



Published in final edited form as:

J Autism Dev Disord. 2015 February ; 45(2): 524–536. doi:10.1007/s10803-013-1960-2.

Use of Transcranial Magnetic Stimulation in Autism Spectrum Disorders

Lindsay M. Oberman, PhD^{1,2}, Alexander Rotenberg, MD, PhD^{1,2}, and Alvaro Pascual-Leone, MD, PhD¹

¹Berenson-Allen Center for Noninvasive Brain Stimulation, and Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical Center and Harvard Medical School

²Division of Epilepsy and Clinical Neurophysiology, Department of Neurology Children's Hospital, Boston

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, Gholizadeh, & Pacey, 2012), but there is currently no pharmacotherapy shown to effectively treat the core symptoms of ASD (see Oberman, 2012 for a review).

Corresponding Author: Alvaro Pascual-Leone, MD, PhD, Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, KS 158, Boston, MA 02215, Phone: 617-667-0203, Fax: 617-975-5322, apleone@bidmc.harvard.edu.

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 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, Jalinous, & Freeston, 1985; Wagner, Valero-Cabre, & Pascual-Leone, 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, Davey., Rothwell, Wasserman, & Puri, 2002). The first TMS coils were large circular loops with limited focality of stimulation (Barker, Jalinous, & Freeston, 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 cm² region lying directly under the intersection of the figure-of-eight (Brasil-Neto, McShane, Fuhr, Hallett, & Cohen, 1992). We note that even though the electrical current induced by TMS on the scalp attenuates very rapidly (Rudiak & 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 & Pascual-Leone, 2003). TMS can also be applied in pairs of pulses (paired pulse stimulation, ppTMS) (Claus, Weis, Jahnke, Plewe, & Brunholzl, 1992; Kujirai, et al., 1993; Valls-Sole, Pascual-Leone, Wassermann, & Hallett, 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 & Fatemi; Hussman, 2001; Pizzarelli & Cherubini, 2011) and E/I ratios (Rubenstein & 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 1Hz, 5Hz, 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, 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, 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, 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-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, Nowak, Kammer, Wolf, & Schonfeldt-Lecuona, 2010; Huang, Chen, Rothwell, & Wen, 2007; Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005).

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 & 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, Mondragon-Llorca, & Pascual-Leone; Nardone, et al., 2011), 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, Pesiridou, & O'Reardon, 2009; Machado et al., 2008; Schulz, Gerloff, & Hummel, 2013; Wassermann & 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, 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, 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 less than 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 & 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 & Ramachandran, 2007; Williams, et al., 2006). Others have focused on abnormalities in brain growth (Courchesne, et al., 2001), connectivity (Geschwind & Levitt, 2007), excitation and inhibition (Rubenstein & Merzenich, 2003; Casanova, Buxhoeveden, Switala, & Roy, 2002) and synaptic plasticity (Dolen & Bear, 2009; Markram, Rinaldi, & Markram, 2007; Oberman & 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, Rotenberg, & Pascual-Leone, in press; Oberman et al., 2012; Rubenstein & 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, Tsumoto, Kinoshita, & Hatanaka, 1997; Huber, Sawtell, & Bear, 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, Moore, Bailey, & Monaco, 2000; Persico & Bourgeron, 2006). In addition, single gene disorders associated with autism implicate proteins which play important roles in synaptic plasticity (Dolen & 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, Gallagher, Warren, & Bear, 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 & Merzenich, 2003). Multiple post mortem studies note a reduction in GABAergic receptors (Fatemi, Folsom, Reutiman, & Thuras, 2009; Fatemi, et al., 2010; Fatemi, Reutiman, Folsom, & Thuras, 2009) as well as a 50% reduction in enzymes that synthesize GABA (*glutamic acid decarboxylase* (GAD) 65 and 67) (Fatemi, et al., 2002; Yip, Soghomonian, & Blatt, 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, Ives, Kampmann, Pastor, & Pascual-Leone, 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., 2013a; Enticott, et al., 2010; 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 & 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., 2013). 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. 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 & 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 cortico-spinal excitability at baseline and during the observation of static visual stimuli and two handed interactive stimuli (Enticott, et al., 2012a; Enticott et al., 2013b; 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, & Pascual-Leone, 2001; Mottaghy, Doring, Muller-Gartner, Topper, & Krause, 2002), and affective processing (see Lee, Blumberger, Fitzgerald, Daskalakis, & Levinson, 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, Keenan, Tormos, Topka, & Pascual-Leone, 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, 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).

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

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

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 and colleagues (Sokhadze, et al., 2009) applied low-frequency (0.5 Hz, 150 pulses) stimulation to left DLPFC two times per week for three 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 (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 (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 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). 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 & 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 (Enticott, personal communication). 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 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.

References

- Akaneya Y, Tsumoto T, Kinoshita S, Hatanaka H. Brain-derived neurotrophic factor enhances long-term potentiation in rat visual cortex. *Journal of Neuroscience*. 1997; 17(17):6707–6716. [PubMed: 9254683]
- Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. *Nature Reviews Neuroscience*. 2006; 7(4):268–277. [PubMed: 16552413]
- Baio J. Prevalence of autism spectrum disorders autism and developmental disabilities monitoring network, 14 sites, United States, 2008. *MMWR Surveillance Summary*. 2012; 61:1–19.
- Barker AT. The history and basic principles of magnetic nerve stimulation. *Electroencephalography and Clin Neurophysiology Supplement*. 1999; 51:3–21.
- Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet*. 1985; 1(8437):1106–1107. [PubMed: 2860322]
- Baruth JM, Casanova MF, El-Baz A, Horrell T, Mathai G, Sears L, Sokhadze E. Low-frequency repetitive transcranial magnetic Stimulation (rTMS) modulates evoked-gamma frequency oscillations in autism spectrum disorder (ASD). *Journal of Neurotherapy*. 2010; 14(3):179–194. [PubMed: 21116441]
- Baudouin SJ, Gaudias J, Gerharz S, Hatstatt L, Zhou K, Punnakkal P, Tanaka KF, Spooren W, Hen R, De Zeeuw CI, Vogt K, Scheiffele P. Shared synaptic pathophysiology in syndromic and nonsyndromic rodent models of autism. *Science*. 2012; 338(6103):128–132. [PubMed: 22983708]
- Blatt GJ, Fatemi SH. Alterations in GABAergic biomarkers in the autism brain: research findings and clinical implications. *Anatomical Record (Hoboken)*. 2011; 294(10):1646–1652.
- Brasil-Neto JP, McShane LM, Fuhr P, Hallett M, Cohen LG. Topographic mapping of the human motor cortex with magnetic stimulation: factors affecting accuracy and reproducibility. *Electroencephalography and Clinical Neurophysiology*. 1992; 85(1):9–16. [PubMed: 1371748]
- Cardenas-Morales L, Nowak DA, Kammer T, Wolf RC, Schonfeldt-Lecuona C. Mechanisms and applications of theta-burst rTMS on the human motor cortex. *Brain Topography*. 2010; 22(4):294–306. [PubMed: 19288184]
- Casanova MF, Baruth JM, El-Baz A, Tasman A, Sears L, Sokhadze E. Repetitive transcranial magnetic stimulation (rTMS) modulates event-related potential (ERP) indices of attention in autism. *Translational Neuroscience*. 2012; 3(2):170–180. [PubMed: 24683490]
- Casanova MF, Buxhoeveden DP, Switala AE, Roy E. Minicolumnar pathology in autism. *Neurology*. 2002; 58(3):428–432. [PubMed: 11839843]
- Casanova MF, van Kooten IA, Switala AE, van Engeland H, Heinsen H, Steinbusch HW, Hof PR, Trippe J, Stone J, Schmitz C. Minicolumnar abnormalities in autism. *Acta Neuropathologica*. 2006; 112(3):287–303. [PubMed: 16819561]
- Chez MG, Chang M, Krasne V, Coughlan C, Kominsky M, Schwartz A. Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005. *Epilepsy and Behavior*. 2006; 8:267–271. [PubMed: 16403678]
- Child and Adolescent Health Measurement Initiative. [Accessed June 9, 2013] Data Resource Center for Child and Adolescent Health. 2012. <http://www.childhealthdata.org/>
- Classen J, Wolters A, Stefan K, Wycislo M, Sandbrink F, Schmidt A, Kunesch E. Paired associative stimulation. *Suppl Clin Neurophysiol*. 2004; 57:563–569. [PubMed: 16106657]
- Claus D, Weis M, Jahnke U, Plewe A, Brunholz C. Corticospinal conduction studied with magnetic double stimulation in the intact human. *Journal of Neurological Sciences*. 1992; 111(2):180–188.

- Cook EH Jr. Genetics of autism. *Child & Adolescent Psychiatric Clinics of North America*. 2001; 10(2):333–350. [PubMed: 11351802]
- Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, Chisum HJ, Moses P, Pierce K, Lord C, Lincoln AJ, Pizzo S, Schreibman L, Haas RH, Akshoomoff NA, Courchesne RY. Unusual brain growth patterns in early life in patients with autistic disorder: an MRI study. *Neurology*. 2001; 57(2):245–254. [PubMed: 11468308]
- Dani VS, Chang Q, Maffei A, Turrigiano GG, Jaenisch R, Nelson SB. Reduced cortical activity due to a shift in the balance between excitation and inhibition in a mouse model of Rett syndrome. *Proceedings of the National Academy of Science U S A*. 2005; 102(35):12560–12565.
- Dolen G, Bear MF. Fragile x syndrome and autism: from disease model to therapeutic targets. *Journal of Neurodevelopmental Disorders*. 2009; 1(2):133–140. [PubMed: 21547712]
- Durand CM, Betancur C, Boeckers TM, Bockmann J, Chaste P, Fauchereau F, Nygren G, Rastam M, Gillberg IC, Anckarsater H, Sponheim E, Goubran-Botros H, Delorme R, Chabane N, Mouren-Simeoni MC, de Mas P, Bieth E, Roge B, Heron D, Burglen L, Gillberg C, Leboyer M, Bourgeron T. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. *Nature Genetics*. 2007; 39(1):25–27. [PubMed: 17173049]
- Enticott PG, Kennedy HA, Rinehart NJ, Bradshaw JL, Tonge BJ, Daskalakis ZJ, Fitzgerald PB. Interpersonal motor resonance in autism spectrum disorder: evidence against a global "mirror system" deficit. *Frontiers in Human Neuroscience*. 2013b; 7:218–225. [PubMed: 23734121]
- Enticott PG, Kennedy HA, Rinehart NJ, Tonge BJ, Bradshaw JL, Fitzgerald PB. GABAergic activity in autism spectrum disorders: An investigation of cortical inhibition via transcranial magnetic stimulation. *Neuropharmacology*. 2013a; 68:202–209. [PubMed: 22727823]
- Enticott PG, Kennedy HA, Rinehart NJ, Tonge BJ, Bradshaw JL, Taffe JR, Daskalakis ZJ, Fitzgerald PB. Mirror neuron activity associated with social impairments but not age in autism spectrum disorder. *Biological Psychiatry*. 2012a; 71(5):427–433. [PubMed: 21974786]
- Enticott PG, Kennedy HA, Zangen A, Fitzgerald PB. Deep repetitive transcranial magnetic stimulation associated with improved social functioning in a young woman with an autism spectrum disorder. *Journal of Electroconvulsive Therapy*. 2011; 27(1):41–43. [PubMed: 20966773]
- Enticott PG, Rinehart NJ, Tonge BJ, Bradshaw JL, Fitzgerald PB. Repetitive transcranial magnetic stimulation (rTMS) improves movement-related cortical potentials in autism spectrum disorders. *Brain Stimulation*. 2012b; 5(1):30–37. [PubMed: 22037133]
- Enticott PG, Rinehart NJ, Tonge BJ, Bradshaw JL, Fitzgerald PB. A preliminary transcranial magnetic stimulation study of cortical inhibition and excitability in high-functioning autism and Asperger disorder. *Developmental Medicine and Child Neurology*. 2010; 52:e179–e183. [PubMed: 20370810]
- Fatemi SH, Folsom TD, Reutiman TJ, Thuras PD. Expression of GABA(B) receptors is altered in brains of subjects with autism. *Cerebellum*. 2009; 8(1):64–69. [PubMed: 19002745]
- Fatemi SH, Halt AR, Sary JM, Kanodia R, Schulz SC, Realmuto GR. Glutamic acid decarboxylase 65 and 67 kDa proteins are reduced in autistic parietal and cerebellar cortices. *Biological Psychiatry*. 2002; 52(8):805–810. [PubMed: 12372652]
- Fatemi SH, Reutiman TJ, Folsom TD, Rooney RJ, Patel DH, Thuras PD. mRNA and protein levels for GABAAalpha4, alpha5, beta1 and GABABR1 receptors are altered in brains from subjects with autism. *Journal of Autism and Developmental Disorders*. 2010; 40(6):743–750. [PubMed: 20066485]
- Fatemi SH, Reutiman TJ, Folsom TD, Thuras PD. GABA(A) receptor downregulation in brains of subjects with autism. *Journal of Autism and Developmental Disorders*. 2009; 39(2):223–230. [PubMed: 18821008]
- Fecteau S, Agosta S, Oberman L, Pascual-Leone A. Brain stimulation over Broca's area differentially modulates naming skills in neurotypical adults and individuals with Asperger's syndrome. *European Journal Neuroscience*. 2011; 34(1):158–164.
- Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clinical Neurophysiology*. 2006; 117(12):2584–2596. [PubMed: 16890483]

- Fitzgerald PB, Hoy K, Daskalakis ZJ, Kulkarni J. A randomized trial of the anti-depressant effects of low- and high-frequency transcranial magnetic stimulation in treatment-resistant depression. *Depression and Anxiety*. 2009; 26(3):229–234. [PubMed: 19105212]
- Freitas C, Mondragon-Llorca H, Pascual-Leone A. Noninvasive brain stimulation in Alzheimer's disease: systematic review and perspectives for the future. *Experimental Gerontology*. 2011; 46(8):611–627. [PubMed: 21511025]
- Frith CD, Frith U. Interacting minds--a biological basis. *Science*. 1999; 286(5445):1692–1695. [PubMed: 10576727]
- Geschwind DH, Levitt P. Autism spectrum disorders: developmental disconnection syndromes. *Current Opinion in Neurobiology*. 2007; 17(1):103–111. [PubMed: 17275283]
- Gogolla N, Leblanc JJ, Quast KB, Sudhof TC, Fagiolini M, Hensch TK. Common circuit defect of excitatory-inhibitory balance in mouse models of autism. *Journal of Neurodevelopmental Disorders*. 2009; 1(2):172–181. [PubMed: 20664807]
- Grossheinrich N, Rau A, Pogarell O, Hennig-Fast K, Reinl M, Karch S, Dieler A, Leicht G, Mulert C, Sterr A, Padberg F. Theta burst stimulation of the prefrontal cortex: safety and impact on cognition, mood, and resting electroencephalogram. *Biological Psychiatry*. 2009; 65(9):778–784. [PubMed: 19070834]
- Hampson DR, Gholizadeh S, Pacey LK. Pathways to drug development for autism spectrum disorders. *Clinical Pharmacology and Therapeutics*. 2012; 91(2):189–200. [PubMed: 22205199]
- Hilgetag CC, Theoret H, Pascual-Leone A. Enhanced visual spatial attention ipsilateral to rTMS-induced 'virtual lesions' of human parietal cortex. *Nature Neuroscience*. 2001; 4(9):953–957. [PubMed: 11528429]
- Hoogendam JM, Ramakers GM, Di Lazzaro V. Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimulation*. 2010; 3(2):95–118. [PubMed: 20633438]
- Huang YZ, Chen RS, Rothwell JC, Wen HY. The after-effect of human theta burst stimulation is NMDA receptor dependent. *Clinical Neurophysiology*. 2007; 118(5):1028–1032. [PubMed: 17368094]
- Huang YZ, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. *Neuron*. 2005; 45(2):201–206. [PubMed: 15664172]
- Huber KM, Gallagher SM, Warren ST, Bear MF. Altered synaptic plasticity in a mouse model of fragile X mental retardation. *Proceedings of the National Academy of Sciences U S A*. 2002; 99(11):7746–7750.
- Huber KM, Sawtell NB, Bear MF. Brain-derived neurotrophic factor alters the synaptic modification threshold in visual cortex. *Neuropharmacology*. 1998; 37(4–5):571–579. [PubMed: 9704998]
- Hussman JP. Suppressed GABAergic inhibition as a common factor in suspected etiologies of autism. *Journal of Autism and Developmental Disorders*. 2001; 31(2):247–248. [PubMed: 11450824]
- Huttenlocher, PR. *Neural Plasticity*. Cambridge: Harvard University Press; 2002.
- Isenberg K, Downs D, Pierce K, Svarakic D, Garcia K, Jarvis M, North C, Kormos TC. Low frequency rTMS stimulation of the right frontal cortex is as effective as high frequency rTMS stimulation of the left frontal cortex for antidepressant-free, treatment-resistant depressed patients. *Annals of Clinical Psychiatry*. 2005; 17(3):153–159. [PubMed: 16433057]
- Jamain S, Quach H, Betancur C, Rastam M, Colineaux C, Gillberg IC, Soderstrom H, Giros B, Leboyer M, Gillberg C, Bourgeron T. Mutations of the X-linked genes encoding neuroligins NLGN3 and NLGN4 are associated with autism. *Nature Genetics*. 2003; 34(1):27–29. [PubMed: 12669065]
- Jiang B, Akaneya Y, Ohshima M, Ichisaka S, Hata Y, Tsumoto T. Brain-derived neurotrophic factor induces long-lasting potentiation of synaptic transmission in visual cortex in vivo in young rats, but not in the adult. *European Journal of Neuroscience*. 2001; 14(8):1219–1228. [PubMed: 11703451]
- Jung N, Janzarik W, Delvendahl I, Munchau A, Biscaldi M, Mainberger F, Bäumer T, Rauh R, Mall V. Impaired induction of long-term potentiation (LTP)-like plasticity in patients with high functioning autism and Asperger syndrome (HFA/AS). *Developmental Medicine and Child Neurology*. 2013; 55(1):83–89. [PubMed: 23157428]

- Kim DR, Pesiridou A, O'Reardon JP. Transcranial magnetic Stimulation in the treatment of psychiatric disorders. *Current Psychiatry Reports*. 2009; 11(6):447–452. [PubMed: 19909666]
- Kimura H, Kurimura M, Kurokawa K, Nagaoka U, Arawaka S, Wada M, Kawanami T, Kurita K, Kato T. A comprehensive study of repetitive transcranial magnetic stimulation in Parkinson's disease. *ISRN Neurology*. 2011:845453. [PubMed: 22389830]
- Kobayashi M, Pascual-Leone A. Transcranial magnetic stimulation in neurology. *Lancet Neurology*. 2003; 2(3):145–156. [PubMed: 12849236]
- Korte M, Carroll P, Wolf E, Brem G, Thoenen H, Bonhoeffer T. Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. *Proceedings of the National Academy of Science U S A*. 1995; 92(19):8856–8860.
- Kosslyn SM, Pascual-Leone A, Felician O, Camposano S, Keenan JP, Thompson WL, Ganis G, Sukel KE, Alpert NM. The role of area 17 in visual imagery: convergent evidence from PET and rTMS. *Science*. 1999; 284(5411):167–170. [PubMed: 10102821]
- Kujirai T, Caramia MD, Rothwell JC, Day BL, Thompson PD, Ferbert A, Wroe S, Asselman P, Marsden CD. Corticocortical inhibition in human motor cortex. *Journal of Physiology*. 1993; 471:501–519. [PubMed: 8120818]
- Lamb JA, Moore J, Bailey A, Monaco AP. Autism: recent molecular genetic advances. *Human Molecular Genetics*. 2000; 9(6):861–868. [PubMed: 10767308]
- Lee JC, Blumberger DM, Fitzgerald P, Daskalakis Z, Levinson A. The Role of Transcranial Magnetic Stimulation in Treatment-Resistant Depression: A Review. *Current Pharmacological Design*. 2012; 18(36):5846–5852.
- Machado S, Bittencourt J, Minc D, Portella CE, Velasques B, Cunha M, Budde H, Basile LF, Chadi G, Cagy M, Piedade R, Riberio P. Therapeutic applications of repetitive transcranial magnetic stimulation in clinical neurorehabilitation. *Functional Neurology*. 2008; 23(3):113–122. [PubMed: 19152730]
- Maeda F, Keenan JP, Tormos JM, Topka H, Pascual-Leone A. Modulation of corticospinal excitability by repetitive transcranial magnetic stimulation. *Clinical Neurophysiology*. 2000; 111(5):800–805. [PubMed: 10802449]
- Markram H, Rinaldi T, Markram K. The intense world syndrome--an alternative hypothesis for autism. *Frontiers in Neuroscience*. 2007; 1(1):77–96. [PubMed: 18982120]
- Minio-Paluello I, Baron-Cohen S, Avenanti A, Walsh V, Aglioti SM. Absence of embodied empathy during pain observation in Asperger syndrome. *Biological Psychiatry*. 2009; 65(1):55–62. [PubMed: 18814863]
- Mitchell JP, Cloutier J, Banaji MR, Macrae CN. Medial prefrontal dissociations during processing of trait diagnostic and nondiagnostic person information. *Social Cognitive and Affective Neuroscience*. 2006; 1(1):49–55. [PubMed: 18985100]
- Morrow EM, Yoo SY, Flavell SW, Kim TK, Lin Y, Hill RS, Mukaddes NM, Balkhy S, Gascon G, Hashmi A, Al-Saad S, Ware J, Joseph RM, Greenblatt R, Gleason D, Ertelt JA, Apse KA, Bodell A, Partlow JN, Barry B, Yao H, Markianos K, Ferland RJ, Greenberg ME, Walsh CA. Identifying autism loci and genes by tracing recent shared ancestry. *Science*. 2008; 321(5886):218–223. [PubMed: 18621663]
- Mostofsky SH, Powell SK, Simmonds DJ, Goldberg MC, Caffo B, Pekar JJ. Decreased connectivity and cerebellar activity in autism during motor task performance. *Brain*. 2009; 132(Pt 9):2413–2425. [PubMed: 19389870]
- Mottaghy FM, Doring T, Muller-Gartner HW, Topper R, Krause BJ. Bilateral parieto-frontal network for verbal working memory: an interference approach using repetitive transcranial magnetic stimulation (rTMS). *European Journal of Neuroscience*. 2002; 16(8):1627–1632. [PubMed: 12405977]
- Nardone R, Bergmann J, Christova M, Caleri F, Tezzon F, Ladurner G, Trinkka E, Golaszewski S. Effect of transcranial brain stimulation for the treatment of Alzheimer disease: a review. *International Journal of Alzheimers Disease*. 2012:1–5.
- Oberman LM. mGluR antagonists and GABA agonists as novel pharmacological agents for the treatment of autism spectrum disorders. *Expert Opinion on Investigational Drugs*. 2012; 21(12):1819–1825. [PubMed: 23013434]

- Oberman LM, Eldaief M, Fecteau S, Ifert-Miller F, Tormos JM, Pascual-Leone A. Abnormal modulation of corticospinal excitability in adults with Asperger's syndrome. *European Journal of Neuroscience*. 2012; 36(6):2782–2788. [PubMed: 22738084]
- Oberman LM, Ifert-Miller F, Najib U, Bashir S, Woollacott I, Gonzalez-Heydrich J, Picker J, Rotenberg A, Pascual-Leone A. Transcranial magnetic stimulation provides means to assess cortical plasticity and excitability in humans with fragile x syndrome and autism spectrum disorder. *Frontiers in Synaptic Neuroscience*. 2010; 2:26. [PubMed: 21423512]
- Oberman LM, Pascual-Leone A. Cortical plasticity: A proposed mechanism by which genomic factors lead to the behavioral and neurological phenotype of autism spectrum and psychotic spectrum disorders. *Behavioral and Brain Sciences*. 2008; 31:241–320. [PubMed: 18578904]
- Oberman LM, Ramachandran VS. The simulating social mind: the role of the mirror neuron system and simulation in the social and communicative deficits of autism spectrum disorders. *Psychological Bulletin*. 2007; 133(2):310–327. [PubMed: 17338602]
- Oberman, LM.; Rotenberg, A.; Pascual-Leone, A. Aberrant brain plasticity in autism spectrum disorders. In: Tracy, J.; Hampstead, B.; Sathian, K., editors. *Plasticity of Cognition in Neurologic Disorders*. New York: Oxford University Press; in press
- Pascual-Leone, A.; Davey, NJ.; Rothwell, J.; Wasserman, EM.; Puri, BK. *Handbook of Transcranial Magnetic Stimulation*. New York: Oxford University Press; 2002.
- Pascual-Leone A, Freitas C, Oberman L, Horvath JC, Halko M, Eldaief M, Bashir S, Vernet M, Shafi M, Westover B, Vahabzadeh-Hagh AM, Rotenberg A. Characterizing brain cortical plasticity and network dynamics across the age-span in health and disease with TMS-EEG and TMS-fMRI. *Brain Topography*. 2011; 24(3–4):302–315. [PubMed: 21842407]
- Pascual-Leone A, Valls-Sole J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. *Brain*. 1994; 117(Pt 4):847–858. [PubMed: 7922470]
- Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, Kandel ER. Recombinant BDNF rescues deficits in basal synaptic transmission and hippocampal LTP in BDNF knockout mice. *Neuron*. 1996; 16(6):1137–1145. [PubMed: 8663990]
- Perry EK, Lee ML, Martin-Ruiz CM, Court JA, Volsen SG, Merrit J, Folly E, Iversen PE, Bauman ML, Perry RH, Wenk GL. Cholinergic activity in autism: abnormalities in the cerebral cortex and basal forebrain. *American Journal of Psychiatry*. 2001; 158(7):1058–1066. [PubMed: 11431227]
- Persico AM, Bourgeron T. Searching for ways out of the autism maze: genetic, epigenetic and environmental clues. *Trends in Neuroscience*. 2006; 29(7):349–358.
- Pizzarelli R, Cherubini E. Alterations of GABAergic signaling in autism spectrum disorders. *Neural Plasticity*. 2011; 2011:297153. [PubMed: 21766041]
- Reichow B. Overview of meta-analyses on early intensive behavioral intervention for young children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*. 2012; 42(4): 512–520. [PubMed: 21404083]
- Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*. 2009; 120(12):2008–2039. [PubMed: 19833552]
- Rubenstein JL, Merzenich MM. Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain, and Behavior*. 2003; 2(5):255–267.
- Rudiak D, Marg E. Finding the depth of magnetic brain stimulation: a re-evaluation. *Electroencephalography and Clinical Neurophysiology*. 1994; 93(5):358–371. [PubMed: 7525244]
- Saxe R, Powell LJ. It's the thought that counts: specific brain regions for one component of theory of mind. *Psychological Science*. 2006; 17(8):692–699. [PubMed: 16913952]
- Schulz R, Gerloff C, Hummel FC. Non-invasive brain stimulation in neurological diseases. *Neuropharmacology*. 2009; 64:579–587. [PubMed: 22687520]
- Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychological Medicine*. 2009; 39(1):65–75. [PubMed: 18447962]
- Silvanto J, Pascual-Leone A. State-dependency of transcranial magnetic stimulation. *Brain Topography*. 2008; 21(1):1–10. [PubMed: 18791818]

- Sokhadze EM, Baruth JM, Sears L, Sokhadze GE, El-Baz AS, Casanova MF. Prefrontal neuromodulation using rTMS improves error monitoring and correction function in autism. *Applied Psychophysiology and Biofeedback*. 2012; 37(2):91–102. [PubMed: 22311204]
- Sokhadze E, Baruth J, Tasman A, Mansoor M, Ramaswamy R, Sears L, Mathai G, El-Baz A, Casanova MF. Low-frequency repetitive transcranial magnetic stimulation (rTMS) affects event-related potential measures of novelty processing in autism. *Applied Psychophysiology and Biofeedback*. 2010; 35(2):147–161. [PubMed: 19941058]
- Sokhadze EM, El-Baz A, Baruth J, Mathai G, Sears L, Casanova MF. Effects of low frequency repetitive transcranial magnetic stimulation (rTMS) on gamma frequency oscillations and event-related potentials during processing of illusory figures in autism. *Journal of Autism and Developmental Disorders*. 2009; 39(4):619–634. [PubMed: 19030976]
- Spence SJ, Schneider MT. The role of epilepsy and epileptiform EEGs in autism spectrum disorders. *Pediatric Research*. 2009; 65(6):599–606. [PubMed: 19454962]
- Stefan K, Kunesch E, Cohen LG, Benecke R, Classen J. Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain*. 2000; 123(Pt 3):572–584. [PubMed: 10686179]
- Stern WM, Tormos JM, Press DZ, Pearlman C, Pascual-Leone A. Antidepressant effects of high and low frequency repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex: a double-blind, randomized, placebo-controlled trial. *Journal of Neuropsychiatry and Clinical Neuroscience*. 2007; 19(2):179–186.
- Sun W, Mao W, Meng X, Wang D, Qiao L, Tao W, Li L, Jia X, Han C, Fu M, Tong X, Wu X, Wang Y. Low-frequency repetitive transcranial magnetic stimulation for the treatment of refractory partial epilepsy: A controlled clinical study. *Epilepsia*. 2012; 53(10):1782–1789. [PubMed: 22950513]
- Theoret H, Halligan E, Kobayashi M, Fregni F, Tager-Flusberg H, Pascual-Leone A. Impaired motor facilitation during action observation in individuals with autism spectrum disorder. *Current Biology*. 2005; 15(3):R84–R85. [PubMed: 15694294]
- Thut G, Ives JR, Kampmann F, Pastor MA, Pascual-Leone A. A new device and protocol for combining TMS and online recordings of EEG and evoked potentials. *Journal of Neuroscience Methods*. 2005; 141(2):207–217. [PubMed: 15661302]
- Tordjman S, Drapier D, Bonnot O, Graignic R, Fortes S, Cohen D, Millet B, Laurent C, Roubertoux PL. Animal models relevant to schizophrenia and autism: validity and limitations. *Behavioral Genetics*. 2007; 37(1):61–78.
- Valls-Sole J, Pascual-Leone A, Wassermann EM, Hallett M. Human motor evoked responses to paired transcranial magnetic stimuli. *Electroencephalography and Clinical Neurophysiology*. 1992; 85(6):355–364.
- Wagner T, Valero-Cabre A, Pascual-Leone A. Noninvasive human brain stimulation. *Annu Rev Biomedical Engineering*. 2007; 9:527–565.
- Williams JH, Waiter GD, Gilchrist A, Perrett DI, Murray AD, Whiten A. Neural mechanisms of imitation and 'mirror neuron' functioning in autistic spectrum disorder. *Neuropsychologia*. 2006; 44(4):610–621. [PubMed: 16140346]
- Yip J, Soghomonian JJ, Blatt GJ. Decreased GAD67 mRNA levels in cerebellar Purkinje cells in autism: pathophysiological implications. *Acta Neuropathologica*. 2007; 113(5):559–568. [PubMed: 17235515]
- Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, O'Shea DJ, Sohal VS, Goshen I, Finkelstein J, Paz JT, Stehfest K, Fudim R, Ramakrishnan C, Huguenard JR, Hegemann P, Deisseroth K. Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*. 2011; 477(7363):171–178. [PubMed: 21796121]
- Wassermann EM, Zimmermann T. Transcranial magnetic stimulation: therapeutic promises and scientific gaps. *Pharmacology and Therapeutics*. 2012; 133(1):98–107. [PubMed: 21924290]
- Ziemann U. Intracortical inhibition and facilitation in the conventional paired TMS paradigm. *Electroencephalography and Clinical Neurophysiology Supplement*. 1999; 51:127–136. [PubMed: 10590943]
- Ziemann U. TMS induced plasticity in human cortex. *Reviews in Neuroscience*. 2004; 15(4):253–266.

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., 2012a	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

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	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 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	10 AS (DSM-IV, ADOS, ADI-R)	M = 36.6 (SD = 16.0)	1800 pulses at 1 Hz and 70% stimulator output over left and	Double Blind Sham Controlled	Compared to the sham condition, stimulation of left pars triangularis improved	There were two reports of a stiff neck and one report of subtle disorientation following sham

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., 2012	20	Not Indicated (DSM-IV-TR, ADI-R)	9–21	right pars triangularis and pars opercularis and sham (a single session at each location separated by at least 5 days). 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	naming skills while stimulation of the adjacent left pars opercularis impaired naming skills. 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 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, Rinehart et al., 2012	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 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

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.