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Use of Transcranial Magnetic Stimulation in Autism Spectrum Disorders

The Centers for Disease Control and Prevention currently estimates 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) (<http://www.cdc.gov/mmwr/preview/mmwrhtml/ss6103a1.htm?scid=ss6103a1w>). This is more children than are affected by diabetes, AIDS, cancer, cerebral palsy, cystic fibrosis, muscular dystrophy and Down syndrome combined. ASD is diagnosed clinically, based on the presence of key behavioral symptoms, but the underlying brain mechanisms causing these symptoms are still unknown and there currently exists no cure. Interventions that may result in clinical benefit for affected children and adults are urgently needed. Effective treatments likely require early, reliable diagnosis and improved understanding of the pathophysiology underlying the ASD symptoms. Unfortunately, the translation of novel, evidence-based diagnostic measures and therapeutic interventions from laboratory to clinical practice is complex, and frequently unacceptably slow for many patients, parents and practitioners who desperately seek help. In the face of the increasing prevalence of ASD and its associated disabling symptoms, this leads to growing sense of urgency and a willingness to try untested diagnostic and therapeutic interventions before systematic clinical and translational research efforts have been completed.

Even a cursory internet search reveals that noninvasive brain stimulation methods have become in recent years an example of such practices, which raises concerns about safety and long term consequences. For example, the “Brain Treatment Center” (<http://www.braintreatmentcenter.com/autism>) offers repetitive transcranial magnetic stimulation (rTMS) as a treatment for ASD, and shares the testimonial of parents of 8-year-old Ryan, who reportedly derived “significant improvement.” The “Center For Medical and Brain Sciences” (<http://www.harrydschneidermd.com/html/autism.html>) offers a different type of non-invasive brain stimulation, transcranial direct current stimulation (tDCS), to treat language impairments in ASD, though no data is provided to support the claims. Rene Okoye, a board certified pediatric occupational therapist and clinical director of Dove Rehabilitation Services in Long Island, New York (<http://www.doverehab.com>) offers yet another type of noninvasive electrical stimulation (cranio-electrical stimulation, CES) for the treatment of hyperarousal, attention, social skills, gaze aversion, language skills, and fine motor skills in children with ASD, citing unpublished, non-peer-reviewed reports by Chip Fisher (President of Fisher Wallace Laboratories, maker of a CES device).

In addition, patients have also published their own accounts on the web describing their personal experiences with non-invasive brain stimulation. For example, on his blog (jerobison.blogspot.com), John Elder Robison describes his experiences following rTMS (at 1 Hz stimulation frequency targeting the right inferior frontal gyrus). He writes “I noticed something very strange – I am looking people in the eyes. And I sense a connection, one that is totally new. I talk louder, and I seem more expressive. People have noticed. As of Tuesday noon, for the first time in my life, I looked people in the eyes and did not instinctively flinch away. But more than that, there is a new sensitivity to what people are feeling that goes far beyond the “flash card face recognition” ability I had before. I am sensing more, in nonverbal ways.” Others have reported similar experiences following this same protocol. Another patient with Asperger’s Syndrome was overcome with emotion following her stimulation noting, “I could speak naturally with emotion. I really got a view of what I have been missing. No wonder most people enjoy social conversation, when it has so much depth to it. No wonder I don't like it, since I miss a lot of what's going on.”

In the absence of established treatments, it is tempting to accept as evidence such moving anecdotal personal reports and claims. However, premature adoption of new methods and its use without critical assessment is dangerous. Here we critically review the current state of scientific knowledge on the uses of TMS in patients with ASD. Existing evidence supports the call for carefully designed, controlled studies, but we caution from premature widespread clinical adoption. In the first part of this review, we give a brief introduction to TMS, its safety, capabilities 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 spectrum. Lastly, we summarize the current evidence for the safety, tolerability and efficacy of rTMS as a therapeutic intervention in ASD.

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. We must also 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.

TMS Basics

TMS machines are essentially extremely large capacitors that are capable of sending a pulse of electrical current through a cable to a hand-held coil made up of copper wire. 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, Jalinous, & Freeston, 1985; Wagner, Valero-Cabre, & Pascual-Leone, 2007). How much brain tissue is stimulated is dependent on the shape of the coil. The first TMS coils were large circular loops with limited focality of stimulation. 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 cm² region lying directly under the intersection of the figure-of-eight. It should be noted that the direct behavioural effects of TMS are limited to functions that are mediated by the relatively focal cortical regions or brain areas where activity can be modulated by the regions that are stimulated as the electrical current induced by the fluctuating magnetic field on the scalp attenuates very rapidly as a function of distance from coil. Other parameters that are also critical to the degree and direction of the stimulation effects include the intensity of the magnetic field induced in the coil and the orientation of the coil in relation to the underlying structure of the cortex.

When TMS is applied in single pulses, the induced electrical current can be of sufficient magnitude to depolarize a small population of neurons in a targeted brain region. TMS can also be applied in pairs of pulses (paired pulse stimulation), where two pulses are presented in rapid succession. In the conventional paired pulse paradigm, two consecutive magnetic stimuli, a conditioning stimulus (CS) and a test stimulus (TS), are delivered through a TMS-coil over the motor cortex (Claus, Weis, Jahnke, Plewe, & Brunholzl, 1992; Kujirai, et al., 1993; Valls-Sole, Pascual-Leone, Wassermann, & Hallett, 1992; Ziemann, 1999). An inter-pulse interval of 1–6 ms is thought to evaluate short interval intracortical inhibition (SICI). It is hypothesized that SICI is mediated by GABAergic intracortical inhibitory neurons and specifically by the GABA_A receptor (Kujirai, et al., 1993). An inter-pulse interval of 10-15 ms is thought to evaluate intracortical facilitation (ICF). It is hypothesized that the facilitation observed during ICF is a consequence of excitatory (NMDA glutamate receptor)

effects (Liepert, Schwenkreis, Tegenthoff, & Malin, 1997). Two suprathreshold pulses delivered at an inter-pulse interval of 50–200 ms is thought to evaluate long interval intracortical inhibition (LICI) and thought to reflect long-lasting cortical inhibition mediated by the GABA_B receptor (Valls-Sole, et al., 1992).

Trains of repeated TMS (rTMS) pulses can be applied at various stimulation frequencies and patterns to modulate (suppress or facilitate) local cortical excitability beyond the duration of the stimulation itself. Depending on the parameters of stimulation the excitability can be either facilitated or suppressed (Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 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, Fountain, & Daskalakis, 2006; Hoogendam, Ramakers, & Di Lazzaro). Due to this capacity to induce long-term changes in brain activity, rTMS is considered in the treatment of a number of neurological and psychiatric conditions such as major depression (Schutter, 2009) where it has been FDA approved, Parkinson's Disease (Kimura, et al.), Alzheimer's Disease (Freitas, Mondragon-Llorca, & Pascual-Leone; Nardone, et al.), and epilepsy (Sun, et al.). 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, most of the evidence comes from small scale studies and need further support from larger-scale, double blind clinical trials.

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, Hallett, Rossini, & Pascual-Leone, 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 or syncope, brain diseases or medications associated with increase seizure risk, the presence of implanted biomedical devices and pregnancy. With the exception of the implanted devices, all the other conditions should be considered only relative contraindication and the risk–benefit of the procedure should be carefully considered before the patients undergo the TMS study.

Seizures are the most serious possible TMS-related adverse event. Less than 20 cases of TMS induced seizures have been reported so far out of tens of thousands examined subjects. The vast majority of seizures were induced during rTMS. Overall the risk of seizure is considered to be less than 0.01% (Rossi, et al., 2009). 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, 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 200) have participated in a TMS protocol, 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 disorder of cortical excitability and plasticity

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. Many have suggested that abnormalities in specific functionally defined systems, such as the mirror neuron system, underlie ASD (Oberman & Ramachandran, 2007; Williams, et al., 2006). Others have focused on abnormalities in brain growth (Courchesne, et al., 2001), connectivity (Geschwind & Levitt, 2007) and synaptic plasticity (Dolen & Bear, 2009; Markram, Rinaldi, & Markram, 2007; Oberman & Pascual-Leone, 2008). All of these theories have been supported by empirical data indicating 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. Recent studies across multiple levels of analysis have implicated synaptic maturation and plasticity mechanisms in the pathogenesis of ASD. 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 & Merzenich, 2003). Consistent with the role of altered synapse 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. 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, targeting frontal and prefrontal cortex may represent potential targets for TMS studies and rTMS clinical applications.

TMS as a diagnostic tool

TMS can theoretically be applied to any cortical region and can be applied as single pulses, paired pulses, or repetitive protocols. 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, Ives, Kampmann, Pastor, & Pascual-Leone, 2005). These paradigms, however, have limited therapeutic potential as the effects of a single pulse are thought to only last a few seconds beyond the pulse itself.

Other protocols have been developed that also can be applied to study cortical function. These include paired-pulse TMS (ppTMS), paired associative stimulation (PAS), and types of rTMS. ppTMS can be used to evaluate GABA-mediated intracortical inhibition and glutamate-mediated intracortical facilitation by introducing two consecutive magnetic pulses at rapid succession (Claus, et al., 1992; Kujirai, et al., 1993; Liepert, et al., 1997; Valls-Sole, et al., 1992; Ziemann, 1999). 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 & Fatemi; Hussman, 2001; Pizzarelli & Cherubini) and E/I ratios (Rubenstein & Merzenich, 2003) in ASD.

Using these protocols, several groups have begun to use TMS as an experimental tool to understand ASD pathophysiology (Summarized in Table 1). [INSERT TABLE 1 HERE] 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, Kennedy, Rinehart, Tonge, Bradshaw, & Fitzgerald, 2012; Oberman, et al., 2012; Theoret, et al., 2005), single pulse (Enticott, Kennedy,

Rinehart, Tonge, Bradshaw, Taffe, et al., 2012; Oberman, et al., 2012) and paired-pulse (Enticott, Kennedy, Rinehart, Tonge, Bradshaw, & Fitzgerald, 2012; Jung, et al., in press; 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, Kennedy, Rinehart, Tonge, Bradshaw, & Fitzgerald, 2012; Oberman, et al., 2010) and long intracortical inhibition (LICI) paradigm (Oberman, et al., 2010) indicating that some individuals may have an insufficient amount of GABAergic 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 & Pascual-Leone, 2008). TMS protocols have been developed to study both Hebbian and non-Hebbian plasticity. One such protocol, PAS is modeled after animal electrical stimulation paradigms whereby long-term potentiation (LTP) and long-term depression (LTD) is induced through repeated pairs of peripheral nerve and cortical stimulation (Stefan, Kunesch, Cohen, Benecke, & Classen, 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 and LTD, and the effects and their time-course are consistent with the notion that TBS indexes mechanisms of cortical non-Hebbian synaptic plasticity (Cardenas-Morales, Nowak, Kammer, Wolf, & Schonfeldt-Lecuona; Huang, Chen, Rothwell, & Wen, 2007; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005).

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., in press). Interestingly, a study recently published using the TBS plasticity paradigm found opposite results. Specifically, in a study conducted by Oberman and colleagues (Oberman, et

al., 2012; Oberman, et al., 2010) 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 rather than a reduced capacity as indicated by Jung and colleagues (Jung, et al., in press). Furthermore, the authors (Oberman, et al., 2012) found that this enhanced modulation following TBS was extremely reliable across cohorts leading the authors to conclude both that a dysfunction in plasticity may represent the enigmatic mechanism underlying ASD (Oberman & Pascual-Leone, 2008) and may provide a potential diagnostic biomarker for this disorder (Oberman, et al., 2012). Finally, regression analyses indicated that across the age-span from 17-65 the degree of modulation in the ASD group remained significantly greater than that observed in the control group.

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 cortico-spinal excitability at baseline and during the observation of static visual stimuli (Enticott, Kennedy, Rinehart, Tonge, Bradshaw, Taffe, et al., 2012; Theoret, et al., 2005), the observation of hand actions in some contexts does not induce the expected corticospinal facilitation that is seen in neurotypical individuals (Enticott, Kennedy, Rinehart, Tonge, Bradshaw, Taffe, et al., 2012; Theoret, et al., 2005). These findings have been used as support for the theories suggesting a 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 brain regions. These protocols include low-frequency (typically 1 Hz), high frequency (typically 10 or 20 Hz applied intermittently), and TBS paradigms. 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, & Pascual-Leone, 2001; Mottaghy, Doring, Muller-Gartner, Topper, & Krause, 2002), and affective processing (see (Lee, Blumberger, Fitzgerald, Daskalakis, & Levinson) for a review). Low frequency protocols and a specific type of TBS (continuous, cTBS) generally induce lasting suppression of the excitability of underlying cortex, while high-frequency and a different type of TBS (intermittent, iTBS) generally induce lasting facilitation of the underlying cortex (Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000). 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 as well as 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 placebo (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, Hoy, Daskalakis, & Kulkarni, 2009; Isenberg, et al., 2005; Stern, Tormos, Press, Pearlman, & Pascual-Leone, 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). [INSERT TABLE 2 HERE]. The first

of these studies, conducted by Sokhadze and colleagues (E. M. Sokhadze, et al., 2009) applied low-frequency (0.5 Hz, 150 pulses) stimulation to left DLPFC two times per week for three weeks and in a small sample of eight individuals with ASD they 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 placebo or 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 (E. Sokhadze, et al., 2010) in 13 individuals with ASD. In the second follow-up study this same group applied bilateral low-frequency TMS (1Hz) 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 measures of error monitoring following 1 Hz stimulation once a week first to left then to right DLPFC in 20 individuals with ASD (E. M. 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. 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 (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. As the focality of TMS is limited to a relatively small area of cortex, any single location of stimulation is unlikely to produce improvements in broad areas of functioning.

The Pascual-Leone lab has also published reports showing improved performance on a behavioral task in patients with ASD following a TMS protocol. Fecteau and colleagues (Fecteau, Agosta, Oberman, & Pascual-Leone, 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). No significant effects were seen in the right hemisphere in the ASD group and stimulation to any of the studied regions had no significant effects in the neurotypical control group. 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). As the targeted brain region corresponded to regions of Broca's area, the predicted behavioral impact was in the domain of language processing.

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, Rinehart, Tonge, Bradshaw, & Fitzgerald, 2012).

This same group is currently conducting a placebo-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 & Frith, 2006; Frith & Frith, 1999; Mitchell, Cloutier, Banaji, & Macrae, 2006; Saxe & 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. An individual who had a very pronounced response (Ms. D) was featured in a case report (Enticott, Kennedy, Zangen, & Fitzgerald, 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 one month and six month 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 and anecdotal reports are extremely enthusiastic, the types of 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. 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 whether modulation of physiologically aberrant indices results in observable behavioral improvements. It is also unclear 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.

Approximately 100 patients with ASD have now undergone rTMS protocols. 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, larger, randomized, placebo-controlled studies are necessary to establish their true potential.

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

Study	Number of ASD Subjects	Age of Participants	TMS Parameters (Number of Sessions, Frequency, Location)	Effects	Adverse-Events/Side Effects
Theoret et al., 2005	10	23-58 years old	One session of Single Pulses over M1	No group difference in RMT or response to Paired-pulse paradigms. Impaired corticospinal facilitation in response to finger movements viewed from the egocentric point of view.	Not Indicated
Oberman et al., 2010	5	26-54 years old	Two sessions of Single Pulses, Paired Pulses, and Theta Burst Stimulation over M1	Heterogeneous response to paired-pulse paradigms. Greater and longer-lasting response to Theta Burst paradigms.	None
Oberman et al., 2012	35	18-64 years old	Two sessions of Single Pulses and Theta Burst Stimulation over M1	No group difference in RMT or Active Motor Threshold or response to single pulse TMS at baseline. Greater and longer-lasting response to Theta Burst paradigms.	None
Enticott et al., 2012a	36	M = 26 years old (SD = 10.48 years)	One session of Single Pulses and Paired Pulses over M1	No group difference in RMT, Heterogeneous response to Paired-pulse paradigms.	Not Indicated
Enticott et al., 2012b	34	M = 26.32 years old (SD = 10.70 years)	One session of Single Pulses over M1	No group difference in degree of corticospinal excitability in response to observation of static hand stimuli. Impaired corticospinal facilitation in response to transitive hand actions.	Not Indicated
Jung et al., in press	9	M = 17.8 years old (SD = 3.5 years)	One session of Paired-pulses and Paired Associative Stimulation	No group difference in response to paired-pulse paradigms. Impaired facilitation in response to Paired Associative Stimulation Paradigm.	None

M1 = Primary Motor Cortex, RMT = Resting Motor Cortex

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

Study	Number of ASD Subjects	Age of Participants	TMS Parameters (Number of Sessions, Frequency, Location)	Open Label or Sham Controlled?	Effects	Adverse-Events/Side Effects
Sokhadze et al., 2009	8	12-27 years old	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	9-27 years old	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	9-26 years old	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	20 years old	1500 (thirty 10-second trains with a 20 second interval between the trains) at 5 Hz and 54% of stimulator output over medial prefrontal cortex (deep rTMS) 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

Fecteau et al., 2011	10	M = 36.6 years old (SD = 16.0 years)	1800 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.	Two participants reported a stiff neck and one reported subtle disorientation following sham stimulation. One subject reported a stiff neck and sleepiness following left pars opercularis stimulation. Two participants reported sleepiness, one reported a stiff neck, one reported being more emotional and one reported dizziness following left pars triangularis stimulation. Two participants reported trouble concentrating, two participants reported sleepiness, and one participant reported discomfort at the stimulation site following right pars opercularis stimulation. One participant reported trouble concentrating, one reported sleepiness, one reported being more emotional, and one reported a headache following right pars triangularis stimulation.
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Sokhadze et al., 2012	20	9-21 years old	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	9-19 years old	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., 2012	11	14-26 years old	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 one 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

RMT = Resting Motor Threshold, DLPFC = Dorsal Lateral Prefrontal Cortex, M1 = Primary Motor Cortex, SMA = Supplementary Motor Cortex