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Use of Transcranial Magnetic Stimulation in Autism Spectrum Disorders

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Abstract The clinical, social and financial burden of autism spectrum disorder (ASD) is staggering. We urgently need valid and reliable biomarkers for diagnosis and effective treatments targeting the often debilitating symptoms. Transcranial magnetic stimulation (TMS) is beginning to be used by a number of centers worldwide and may represent a novel technique with both diagnostic and therapeutic potential. Here we critically review the current scientific evidence for the use of TMS in ASD. Though preliminary data suggests promise, there is simply not enough evidence yet to conclusively support the clinical widespread use of TMS in ASD, neither diagnostically nor therapeutically. Carefully designed and properly controlled clinical trials are warranted to evaluate the true potential of TMS in ASD.

Keywords Autism spectrum disorder · Transcranial magnetic stimulation · TMS · Diagnosis · Therapy

The Centers for Disease Control and Prevention currently estimate the prevalence of autism spectrum disorder (ASD) in the United States at 1 in 88 children (1 in 54 boys and 1 in 252 girls) (Baio 2012). This is more children than are affected by diabetes, AIDS, cancer, cerebral palsy, cystic fibrosis, muscular dystrophy and Down syndrome combined (Child and Adolescent Health Measurement Initiative 2012) ASD is diagnosed clinically, based on the presence of key behavioral symptoms, but the underlying brain mechanisms causing these symptoms are unknown and there currently exists no cure. Most empirically supported treatments for the core symptoms of ASD focus on early intensive behavioral interventions (Reichow 2012). Pharmacological treatments are at times effective in treating secondary and comorbid features of ASD, such as aggression or hyperactivity and attention deficit, or epilepsy (Hampson et al. 2012), but there is currently no pharmacotherapy shown to effectively treat the core symptoms of ASD (see Oberman 2012 for a review).

With some clinical trials of pharmaceuticals or other interventions for core ASD symptoms ongoing and many more in planning stages, early and objective ASD diagnosis and improved understanding of the underlying ASD pathophysiology will be necessary. One way this may be accomplished is with transcranial magnetic stimulation (TMS), a noninvasive method for cortical stimulation that may avail to the field a physiologic biomarker to aid with ASD diagnosis and perhaps obtain deeper insight into ASD physiology. As well, and relevant to our report, TMS may have therapeutic prospects as well.

Here we critically review the current state of scientific knowledge on the uses of TMS in patients with ASD. In the first part of this review, we give a brief introduction to TMS, its safety, its clinical potential as well as its limitations. The second section focuses on the current knowledge about the etiology of ASD and how TMS can be utilized to study the neurobiological substrates, noninvasively, in patients across the autism spectrum. Last, we summarize the current evidence for the safety, tolerability and efficacy

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of repetitive TMS (rTMS) as a therapeutic intervention in ASD.

Studies included in this review were obtained using a PubMed search in May of 2013 with the following key words "TMS autism", "TMS Asperger" "transcranial magnetic stimulation autism" and "transcranial magnetic stimulation Asperger". A total of 17 studies were identified that applied any form of TMS to individuals with ASD.

TMS Basics

All TMS devices have the same essential components: a large capacitor, a control mechanism that enables the capacitor to be rapidly discharged, and a conductive coil (usually hand-held) through which the current travels to generate a powerful and fluctuating magnetic field (Barker 1999). Through a process of electromagnetic induction, this rapid pulse of electrical current induces a rapidly fluctuating magnetic field, which in turn induces an electrical current in the underlying brain tissue (Barker et al. 1985; Wagner et al. 2007). How much brain tissue is stimulated is dependent on the shape of the coil as well as the intensity of the stimulation (amount of current discharged by the machine) (Pascual-Leone et al. 2002). The first TMS coils were large circular loops with limited focality of stimulation (Barker et al. 1985). Recent developments, however, have led to coils that instead are a figure-of-eight shape and induce a sufficient amount of current to depolarize cortical neurons in approximately a 1–2 cm^2 region lying directly under the intersection of the figure-of-eight (Brasil-Neto et al. 1992). We note that even though the electrical current induced by TMS on the scalp attenuates very rapidly (Rudiak and Marg 1994), the behavioral effects of TMS are not limited to functions that are mediated by the relatively focal cortical regions, directly under the coil, but also brain areas whose activity is modulated by the stimulated regions through connectivity. Thus TMS to any one single region of cortex can affect an entire network or system.

TMS can be used both experimentally and therapeutically. In the experimental domain TMS can be applied in single pulses to depolarize a small population of neurons in a targeted brain region (Barker et al. 1985). This protocol can be used, for example, to map cortical motor outputs, study central motor conduction time, or evaluate the cortical silent period (a measure of intracortical inhibition) all of which may be affected by pathologies of the central nervous system such as ASD (Kobayashi and Pascual-Leone 2003). TMS can also be applied in pairs of pulses (paired pulse stimulation, ppTMS) (Claus et al. 1992; Kujirai et al. 1993; Valls-Sole et al. 1992; Ziemann 1999), where two pulses are presented in rapid succession to study intracortical inhibition and facilitation. ppTMS measures may be particularly informative in detecting abnormalities in excitation-inhibition ratios in ASD, especially given the current theories related to the role of GABA signalling (Blatt and Fatemi 2011; Hussman 2001; Pizzarelli and Cherubini 2011) and E/I ratios (Rubenstein and Merzenich 2003) in ASD.

Trains of repeated TMS (rTMS) pulses can be applied at various stimulation frequencies and patterns to modulate local cortical excitability beyond the duration of the stimulation itself (some common rTMS protocols include 1 Hz, 5 Hz, Paired Associative Stimulation, and Theta Burst Stimulation (TBS) protocols). Depending on the parameters of stimulation the excitability can be either facilitated or suppressed (Pascual-Leone et al. 1994). The after-effects of rTMS are thought to be related to changes in efficacy (in either the positive or negative direction) of synaptic connections of the neurons being stimulated (Fitzgerald et al. 2006; Hoogendam et al. 2010), thus have been used to study cortical plasticity mechanisms in a number of populations (Pascual-Leone et al. 2011).

TMS protocols have been developed to study both Hebbian and non-Hebbian plasticity. One such protocol, paired associative stimulation (PAS) is modeled after animal electrical stimulation paradigms whereby long-term potentiation-like (LTP-like) and long-term depression-like (LTD-like) plasticity is induced through repeated pairs of electrical peripheral nerve and cortical stimulation by TMS (Stefan et al. 2000). When these pairs of stimulation are presented with a defined interstimulus interval, the resulting motor evoked potential induced by a single pulse of TMS is modulated (Classen et al. 2004). The amount of modulation that is induced by this pairing is a putative measure of NMDA dependent Hebbian plasticity of the corticospinal tract (Ziemann 2004).

Another common TMS paradigm designed to investigate plasticity mechanisms is theta burst stimulation (TBS). Unlike PAS, TBS is modeled after in vitro protocols that induce non-Hebbian plasticity by introducing brief rapid trains of stimulation to the cortex. Physiologic and pharmacologic studies of TBS in humans reveal involvement of glutamatergic and GABAergic mediators consistent with LTP-like and LTD-like mechanisms, and the effects and their time-course are consistent with the notion that TBS indexes mechanisms of cortical non-Hebbian synaptic plasticity (Cardenas-Morales et al. 2010; Huang et al. 2005, 2007).

Due to the capacity to induce long-term changes in brain activity, rTMS is considered in the treatment of a number of neurological and psychiatric conditions (Kobayashi and Pascual-Leone 2003) such as major depression (Schutter 2009) where it has been FDA approved, Parkinson's Disease (Kimura et al. 2011), Alzheimer's Disease (Freitas

et al. 2011; Nardone et al. 2012), and epilepsy (Sun et al. 2012). Notably, the degree and direction of the effect of rTMS, both at the level of the brain and behavior, depends on a number of factors. This is not a one-size-fits-all treatment and the difference between having a positive effect, no effect, or a negative effect on the desired symptom depends on the exact parameters (location of stimulation, intensity of stimulation, frequency of stimulation, number of sessions, and frequency of sessions, just to name a few). Though there is significant potential for the use of TMS in clinical disorders, such as those above as well as others, (for current reviews see Kim et al. 2009; Machado et al. 2008; Schulz et al. 2013; Wassermann and Zimmermann 2012) most of the evidence for therapeutic potential comes from small scale studies and needs further support from larger-scale, double blind clinical trials to elucidate its true potential.

In summary, TMS has the potential to induce either acute or long-lasting changes to the cortical functions. The exact effect that is induced is dependent on parameters including location of stimulation, coil geometry and orientation, intensity and frequency of the magnetic pulses. With these capabilities, TMS is a valuable tool for both the researcher and the clinician looking for a noninvasive way to study and treat neurological and psychological disorders where the behavioral disability is due to altered cortical excitability or plasticity. As described below, ASD may represent such a disorder where TMS may be used both to study and potentially treat some of the symptoms.

TMS Safety

TMS is considered quite safe if applied within current safety guidelines; however, TMS does pose some risk for adverse side effects (Rossi et al. 2009). To highlight possible contraindications that might put a patient at risk for an adverse effect, it is recommended that a short safety check list be used to screen patients before they undergo TMS investigations, including, a history of seizures, syncope, head injury, brain diseases or medications associated with increase seizure risk, the presence of metal in the cranium, implanted biomedical devices, and pregnancy. All of these conditions should be considered only relative contraindication and the risk–benefit ratio of the procedure should be carefully considered before the patients undergo TMS.

Seizures are the most serious possible TMS-related adverse event. Less than 20 cases of TMS induced seizures have been reported out of tens of thousands of examined subjects over the past 25 years. Overall the risk of seizure is considered to be <0.01 % (Rossi et al. 2009). However, it should be noted that individuals with ASD have a greater than average prevalence of epilepsy, approximately 30 % (Spence and Schneider 2009), and EEG abnormalities are present in approximately 60 % of children with ASD who do not have epilepsy (Chez et al. 2006).

To date no seizures have been reported during TMS in any individual with ASD, and given the paucity of TMS safety data in ASD, it is currently reasonable to default to the safety guidelines established by the "Safety of TMS Consensus Group" (Rossi et al. 2009). We anticipate in the coming years as more patient populations are being studied using TMS that specialized guidelines for ASD and other patient groups will be forthcoming.

Some patients have also experienced presyncopal reactions following stimulation (Grossheinrich et al. 2009), but it is hard to disentangle the direct effects of stimulation from that of a vasovagal response to anxiety or discomfort in these cases. Other, more common side effects that have been associated with TMS are considered relatively minor and include headache, neck pain, discomfort at the site of stimulation, and transient increases in auditory thresholds. TMS can also cause transient or long-lasting changes in cognition or mood. These effects are often the desired effects of the stimulation, however, one must keep in mind that any given TMS protocol may have varying effects in both degree and direction in any given individual, especially when that individual has a preexisting neuropsychological disorder. Thus, one must be very cautious when applying TMS, especially rTMS to a participant and follow established safety guidelines (Rossi et al. 2009). Though relatively few patients with ASD (approximately 250) have participated in a TMS protocol for either investigative or therapeutic purposes, it appears thus far that the distribution of side effects follows that seen in the general population. As with any other condition, however, factors including medications as well as medical and family medical history needs to be taken into consideration when determining risk for adverse events in any given individual.

Autism: A Neurodevelopmental Disorder

Development of novel treatment for such complex and heterogenous disorders as ASD requires a deeper understanding of the underlying pathophysiology. Such efforts may not only catalyze the identification of new and effective therapeutic interventions, may also deliver valuable biomarkers for diagnosis and longitudinal assessment of disease progression and treatment efficacy.

It is now generally accepted that the ASD symptoms emerge as a result of abnormal neural development. There is much debate in the literature, however, of the exact neuropathological etiology. Some have suggested that abnormalities in specific functionally defined systems, such as the mirror neuron system, underlie ASD (Oberman and

Ramachandran 2007; Williams et al. 2006). Others have focused on abnormalities in brain growth (Courchesne et al. 2001), connectivity (Geschwind and Levitt 2007; Mostofsky et al. 2009), excitation and inhibition (Rubenstein and Merzenich 2003; Casanova et al. 2002) and synaptic plasticity (Dolen and Bear 2009; Markram et al. 2007; Oberman and Pascual-Leone 2008). Though all of these theories have been supported by empirical data the exact direction (too much or too little), conditions under which any of these abnormalities are present and heterogeneity of the pathology across individuals makes it difficult to make strong claims implicating any single causal mechanism. What is clear is that multiple brain systems are anatomically and functionally different in individuals with ASD as compared to matched typically developing individuals.

The exact etiology is unknown in most individuals with ASD, and is likely a combination of multiple genetic and environmental factors. Recently, our group and others have focused on the role of abnormal cortical excitability and plasticity in the pathogenesis of ASD (Oberman et al. 2012, in press; Rubenstein and Merzenich 2003; Markram et al. 2007). Multiple lines of evidence support the theory of altered plasticity in ASD. Firstly, most candidate genes linked to ASD play a role in developmental and experience-dependent plasticity (Akaneya et al. 1997; Huber et al. 1998; Jiang et al. 2001; Korte et al. 1995; Patterson et al. 1996; Perry et al. 2001; Durand et al. 2007; Jamain et al. 2003; Morrow et al. 2008; Cook 2001; Lamb et al. 2000; Persico and Bourgeron 2006). In addition, single gene disorders associated with autism implicate proteins which play important roles in synaptic plasticity (Dolen and Bear 2009). Animal ASD models also reveal abnormal plasticity mechanisms (reviewed in (Tordjman et al. 2007)) in models of both syndromic (Dani et al. 2005; Huber et al. 2002) and nonsyndromic forms of ASD (Gogolla et al. 2009; Baudouin et al., 2012).

Consistent with the role of altered cortical development in ASD, regions related to language production and social skills in the frontal and prefrontal cortex have a spike in synaptogenesis and plasticity between years 1 and 3 (Huttenlocher 2002) when autistic symptoms related to these processes usually become apparent. The specific pathology of synapse maturation and plasticity during development seen in ASD has been proposed to lead to an imbalance of excitation and inhibition, and specifically a disproportionately high level of excitation (Rubenstein and Merzenich 2003). Multiple post mortem studies note a reduction in GABAergic receptors (Fatemi et al. 2009a, b, 2010) as well as a 50 % reduction in enzymes that synthesize GABA (*glutamic acid decarboxylase* (GAD) 65 and 67) (Fatemi et al. 2002; Yip et al. 2007) in individuals with autism. Additionally, recent animal studies suggest that a modulation in this balance toward excitation in the mouse medial prefrontal cortex resulted in autistic-like behaviors and subsequent compensatory elevation of inhibitory factors partially rescued the social deficits caused by the excitation/inhibition imbalance (Yizhar et al. 2011). Thus, modulation of cortical excitability in frontal and prefrontal cortex may represent potential targets for TMS studies and rTMS clinical applications.

TMS as an Investigative Tool

When single pulses are applied to the primary motor cortex a TMS-induced motor evoked potential can be recorded using electromyography (EMG) from the contralateral muscle group corresponding to the region of primary motor cortex that is being stimulated. The physiological effect of TMS to other cortical regions can be evaluated by combining TMS and EEG and measuring evoked potentials and other EEG-related indices of cortical activation (Thut et al. 2005).

Using these protocols, several groups have begun to use TMS as an experimental tool to understand ASD pathophysiology (Summarized in Table 1). The results of these studies have shown, consistent with findings from other approaches, that a number of basic mechanisms and circuits are atypical in individuals with ASD while other measures appear to be normal. Specifically, multiple studies have reported normal measures of basic excitability and intracortical inhibition and facilitation of the primary motor cortex and cortico-spinal projections as measured by resting and active motor threshold (Enticott et al. 2013a; Oberman et al. 2010; Theoret et al. 2005), single pulse (Enticott et al. 2012a; Oberman et al. 2012) and paired-pulse (Enticott et al. 2013a; Jung et al. 2013; Theoret et al. 2005) TMS paradigms. However, two studies have reported heterogeneity in the response to ppTMS with some individuals with ASD showing a reduced response (and in some cases paradoxical facilitation) in response to the short intracortical inhibition (SICI) paradigm (Enticott et al. 2010, 2013a; Oberman et al. 2010) and long intracortical inhibition (LICI) paradigm (Oberman et al. 2010) indicating that some individuals may have an insufficient amount of inhibitory tone.

In addition to studying cortical excitability and intracortical inhibition, TMS can also be used to investigate cortical and cortico-spinal plasticity mechanisms. These mechanisms have also been implicated in the ASD pathophysiology (Markram et al. 2007; Oberman and Pascual-Leone 2008).

In a recent study using PAS, researchers were unable to induce a significant LTP-like plastic modulation of the motor cortex in high-functioning individuals with ASD. This study suggests that Hebbian plasticity mechanisms may be abnormal in individuals with ASD (Jung et al.

Table 1 Summary of Published studies using TMS as a diagnostic tool

Study	Number of ASD subjects	Distribution of autism vs. AS (diagnostic criteria)	Age of participants (years)	TMS parameters (number of sessions, frequency, location)	Effects	Adverse-events/ side effects
Theoret et al. (2005)	10	Not Indicated (DSM-IV-R)	23–58	One session of spTMS and ppTMS over M1	No group difference in RMT or response to ppTMS. Impaired corticospinal facilitation in response to finger movements viewed from the egocentric point of view in ASD group.	Not Indicated
Minio-Paluello et al. (2009)	16	16 AS (DSM-IV)	M = 28.0 (SD = 7.2)	One session of spTMS over M1	No modulation of corticospinal excitability in response to the observation of painful stimuli affecting another individual in AS group.	Not Indicated
Oberman et al. (2010)	5	5 AS (DSM-IV-TR)	26–54	Two sessions of spTMS, ppTMS, and TBS over M1	Heterogeneous response to ppTMS. Greater and longer-lasting response to TBS in AS group.	None
Enticott et al. (2010)	25	11 HFA, 14 AS (DSM-IV)	M = 16.67 (SD = 4.33)	One session of spTMS and ppTMS over M1	Reduced intracortical inhibition in the HFA group as compared to the AS or control group	Not Indicated
Oberman et al. (2012)	35	35 AS (DSM-IV, ADOS and ADI-R)	18–64	Two sessions of spTMS and TBS over M1	No group difference in RMT or AMT or response to spTMS at baseline. Greater and longer-lasting response to TBS in AS group.	None
Enticott et al. (2012a)	34	Not Indicated (DSM-IV)	M = 26.32 (SD = 10.70)	One session of spTMS over M1	No group difference in degree of corticospinal excitability in response to observation of single static hand stimuli. Impaired corticospinal facilitation in response to single hand transitive hand actions in ASD group.	Not Indicated
Enticott et al. (2013a)	36	Not Indicated (DSM-IV)	M = 26 (SD = 10.48)	One session of spTMS and ppTMS over M1	No group difference in RMT. Heterogeneous response to ppTMS in ASD group.	Not Indicated
Jung et al. (2013)	15	7 HFA, 6 AS, 2 PDD-NOS (ICD 10 and DSM-IV)	M = 17.8 (SD = 3.5)	One session of ppTMS and PAS	No group difference in response to ppTMS. Impaired PAS facilitation in ASD group.	None
Enticott et al. (2013b)	32	Not Indicated (DSM-IV)	M = 24.75 (SD = 8.11)	One session of spTMS over M1	No group difference in degree of corticospinal excitability in response to single static hand stimuli or two person interactive hand actions	Not Indicated

M1 primary motor cortex, *RMT* resting motor threshold, *AMT* active motor threshold, *HFA* high functioning autism, *AS* Asperger's syndrome, *PDD-NOS* pervasive developmental disorder, not otherwise specified, *spTMS* single pulse TMS, *ppTMS* paired pulse TMS, *TBS* theta burst stimulation, *PAS* paired associative stimulation

2013). Interestingly, a study recently published using the TBS plasticity paradigm found opposite results. Specifically, in a study conducted by Oberman et al. 2010, 2012) researchers found significantly greater and longer-lasting modulation of excitability in the ASD group as compared to neurotypical individuals indicating a greater propensity for plastic change. Furthermore, the authors (Oberman et al. 2012) found that this enhanced modulation following TBS was extremely reliable across cohorts leading the authors to conclude that a dysfunction in plasticity may represent the enigmatic mechanism underlying ASD (Oberman and Pascual-Leone 2008) and may provide a potential diagnostic biomarker for this disorder (Oberman et al. 2012).

Another series of studies using TMS have combined single-pulse paradigms with behavioral tasks to evaluate the effect of visual stimuli on cortical excitability. Though individuals with ASD typically have comparable corticospinal excitability at baseline and during the observation of static visual stimuli and two handed interactive stimuli (Enticott et al. 2012a, b; Theoret et al. 2005), the observation of hand stimuli engaged in specific motor movements or receiving a painful needle prick does not induce the expected corticospinal modulation that is seen in

neurotypical individuals (Enticott et al. 2012a; Minio-Paluello et al. 2009; Theoret et al. 2005). These findings have been used as support for the theories suggesting a possible partial, not global, dysfunction in the mirror neuron system in ASD.

TMS as a Therapeutic Tool

The aforementioned TMS protocols are particularly useful in studying the ASD pathophysiology, especially in light of the current theories suggesting a role of altered excitation/inhibition balance and aberrant synaptic plasticity in ASD. In addition to its potential as a research tool, the potential of rTMS to induce a long-lasting modulation of cortical excitability and plasticity offers the possibility of its use for therapeutic purposes in neurological and psychological conditions thought to be a result of altered excitability or plasticity of specific neural circuits. Again, we underscore that rTMS physiologic effects will differ depending on the type of protocol used (as determined by frequency and intertrain interval) and where it is applied.

Though the physiological effects of rTMS are most often quantified in the motor cortex, there is much evidence that the long-lasting effects of rTMS are not limited to this region. Studies examining behavioral performance prior to and following rTMS have shown rTMS-induced changes in sensory (Kosslyn et al. 1999), cognitive (Hilgetag Theoret and Pascual-Leone 2001; Mottaghy et al. 2002), and affective processing (see Lee et al. 2012 for a review). Low frequency protocols and a specific type of TBS (continuous, cTBS) generally induce lasting suppression of the excitability, while high-frequency and a different type of TBS (intermittent, iTBS) generally induce lasting facilitation (Maeda et al. 2000). However, it should be noted that these effects are state-dependant and there is significant intersubject and intrasubject variability (Silvanto and Pascual-Leone 2008). Thus, in order to induce the desired effect, one must consider the brain region, as even a small shift in the targeted region may greatly affect the behavioral impact, the current state of the stimulated cortex as state-dependent changes have been observed, and the exact protocol that is being applied as opposite effects can be induced by even slight modifications of the parameters.

Treatment of depression is the most thoroughly studied therapeutic application of rTMS. Protocols have been developed that target left dorsolateral prefrontal cortex (DLPFC) with high frequency (10 or 20 Hz) stimulation and result in significant alleviation of depressive symptoms compared to sham stimulation (see Schutter 2009 for a recent meta-analysis). A device capable of applying this type of stimulation has now been approved by the FDA for treatment of medication resistant depression (Neurostar TMS Therapy, Neuronetics, Malvern, PA). A different protocol involving low-frequency repetitive stimulation to right DLPFC has also been shown to be effective for depression (Fitzgerald et al. 2009; Isenberg et al. 2005; Stern et al. 2007), but has yet to receive FDA approval. Though the Neurostar TMS Therapy (Malvern, PA) is the only FDA approved TMS device and therapeutic protocol, the potential of rTMS to improve symptoms of many other neurological and psychiatric diseases is beginning to be explored through research studies, clinical trials, and off-label treatments.

Specifically as it relates to ASD, recent studies from two sites in the United States (Harvard Medical School, Boston, MA and University of Louisville School of Medicine, Louisville, KY) and one site in Australia (Monash University, Melbourne, Australia) have reported preliminary data suggesting an improvement in both physiological indices and specific behavioral symptoms following rTMS (Summarized in Table 2).

The first of these studies, was based on the finding that individuals with ASD showed abnormal structure of minicolumns with reduced neuronal size and increased density attributable to reductions in the inhibitory peripheral neuropil space (Casanova et al. 2002). This finding was most prominent in the prefrontal cortex (Casanova et al. 2006). Thus, using a rTMS protocol aimed at increasing inhibitory tone, Sokhadze et al. (2009) applied low-frequency (0.5 Hz, 150 pulses) stimulation to left DLPFC two times per week for 3 weeks in a small sample of eight individuals with ASD. The results of this first study showed a normalization in event-related potentials (ERPs) and induced gamma frequency electroencephalographic (EEG) activity over frontal and parietal sites and a reduction in repetitive-ritualistic behavior as reported by their caregivers. This result was quite promising, though the study should be considered extremely preliminary given its small sample size and lack of sham control condition. Following this initial study, the same group conducted several follow-up studies with slightly larger samples. In the first of these follow-up studies the group replicated their previous finding of normalized ERPs and a reduction in repetitive-ritualistic behaviors following the same protocol (Sokhadze et al. 2010) in 13 individuals with ASD. In the second follow-up study this same group applied bilateral low-frequency TMS (1 Hz) whereby TMS was applied once a week for 12 weeks with the first six treatments to the left DLPFC and the next six to the right DLPFC in 16 patients with ASD. EEG and behavioral evaluations pre- and post-rTMS revealed normalization of induced gamma activity and a reduction in both repetitive behaviors and irritability (Baruth et al. 2010). Using this same protocol, this group explored error monitoring pre- and post rTMS and found improvements in both ERP indices and behavioral

Table 2 Summary of Published studies using rTMS as a therapeutic tool

Study	Number of ASD subjects	Distribution of autism vs. AS (diagnostic criteria)	Age of participants (years)	TMS parameters (number of sessions, frequency, location)	Open label or sham controlled?	Effects	Adverse-events/side effects
Sokhadze et al. (2009)	8	8 Autism (DSM-IV-TR, ADI-R)	12–27	150 pulses (fifteen 10 s trains with a 20–30 s interval between the trains) at 0.5 Hz and 90 % RMT over left DLPFC twice per week for 3 weeks.	Open Label	Compared to the "waitlist control group" the stimulation group showed a normalization in event-related potentials (ERPs) and induced gamma frequency electroencephalography (EEG) activity and a reduction in repetitive-ritualistic behavior as reported by their caregivers.	Not Indicated
Sokhadze et al. (2010)	13	Not Indicated (DSM-IV-TR, ADI-R)	9–27	150 pulses (fifteen 10 s trains with a 20–30 s interval between the trains) at 0.5 Hz and 90 % RMT over left DLPFC twice per week for 3 weeks.	Open Label	Compared to the participant's pretest scores, the posttest scores showed the stimulation group showed a normalization in event-related potentials (ERPs) a reduction in repetitive-ritualistic behavior as reported by their caregivers. No differences were seen in the "waitlist" group.	None
Baruth et al. (2010)	16	Not Indicated (DSM-IV-TR, ADI-R)	9–26	150 pulses (fifteen 10 s trains with a 20–30 s interval between the trains) at 1 Hz and 90 % RMT over left DLPFC once per week for 6 weeks then the same procedure over the right DLPFC once per week for 6 weeks.	Open Label	Compared to the participant's pretest scores, the posttest scores showed improvement in discriminatory evoked gamma responses and improvements in irritability and repetitive behavior as reported by their caregivers. No differences were seen in the "waitlist" group.	Five participants reported an itching sensation around the nose during stimulation and one participant reported a transient headache in the hours following stimulation.
Enticott et al. (2011)	1	1 AS (Not Indicated)	20	1,500 (thirty 10-s trains with a 20 s interval between the trains) at 5 Hz and 54 % of stimulator output over medial prefrontal cortex each consecutive weekday for an 11-day period for a total of 9 sessions.	Double Blind Sham Controlled	Compared to before stimulation, both the participant and her family members noted improvements in social relating and interpersonal understanding.	Not Indicated

Table 2 continued

Study	Number of ASD subjects	Distribution of autism vs. AS (diagnostic criteria)	Age of participants (years)	TMS parameters (number of sessions, frequency, location)	Open label or sham controlled?	Effects	Adverse-events/side effects
Fecteau et al. (2011)	10	10 AS (DSM-IV, ADOS, ADI-R)	M = 36.6 (SD = 16.0)	1,800 pulses at 1 Hz and 70 % stimulator output over left and right pars triangularis and pars opercularis and sham (a single session at each location separated by at least 5 days).	Double Blind Sham Controlled	Compared to the sham condition, stimulation of left pars triangularis improved naming skills while stimulation of the adjacent left pars opercularis impaired naming skills.	There were two reports of a stiff neck and one report of subtle disorientation following sham stimulation. There were two reports of a stiff neck, six reports of sleepiness, two reports of being more emotional, one report of dizziness, three reports of trouble concentrating, one report of discomfort at the stimulation site and one report of a headache following active stimulation.
Sokhadze et al. (2012)	20	Not Indicated (DSM-IV-TR, ADI-R)	9–21	150 pulses (fifteen 10 s trains with a 20–30 s interval between the trains) at 1 Hz and 90 % RMT over left DLPFC once per week for 6 weeks then the same procedure over the right DLPFC once per week for 6 weeks.	Open Label	Compared to participant's pretest measurements, the posttest measurements showed improvements in both ERP indices and behavioral measures of error monitoring. No difference was seen in the "waitlist" group.	Not Indicated
Casanova et al. (2012)	25	Not Indicated (DSM-IV-TR, ADI-R)	9–19	150 pulses (fifteen 10 s trains with a 20–30 s interval between the trains) at 1 Hz and 90 % RMT over left DLPFC once per week for 6 weeks then the same procedure over the right DLPFC once per week for 6 weeks.	Open Label	Compared to participant's pretest measurements, posttest measurements showed improvements in ERP indices of visual processing, accuracy on a selective attention task, and behavioral measures of repetitive behavior and irritability. No differences were seen in the "waitlist" group.	None
Enticott et al. (2012b)	11	6 HFA, 5 AS (DSM-IV, ADI-R)	14–26	900 pulses at 1 Hz and 100 % RMT over left M1, SMA and sham stimulation over M1. A single session at each location separated by 1 week	Sham Controlled	Compared to the sham condition, stimulation of left M1 resulted in an improvement to the late component of movement-related cortical potentials, while stimulation of SMA resulted in improvement of the early component.	Not Indicated

M1 primary motor cortex, *DLPFC* dorsal lateral prefrontal cortex, *SMA* supplementary motor cortex, *RMT* resting motor threshold, *HFA* high functioning autism, *AS* Asperger's syndrome

measures of error monitoring following 1 Hz stimulation once a week first to left then to right DLPFC in 20 individuals with ASD (Sokhadze et al. 2012). Lastly, using a similar design the same group also recently published a paper describing improvements in ERP indices of visual processing, accuracy on a selective attention task, and behavioral measures of repetitive behavior and irritability of 25 individuals with ASD following the 12-week protocol described above (Casanova et al. 2012). Again, these studies provide promising preliminary data for the use of low-frequency rTMS to DLPFC for the alleviation of aberrant behavior and physiological indices in ASD, but are limited by small sample size (additionally, as all of these studies came out of the same lab, it is unclear whether the same individuals took part in multiple studies) and unblinded designs. It is also unclear in the paradigms where both left and right hemisphere were stimulated whether the effect was driven by one or the other hemisphere or whether the effect was a result of the combination of both. Finally, the behavioral improvements appear to be limited to repetitive behaviors, irritability, and specific measures of attention.

The Pascual-Leone lab has also published reports showing improved performance on a behavioral task in patients with ASD following a TMS protocol. Fecteau et al. (2011) conducted a study where they applied a single session of low-frequency (1 Hz) rTMS to left and right pars triangularis and pars opercularis (the two regions that comprise Broca's area) in 10 individuals with ASD and 10 matched neurotypical control participants in a double-blind, pseudorandomized, sham-controlled study. Compared to the sham condition all 10 individuals with ASD showed reduced latency to name objects on the Boston Naming Test following stimulation to the left pars triangularis (BA 45) while 9/10 showed an increased latency following stimulation to the adjacent left pars opercularis (BA44). The authors suggest that in individuals with ASD left BA45 exerts an abnormally excessive amount of inhibition on left BA44, thus inhibiting left BA45 resulted in a suppression of the excessive inhibitory control and thus a behavioral improvement. Though this interpretation has not been empirically tested. Findings from this study though short-lived, given the single session design, suggest that rTMS to BA45 may lead to improvements in language processing in ASD and warrant further studies aimed at long-term improvements in this domain (Fecteau et al. 2011). This study also demonstrated the importance of strict anatomical targeting as the opposite result was found when the target region was in the adjacent BA44 region.

Another group based in Melbourne Australia is also exploring the potential of rTMS to improve specific symptoms of ASD. In a recent paper they describe a study in which a single session of 1 Hz rTMS was applied to one of two motor cortical regions (Left M1 and Supplementary Motor Area (SMA)) in 11 individuals with ASD. Though not often considered a core impairment in ASD, motor dysfunction is often noted as an associated feature. Following stimulation of M1, there was a significant improvement in a late movement-related cortical potential (MRCP) thought to be associated with the execution of movement while stimulation of SMA resulted in an improvement of the early MRCP suggesting enhanced motor preparation. Though post-stimulation improvements were seen, their MRCPs still remained outside of what would be considered neurotypical levels, though this study did not include a control group. Despite improvements in the electrophysiological response, there was not a significant improvement in behavioral measures of motor functioning (Enticott et al. 2012b).

This same group is currently conducting a sham-controlled, double blind clinical trial of a specific type of high frequency rTMS (deep rTMS) to the medial prefrontal cortex (mPFC) a region thought to play a key role in theory of mind abilities (understanding the mental state of others) (Amodio and Frith 2006; Frith and Frith 1999; Mitchell et al. 2006; Saxe and Powell 2006). Thus, the goal of this study is to develop a therapeutic intervention aimed at improving the individual's capacity for understanding other's mental states. Though this study is still ongoing, the group has reported that several participants have responded to the treatment resulting in a reduction of self-reported clinical symptoms (Enticott, personal communication). An individual who had a very pronounced response (Ms. D) was featured in a case report (Enticott et al. 2011). This patient showed improvements on the Interpersonal Reactivity Index (IRI), the Autism Spectrum Quotient (AQ) and the Ritvo Autism-Asperger Diagnostic Scale. She also reported that she found eye contact "less uncomfortable" and found social situations "more natural" even joining a social club and making new friends. She noted that she "did not have to think so much of what to say" and was more aware of instances when she might be making someone uncomfortable. She also reported an increased capacity for empathy and perspective taking, even for incidents that occurred many years before. She also experienced greater consideration for and affection toward family members following the stimulation protocol. These changes were also noted by her family. Her mother described her as more considerate of others following the stimulation. These improvements seemed to remain at the 1 and 6 months follow-up (Enticott et al. 2011). Still other groups including one in Israel (NCT 01388179) and one in France (NCT 01648868) also have ongoing clinical trials applying rTMS for the treatment of specific ASD symptoms, the results of which have yet to be published.

Conclusion

In conclusion, though results of published studies are promising suggesting that specific rTMS protocols targeting specific regions of cortex may lead to improvement in specific behavioral deficits in some individuals with ASD, both the investigative and therapeutic results have been mixed. Additionally, the large-scale, controlled trials necessary to establish the safety and efficacy these brain stimulation protocols have yet to be conducted. As discussed earlier, rTMS and other electrical stimulation devices have the capacity to modulate the functioning of the brain in either a facilitatory or suppressive manner and when applied over several sessions can have an additive effect that can last several months. Caution is warranted when applying such potentially powerful modulatory effects on the brain, especially the brain of a developing child as results have ranged from improvement to significant exacerbation of symptoms. As technology advances and we are able to have a direct effect on brain functioning, we must critically evaluate the potential for benefit, while being respectful of the incredibly complex workings of the brain and how pathophysiology interacts with development to lead to specific behavioral symptoms. Also note that most of the studies conducted so far have been conducted on older children and adults.

If theories are correct that cortical mechanisms of excitability, connectivity, and plasticity are abnormal in ASD, then rTMS has the capacity to modulate these mechanisms. However, it is unclear what proportion of individuals experience observable behavioral improvements following modulation of these physiologically aberrant indices. One also needs to consider the heterogeneity of the population. Though these mechanisms might be altered in many individuals with ASD, depending on the underlying pathophysiology and genetic background, the direction and degree of this alteration may differ in any given individual. It is also unclear in any given individual what regions of the cortex are most affected and which protocols would be most effective to target. It appears that some rTMS protocols have had a profound impact on their behavioral impairments, while many have reported no significant change. What is clear from the literature is the phenotypic heterogeneity of this population. Thus, it should come as no surprise that there is heterogeneity in the efficacy of rTMS. Perhaps a "one size fits all" approach may not be ideal for this application, but rather an individualized approach based on baseline measures of cortical plasticity and excitability of a given individual and used in combination with other behavioral or pharmacological interventions.

Approximately 100 patients with ASD have now undergone rTMS protocols with therapeutic intent (across 8 studies using all different parameters and locations of stimulation). It is unclear what proportion of them have experienced an improvement of symptoms and what proportion has seen no improvement or worsening of symptoms following rTMS. It is also unclear what protocol is best used to target the specific symptoms of ASD. rTMS protocols vary in stimulation location, frequency, as well as number and timing of sessions. These parameters can be the difference between facilitating or suppressing cortical functioning or having no effect at all. In the hands of trained technicians, rTMS has great potential as both a diagnostic and therapeutic tool for ASD. However, the average sample size in the studies thus far is only 15 and five of the eight studies published thus far are open label. We must restrain our enthusiasm for new techniques until they have been properly vetted through controlled clinical trials and been shown to be both safe and efficacious. Thus, larger, randomized, sham-controlled studies are necessary to establish their true potential.

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