Another 16-year-old male received a similar course of rTMS. His depression improved and there were no reported side effects. A third patient, a 17-year-old male with refractory MDD, mild mental retardation, and ADHD received a similar course of rTMS, with the exception of delivery at 110% MT. Unfortunately, he had no clinical improvement. No adverse effects were reported. Lastly, an 18-year-old woman with bipolar depression received 14 sessions of 1-Hz rTMS delivered to the RDLPFC at 110% MT. She had no clinical improvement but no reported untoward effects (Walter et al., 2001).

Another case series described the treatment of two 16-year-old adolescent girls with MDD who had enrolled in a double-blind, sham-controlled study of 10-Hz rTMS at 110% MT. Both of these young women received active rTMS. The first subject attended 29 sessions of rTMS over 6 weeks. Her depression responded to this and she had minimal residual symptoms and functional impairment 4 months after her final session of rTMS. The other subject missed one rTMS session per week during the trial and had a near two week period with no rTMS sessions. She subsequently returned for 20 sessions over 5 weeks on an open-label basis. During this

rTMS course she concurrently took venlafaxine and methylphenidate. This subject responded slowly but 3 months later had maintained improvement. These two subjects did not report adverse effects and formal neurocognitive assessments did not reveal any negative impact on cognitive functioning (Loo et al., 2006).

Bloch and colleagues (2008) described an open-label rTMS study of nine teenagers with treatment-resistant depression who received 20 sessions of 10 Hz rTMS applied to the LDLPFC at 80% MT for 20 min over 2 weeks. Of note, this sample had a high level of functional impairment, some had been treated with electroconvulsive therapy (ECT) previously and all were taking psychotropic medications concurrently. Three of these subjects responded based on the Childhood Depression Rating Scales (CDRS) (Poznanski, 1984). One subject discontinued treatment early due to anxiety and mood lability, one had hypomania during the treatment course, one attempted suicide 3 weeks after the rTMS sessions and five subjects reported mild headaches. There were no other adverse effects reported (Bloch et al., 2008).

Recently, Wall and colleagues (2011) reported on an open-label trial of adjunctive rTMS in eight adolescents with treatment resistant depression. These subjects were maintained on a stable dose of a selective serotonin reuptake inhibitor (SSRI) and were treated with 30 sessions of 10 Hz rTMS at 120% MT applied to the DLPFC with 3,000 stimulations per treatment sessions. One adolescent did not tolerate rTMS sessions and dropped out. The other subjects tolerated the treatments without difficulty. The mean CDRS score improved significantly from baseline over the course of 30 treatments and at 6-month follow-up. Pre and post-treatment neurocognitive testing did not reveal any decline in functioning. This data is also preliminary as there was no control group but this study did employ aggressive treatment parameters that were well tolerated (Wall et al., 2011).

Schizophrenia

There are five published descriptions of rTMS treatment in children and adolescents with schizophrenia. Walter and colleagues described the treatment of three 18-year-old men with schizophrenia who received 10 daily sessions of 20 Hz rTMS delivered to the right frontal cortex. Two of these individuals showed improvement in rating scales of positive and negative symptoms. The third patient displayed improvement in hallucinations, agitation, and global functioning. There were no adverse effects reported (Walter et al., 2001). Another single case described by Fitzgerald and colleagues described an 18-year-old woman with chronic schizophrenia (with onset at age nine). She had recalcitrant symptoms with various medication trials including clozapine. Subsequently, she was treated with 10 sessions of 1 Hz rTMS at 90% MT applied to the left temporoparietal cortex. There was a reduction in the severity of her hallucinations based on the Hallucinations Change Scale (Doane et al., 1985) and the Positive and Negative Syndrome Scale (Kay et al., 1987). Six months later this patient had a relapse despite treatment with clozapine. At this point she received a subsequent rTMS course with identical parameters which yielded temporary clinical improvement. Three months later, she required a third treatment course (Fitzgerald et al., 2006). Another group reported on the treatment of an 11-year-old boy with medication resistant schizophrenia. This patient had a high level of impairment, aggression, and had struggled with delusions and hallucinations for 2 years. Antipsychotic medications had been ineffective and problematic due to side effects. A fMRI scan displayed increased auditory cortex activity with concurrent auditory hallucinations. This boy subsequently received 10 sessions of 1 Hz rTMS administered to the left temporoparietal cortex. His auditory hallucinations decreased by 50% as assessed by the Auditory Hallucinations Rating Scale (Hoffman et al., 2003). His progress was maintained with repeated sessions over 5 weeks. Based on the Children's Global Assessment Scale (Shaffer et al., 1983) his functioning improved as well. As a result he was discharged home, and returned to school. There were no side effects or adverse effects during the rTMS treatment course (Jardri et al., 2007).

Tourette's syndrome

Experts have explored the idea of applying rTMS as a treatment for Tourette's syndrome (TS) based on the assumption that the underlying pathophysiology involves the basal ganglia and a hyperactive motor cortex. Chae and colleagues (2004) applied either 1 Hz or 15 Hz rTMS at 110% MT or sham stimulation over the left motor cortex or left prefrontal cortex in a randomized, blinded, crossover study of 8 subjects with TS. Two of these subjects were 19 years of age and the others were aged 22 to 60. There was a general improvement in tic and obsessive–compulsive disorder (OCD) symptoms during the study and none of the subjects worsened. There were no significant differences among treatments and rTMS was well tolerated (Chae et al., 2004). A subsequent, open-label trial involved 10 male children (mean age 11.2 ± 2.0 years) with TS, who received ten sessions of 1 Hz rTMS at 100% MT applied to the supplementary motor area (SMA). All subjects completed the trial with no untoward effects and no worsening in symptoms of ADHD, depression, or anxiety. Tic symptoms improved over the course of 12 weeks based on the Yale Global Tourette's Syndrome Severity Scale (YGTSS) (Leckman et al.,

1989) and the Clinical Global Improvement (CGI) scale (Kwon et al., 2011).

Neurophysiologic research with TMS in child and adolescent psychiatry

Single and paired-pulse TMS studies of the motor cortex are commonly used for neurophysiological studies. Stimulation of the motor cortex provides an observable means of quantifying the effect of stimulations as this is monitored visually or via electromyography (EMG) measures of the abductor pollicis brevis muscle. These TMS paradigms measure cortical excitability and cortical inhibition (Bajbouj et al., 2006; Daskalakis et al., 2002b, 2005, 2008b; Ziemann, 1999). Cortical excitability refers to the brain's reactivity to endogenous or exogenous stimuli. The motor threshold and intracortical facilitation are measures of cortical excitability. Cortical excitability is most likely mediated through voltage-gated sodium channels, non-N-methyl-D-aspartate and N-methyl-D-aspartate (NMDA) glutamatergic functioning (Chen et al., 1997; Tergau et al., 2003; Ziemann 2003, 2004; Ziemann et al., 1998). Cortical inhibition is a process by which GABAergic interneurons are selectively activated. Measures of cortical inhibition include: short interval cortical inhibition (SICI) which indexes $GABA_A$ functioning, long interval cortical inhibition (LICI) which indexes $GABA_B$ and the cortical silent period (CSP) which indexes $GABA_B$ functioning (Croarkin et al., 2011a; Daskalakis et al., 2007; Levinson et al., 2010).

Prior work regarding cortical excitability and inhibition in child and adolescent psychiatric disorders is limited. However, developmental trajectories have been proposed by experts. In general, motor threshold measures are high in children and decrease to adult levels by middle adolescence (Garvey et al., 2003; Moll et al., 1999a, 1999b; Nezu et al., 1997). Measures of cortical excitability and inhibition have been studied as a possible endophenotype for attention deficit hyperactivity disorder (Gilbert et al., 2005a, 2005b; Moll et al., 2000), obsessive–compulsive disorder (Greenberg et al., 2000), and Tourette's syndrome (Moll et al., 1999b; Orth & Rothwell, 2009). Recent work by Enticott and colleagues examined differences in cortical inhibition and excitability measures in high-functioning autism, Asperger's disorder, and healthy controls. Cortical inhibition was significantly reduced in the high functioning autism group but there were no significant group differences in cortical excitability measures (Enticott et al., 2010). A recent pilot study also examined changes in cortical excitability in depressed adolescents during the course of rTMS treatment (Croarkin et al., 2011b).

Collectively, this work is promising but typically involves small sample sizes and heterogeneous methodology. Further validation and reliability studies of these neurophysiological measures are imperative for this work to progress. Studies of the motor cortex are also somewhat limited as they have course spatial resolution and arguably do not focus on all relevant neurocircuitry related to psychiatric disorders. Moving forward, studies with interleaved EEG and functional imaging could address these limitations (McClintock et al., 2011).

Developmentally informed neurophysiological information is timely, given the current focus on personalized treatments in psychiatry (Sanislow et al., 2010). Single and paired-pulse studies of cortical excitability and inhibition in child and adolescent psychiatry could assist in developing biomarkers, informing treatment selection and the characterization of endophenotypes and phronotypes (Kozel, 2010). Recent work with newly diagnosed epilepsy subjects is one example. As with child and adolescent psychiatric disorders, epilepsy is a heterogeneous disorder, with unpredictable treatment outcomes. It is estimated that 30% of patients with newly diagnosed epilepsy do not respond to standard anticonvulsant treatment. Badawy and colleagues (2010) examined TMS measures of cortical excitability (motor threshold) to examine the effects of treatment on a large sample of patients with new onset epilepsy. Motor threshold, intracortical inhibition, and intracortical facilitation measures were collected in 99 patients with newly diagnosed epilepsy before treatment and 4–16 weeks after initiating antiepileptic drugs. After one year, 69 of the subjects had no seizures. This group was also unique in that cortical excitability decreased after initiating medication, as evidenced by an increase in motor threshold from baseline. This change was not evident in the group with ongoing seizures. The authors concluded that decreased cortical excitability shortly after the initiation of anticonvulsant medication predicted response to treatment (Badawy et al., 2010). A similar marker for treatment response or resistance would have great utility in child and adolescent psychiatric disorders.

Ethical considerations in the clinical and research application of TMS in minors

Philosophers and the general public have recognized that upcoming decades will lead to an exponential growth in neuroscience knowledge and technology. While ethical issues related to genetics research have been pondered and discussed for over three decades, more recent efforts have focused on the ethics of neuroscience. Specifically, in 2002 the Charles W. Dana Foundation and Stanford University hosted a conference which is often regarded as the birth of

modern neuroethics. This group involved a multidisciplinary team of neuroscientists, researchers, philosophers, and law professors who collectively discussed emerging neuroscience and ethical implications. Experts have commented that, unlike early concerns regarding genetics research, in modern neuroscience there has been no major public outcry for restraint on the part of science. Rather, there is a widespread fascination with the prospect of new technology and the hope that science will extend functionality and mental acuity throughout development. While neuroscience technologies are new and developing rapidly, ethical quandaries regarding mental and behavioural functioning are part of a longstanding discourse and tradition in philosophy (Moreno, 2003). Broadly, neuroethics has been defined as the 'field of philosophy that discusses the rights and wrongs of treatment, or enhancement of, the human brain' (Gazzaniga, 2005). This encompasses issues related to manipulation of the brain (as with psychosurgery, electroconvulsive therapy, and neurostimulation), neuroenhancement (such as in a recent trend in which high functioning college students seek prescriptions for stimulant medications to boost test-taking performance), neuroimaging used to detect deception or to diagnose psychiatric illnesses, definitions of identity and self, decision-making capacity, and longstanding discussions regarding mind–body reductionism. To complicate these considerations further, the ontogeny of modern neuroscience technology is occurring in a profitable environment, which also gave birth to contemporary psychopharmacology. These issues are even more complex and far-reaching in child and adolescent psychiatry. Previous literature has considered the ethical implications of neurostimulation technologies but there are many future challenges (Illes et al., 2006; Jotterand et al., 2010).

Neuroethics is an emerging branch of philosophy focused on the treatment, enhancement, and investigation of the human brain. This field encompasses concerns in research and current clinical practice. These considerations are critical in work with vulnerable populations such as minors. Research involving transcranial magnetic stimulation in children and adolescents serves as one example in applying principles from neuroethics. Ethical issues must remain at the forefront as brain stimulation technology develops and is applied for clinical and research purposes. Clinicians and researchers must consider doctrines of informed consent, beneficence, non-maleficence, justice, autonomy, and shared decision-making (the expert, parents, and child). In general, single and paired-pulse TMS studies are considered safe for children and adolescents. Conversely, experts have expressed concerns that rTMS could have distinctive effects on neurodevelopment (George et al., 2007). For example, rodent studies demonstrate that electrical stimulation produces more pronounced ultrastructural changes related to long-term potentiation in young rodents as opposed to aged ones (Geinisman et al., 1994). Indeed, rTMS international consensus panels have concluded that single pulse and paired-pulse TMS research is safe for children two years of age and older and that children should not participate as subjects in repetitive transcranial magnetic stimulation (rTMS) protocols without compelling grounds, such as the treatment of refractory psychiatric or neurological conditions. Guidelines also maintain that certain principles must guide all TMS research. Informed consent implies that subjects (or a legal guardian) have made a voluntary, educated decision to participate based on a valid informed consent process with standard language. In considering the risk–benefit ratio, an independent review must determine that the potential benefits of the project outweigh all risks. Subject willingness to participate is not sufficient and investigators have the burden to prove that there is no other more desirable, safe means of collecting the data. Clinical studies must likewise ensure that the probability of clinical benefit surpasses all risks. The distribution of the burdens and benefits of research must be equal. Ethical research is not conducted solely on economically, socially, or physically vulnerable subjects who bear all the risks and are unlikely to reap benefits. A disciplined ethical analysis must precede all research and clinical efforts which involve direct manipulation of the brain with tools such as TMS in children and adolescents. Recent work in transcranial magnetic stimulation serves as one example to consider in this context (Rossi et al., 2009).

Conclusions

TMS is a non-invasive tool with applications in clinical and neurophysiological research. At present the majority of psychiatric studies involve adult depression. However, researchers are now utilizing this modality in pediatric populations. Ethical principles and mitigation of risks for vulnerable subjects must remain at the forefront of every study in this area. Future work in this area could serve to develop rTMS as a clinical intervention in child and adolescent psychiatry and a tool for developmental neuroscience. This will involve optimization of stimulation site, stimulation parameters, and the role of rTMS in existing treatment guidelines. These may deviate from adult findings considerably. Single and paired-pulse TMS measures may serve to complement existing translational work regarding the neurophysiology of child and adolescent psychiatric disorders and assist with the development of new treatment targets.

Disclosures Dr Croarkin, research support from NARSAD and Stanley Medical Research Institute. Grant in kind for equipment from Neuronetics; Dr Lee, no disclosures; Dr Wall, AACAP/Eli Lilly Pilot Research Award (2008); Klingenstein Third Generation Foundation Fellowship Program (2011); Mayo Clinic: Department of Psychiatry & Psychology Small Grants Award (2008 & 2010), CTSA CReFF Award (2011) Kids' Cup Funding (2011) Grant in kind for equipment from Neuronetics.

References

Aman, M.G., Singh, N.N., Stewart, A.W. & Field, C.J. (1985). Psychometric characteristics of the aberrant behavior checklist. *American Journal of Mental Deficiency*, 89, 492–502.

Bajbouj, M., Lisanby, S.H., Lang, U.E., Danker-Hopfe, H., Heuser, I. & Neu, P. (2006). Evidence for impaired cortical inhibition in patients with unipolar major depression. *Biological Psychiatry*, *59*, 395–400.

Badawy, R.A., Macdonell, R.A., Berkovic, S.F., Newton, M.R. & Jackson, G.D. (2010). Predicting seizure control: Cortical excitability and antiepileptic medication. *Annals of Neurology*, 67, 64–73.

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J. & Clubley, E. (2001). The autism-spectrum quotient (AQ): Evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, 31, 5–17.

Baruth, J.M., Casanova, M.F., El-Baz, A., Horrell, T., Mathai, G., Sears, L. & Sokhadze, E. (2010). Low-frequency repetitive transcranial magnetic stimulation (rTMS) modulates evoked-gamma frequency oscillations in autism spectrum disorder (ASD). *Journal of Neurotherapy*, *14*, 179–194.

Bloch, Y., Grisaru, N., Harel, E.V., Beitler, G., Faivel, N., Ratzoni, G., … Levkovitz, Y. (2008). Repetitive transcranial magnetic stimulation in the treatment of depression in adolescents: An open-label study. *Journal of ECT*, *24*, 156–159.

Bloch, Y., Harel, H.V., Aviram, S., Govezensky, J., Ratzoni, G. & Levkovitz, Y. (2010). Positive effects of repetitive transcranial magnetic stimulation on attention in ADHD subjects: A randomized controlled pilot study. *World Journal of Biological Psychiatry*, *11*, *755–758.*

Blumberger, D.M., Mulsant, B.H., Fitzgerald, P.B., Rajji, T.K., Ravindran, A.V., Young, L.T., … Daskalakis, Z.J. (2011). A randomized double-blind sham-controlled comparison of unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant major depression. *World Journal of Biological Psychiatry*, in press.

Chae, J.H., Nahas, Z., Wassermann, E., Li, X., Sethuraman, G., Gilbert, D., ... George, M.S. (2004). A pilot safety study of repetitive transcranial magnetic stimulation (rTMS) in Tourette's syndrome. *Cognitive and Behavioral Neurology*, *17*, 109–117.

Chen, R., Samii, A., Canos, M., Wassermann, E.M., & Hallett, M. (1997). Effects of phenytoin on cortical excitability in humans. *Neurology*, *49*, 881–883.

Constantino, J.N., Davis, S.A., Todd, R.D., Schindler, M.K., Gross, M.M., Brophy, S.L., … Reich, W. (2003).Validation of a brief quantitative measure of autistic traits: Comparison of the social responsiveness scale with the autism diagnostic interview-revised. *Journal of Autism and Developmental Disorders*, *33*, 427–433.

Croarkin, P.E., Levinson, A.J. & Daskalakis, Z.J. (2011a). Evidence for GABAergic inhibitory deficits in major depressive disorder. *Neuroscience and Biobehavioral Reviews*, *35*, 818–825.

Croarkin, P.E., Wall, C.A., Nakonezny, P.N., Buyukdura, J.S., Husain, M.M., Sampson, S., … Kozel, F.A. (2011b) Increased cortical excitability with prefrontal high frequency repetitive transcranial magnetic stimulation (rTMS) in adolescents with treatment resistant major depressive disorder (MDD). *Journal of Child and Adolescent Psychopharmacology*, in press.

Croarkin, P.E., Wall, C.A., McClintock, S.M., Kozel, F.A., Husain, M.M. & Sampson, S.M. (2010). The emerging role for repetitive transcranial magnetic stimulation in optimizing the treatment of adolescent depression. *Journal of ECT*, *26*, 323–329.

D'Agati, D., Bloch, Y., Levkovitz, Y. & Reti, I. (2010). rTMS for adolescents: Safety and efficacy considerations. *Psychiatry Research*, *177*, 280–285.

Daskalakis, Z.J., Christensen, B.K., Fitzgerald, P.B. & Chen, R. (2002a). Transcranial magnetic stimulation: A new investigational and treatment tool in psychiatry. *Journal of Neuropsychiatry and Clinical Neuroscience*, *14*, 406–415.

Daskalakis, Z.J., Christensen, B.K., Chen, R., Fitzgerald, P.B., Zipursky, R.B. & Kapur, S. (2002b). Evidence for impaired cortical inhibition in schizophrenia using transcranial magnetic stimulation. *Archives of General Psychiatry*, *59*, 347–354.

Daskalakis, Z.J., Christensen, B.K., Fitzgerald, P.B., Fountain, S.I. & Chen, R. (2005). Reduced cerebellar inhibition in schizophrenia: A preliminary study. *American Journal of Psychiatry*, *162*, 1203–1205.

Daskalakis, Z.J., Farzan, F., Barr, M.S., Maller, J.J., Chen, R. & Fitzgerald, P.B. (2008b). Long-interval cortical inhibition from the dorsolateral prefrontal cortex: A TMS-EEG study. *Neuropsychopharmacology*, *33*, 2860–2869.

Daskalakis, Z.J., Fitzgerald, P.B. & Christensen, B.K. (2007). The role of cortical inhibition in the pathophysiology and treatment of schizophrenia. *Brain Research Reviews*, *56*, 427–442.

Daskalakis, Z.J., Levinson, A.J. & Fitzgerald, P.B. (2008a). Repetitive transcranial magnetic stimulation for major depressive disorder: A review. *Canadian Journal of Psychiatry*, *53*, 555–566.

Davis, M.H. (1980). A multidimensional approach to individual differences in empathy. *Catalog of Selected Documents in Psychology*, *10*, 85.

Doane, J.A., Falloon, I.R., Goldstein, M.J. & Mintz, J. (1985). Parenting affective style and the treatment of schizophrenia. Predicting course of illness and social functioning. *Archives of General Psychiatry*, *13*, 261–276.

DuPaul, G.J., Reid, R., Power, T.J., Anastopoulos, A.D. (1998). *ADHD Rating Scale-IV.* New York: Guilford.

Enticott, P.G., Kennedy, H.A., Zangen, A., & Fitzgerald, P.B. (2011). Deep repetitive transcranial magnetic stimulation associated with improved social functioning in a young woman with an autism spectrum disorder. *Journal of ECT*, *27*, 41–43.

Enticott, P.G., Rinehart, N.J., Tonge, B.J., Bradshaw, J.L. & Fitzgerald, P.B. (2010). A preliminary transcranial magnetic stimulation study of cortical inhibition and excitability in high-functioning autism and Asperger disorder. *Developmental Medicine and Child Neurology*, *52*, e179–183.

Farzan, F., Barr, M.S., Levinson, A.J., Chen, R., Wong, W., Fitzgerald, P.B. & Daskalakis, Z.J. (2010a). Evidence for gamma inhibition deficits in the dorsolateral prefrontal cortex of patients with schizophrenia. *Brain*, *133*, 1505–1514.

Farzan, F., Barr, M.S., Levinson, A.J., Chen, R., Wong, W., Fitzgerald, P.B., Daskalakis, Z.J. (2010b). Reliability of long-interval cortical inhibition in healthy human subjects: A TMS-EEG study. *Journal of Neurophysiology*, *104*, 1339–1346.

Fitzgerald, P.B., Benitez, J., Daskalakis, J.Z., De Castella, A. & Kulkarni, J. (2006). The treatment of recurring auditory hallucinations in schizophrenia with rTMS. *World Journal of Biological Psychiatry*, *7*, 119–122.

Frye, R.E., Rotenberg, A., Ousley, M. & Pascual-Leone, A. (2008). Transcranial magnetic stimulation in child neurology: Current and future directions. *Journal of Child Neurology*, *23*, 79–96.

Garvey, M.A. & Gilbert, D.L. (2004). Transcranial magnetic stimulation in children. *European Journal of Paediatric Neurology*, *8*, 7–19.

Garvey, M.A., Ziemann, U., Bartko, J.J., Denckla, M.B., Barker, C.A. & Wassermann, E.M. (2003). Cortical correlates of neuromotor development in healthy children. *Clinical Neurophysiology*, *114*, 1662–1670.

Gazzaniga, M. (2005) *The Ethical Brain*. Washington, DC: Dana Press.

Geinisman, Y., deToledo, M.L. & Morrell, F. (1994). Comparison of structural synaptic modifications induced by long-term potentiation in the hippocampal gyrus of young adult and aged rats. *Annals of the New York Academy of Sciences*, *747*, 452–466.

George, M.S., Bohing, D.E., Lorberbaum, J.P., Nahas, Z., Andersen, B., Borckardt, J.J., … Rastogi (2007). Overview of transcranial magnetic stimulation: History, mechanisms, physics, and safety. In M.S. George & R. H. Belmaker (Eds), *Transcranial Magnetic Stimulation in Clinical Psychiatry* (pp.) Arlington, VA: American Psychiatric Publishing. 1–25

Gilbert, D.L., Ridel, K.R., Sallee, F.R., Zhang, J., Lipps, T.D. & Wassermann, E.M. (2005a). Comparison of the inhibitory and excitatory effects of ADHD medications methylphenidate and atomoxetine on motor cortex. *Neuropsychopharmacology*, *31*, 442–449.

Gilbert, D.L., Sallee, F.R., Zhang, J., Lipps, T.D. & Wassermann, E.M. (2005b). Transcranial magnetic stimulation-evoked cortical inhibition: A consistent marker of attention-deficit/hyperactivity disorder scores in tourette syndrome. *Biological Psychiatry*, *57*, 1597–1600.

Greenberg, B.D., Ziemann, U., Cora-Locatelli, G., Harmon, A., Murphy, D.L., Keel, J.C. & Wasserman, E.M. (2000). Altered cortical excitability in obsessive–compulsive disorder. *Neurology*, *54*, 142–147.

Guy, W. (1976). *ECDEU Assessment Manual for Psychopharmacology*. Rockville, MD: US Department of Health, Education, and Welfare Public Health Service Alcohol, Drug Abuse, and Mental Health Administration.

Hoffman, R.E., Hawkins, K.A., Gueorguieva, R., Boutros, N.N., Rachid, F., Carroll, K. & Krystal, J.H. (2003). Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. *Archives of General Psychiatry*, *60*, 49–56.

Illes, J., Gallo, M. & Kirschen, M.P. (2006) An ethics perspective on transcranial magnetic stimulation (TMS) and human modulation. *Behavioral Neurology*, *17*, 149–157.

Jardri, R., Lucas, B., Delevoye-Turrell, Y., Delmaire, C., Delion, P., Thomas, P. & Goeb, J.L. (2007). An 11-year-old boy with drug-resistant schizophrenia treated with temporo-parietal rTMS. *Molecular Psychiatry*, *12*, 320.

Jotterand, F., McClintock, S.M., Alexander, A.A. & Husain, M.M. (2010). Ethics and informed consent of vagus nerve stimulation (VNS) for patients with treatment-resistant depression (TRD). *Neuroethics*, 3, 13–22.

Kay, S.R., Fiszbein, A. & Opler, L.A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*, 261–276.

Kozel, F.A. (2010). Identifying phronotypes in psychiatry. *Frontiers in Psychiatry*, *141*, 1–5.

Kozel, F.A., Tian, F., Dhamne, S., Croarkin, P.E., McClintock, S.M., Elliott, A., … Liu, H. (2009). Using simultaneous repetitive Transcranial Magnetic Stimulation/functional Near Infrared Spectroscopy (rTMS/fNIRS) to measure brain activation and connectivity. *Neuroimage*, *47*, 1177–1184.

Kwon, H.J., Lim, W.S., Lim, M.H., Lee, S.J., Hyun, J.K., Chae, J.H. & Paik, K.C. (2011). 1-Hz low frequency repetitive transcranial magnetic stimulation in children with Tourette's syndrome. *Neuroscience Letters*, *492*, 1–4.

Lam, K.S. & Aman, M.G. (2007). The repetitive behavior scale-revised: Independent validation in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *37*, 855–866.

Leckman, J.F., Riddle, M.A., Hardin, M.T., Ort, S.I., Swartz, K.L., Stevenson, J. & Cohen, D.J. (1989). The Yale Global Tic Severity Scale: Initial testing of a clinician-rated scale of tic severity. *Journal of the American Academy of Child and Adolescent Psychiatry*, *28*, 566–573.

Levinson, A.J., Fitzgerald, P.B., Favalli, G., Blumberger, D.M., Daigle, M. & Daskalakis, Z.J. (2010). Evidence of cortical inhibitory deficits in major depressive disorder. *Biological Psychiatry*, *67*, 458–464.

Lisanby, S.H., Husain, M.M., Rosenquist, P.B., Maixner, D., Gutierrez, R., Krystal, A., … George, M.S. (2009). Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: Clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*, *34*, 522–534.

Lisanby, S.H., Kinnunen, L.H. & Crupain, M.J. (2002). Applications of TMS to therapy in psychiatry. *Journal of Clinical Neurophysiology*, *19*, 344–360.

Loo, C., McFarquhar, T. & Walter, G. (2006). Transcranial magnetic stimulation in adolescent depression. *Australasian Psychiatry*, *14*, 81–85.

McClintock, S.M., Freitas, C., Oberman, L., Lisanby, S.H. & Pascual-Leone, A. (2011). Transcranial magnetic stimulation: A neuroscientific probe of cortical function in schizophrenia. *Biological Psychiatry*, *70*, 19–27.

Moll, G.H., Heinrich, H., Trott, G., Wirth, S. & Rothenberger, A. (2000). Deficient intracortical inhibition in drug-naive children with attention-deficit hyperactivity disorder is enhanced by methylphenidate. *Neuroscience Letters*, *284*, 121–125.

Moll, G.H., Heinrich, H., Wischer, S., Tergau, F., Paulus, W. & Rothenberger, A. (1999a). Motor system excitability in healthy children: Developmental aspects from transcranial magnetic stimulation. *Electroencephalography and Clinical Neurophysiology Supplements*, *51*, 243–249.

Moll, G.H., Wischer, S., Heinrich, H., Tergau, F., Paulus, W. & Rothenberger, A. (1999b). Deficient motor control in children with tic disorder: Evidence from transcranial magnetic stimulation. *Neuroscience Letters*, *272*, 37–40.

Moreno, J.D. (2003). Neuroethics: An agenda for neuroscience and society. *Nature Reviews Neuroscience*, *4*, 149–153.

Nezu, A., Kimura, S., Uehara, S., Kobayashi, T., Tanaka, M. & Saito, K. (1997). Magnetic stimulation of motor cortex in children: maturity of corticospinal pathway and problem of clinical application. *Brain Development*, *19*, 176–180.

O'Reardon, J.P., Solvason, H.B., Janicak, P.G., Sampson, S., Isenberg, K.E., Nahas, Z., … Sackeim, H.A. (2007). Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: A multisite randomized controlled trial. *Biological Psychiatry*, *62*, 1208–1216.

Orth, M. & Rothwell, J.C. (2009). Motor cortex excitability and comorbidity in Gilles de la Tourette syndrome. *Journal of Neurology Neurosurgery and Psychiatry*, *80*, 29–34.

Poznanski, E.O., Grossman, J.A., Buchsbaum, Y., Banegas, M., Freeman, L. & Gibbons, R. (1984). Preliminary studies of the reliability and validity of the children's depression rating scale. *Journal of the American Academy of Child and Adolescent Psychiatry*, 23, 191–1917.

Quintana, H. (2005). Transcranial magnetic stimulation in persons younger than the age of 18. *Journal of ECT*, *21*, 88–95.

Ridding, M.C. & Rothwell, J.C. (2007). Is there a future for therapeutic use of transcranial magnetic stimulation? *Nature Reviews Neuroscience*, *8*, 559–567.

Ritvo, R.A., Ritvo, E.R., Guthrie, D., Yuwiller, A., Ritvo, M.J. & Weisbender, L. (2008) A scale to assist the diagnosis of autism and Asperger's disorder in adults (RAADS): A pilot study. *Journal of Autsim and Developmental Disorders*, 38, 213–223.

Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A. & Safety of TMS Consensus Group (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, 120, 2008–2039.

Sanislow, C.A., Pine, D.S., Quinn, K.J., Kozak, M.J., Garvey, M.A., Heinssen, R.K., … Cuthbert, B.N. (2010). Developing constructs for psychopathology research: Research domain criteria. *Journal of Abnormal Psychology*, *119*, 631–639.

Shaffer, D., Gould, M.S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H. & Aluwahlia, S. (1983). A children's global assessment scale (CGAS). *Archives of General Psychiatry*, 40, 1228–1231.

Sokhadze, E., Baruth, J., Tasman, A., Mansoor, M., Ramaswamy, R., Sears. L., … Casanova, M.F. (2010). Low-frequency repetitive transcranial magnetic stimulation (rTMS) affects event-related potential measures of novelty processing in autism. *Applied Psychophysiology Biofeedback*, *35*, 147–161.

Tergau, F., Wischer, S., Somal, H.S., Nitsche, M.A., Mercer, A.J., Paulus, W., Steinhoff, B.J. (2003). Relationship between lamotrigine oral dose, serum level and its inhibitory effect on CNS: Insights from transcranial magnetic stimulation. *Epilepsy Research*, *56*, 67–77.

Wall, C.A., Croarkin, P.E., Sim, L.A., Husain, M.M., Janicak, P.G., Kozel, F.A., … Sampson, S. (2011) Adjunctive use of repetitive transcranial magnetic stimulation in depressed adolescents. *Journal of Clinical Psychiatry*, *72*: 63–69.

Walter, G., Tormos, J.M., Israel, J.A. & Pascual-Leone, A. (2001). Transcranial magnetic stimulation in young persons: A review of known cases. *Journal of Child and Adolescent Psychopharmacology*, *11*, 69–75.

Weaver, L., Mace, W., Akhtar, U. Moss, E., Rostain, A. & O'Reardon, J. (2008). Safety and efficacy of rTMS in treatment of ADHD in adolescents and young persons. *Journal of ECT*, *24*, 105–106.

Ziemann, U. (1999). Intracortical inhibition and facilitation in the conventional paired TMS paradigm. *Electroencephalography and Clinical Neurophysiology Supplements*, *51*, 127–136.

Ziemann, U. (2003). Pharmacology of TMS. *Supplements in Clinical Neurophysiology*, *56*, 226–231.

Ziemann, U. (2004). TMS and drugs. *Clinical Neurophysiology*, *115*, 1717–1729.

Ziemann, U., Chen, R., Cohen, L.G. & Hallett, M. (1998). Dextromethorphan decreases the excitability of the human motor cortex. *Neurology*, *51*, 1320–1324.