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Transcranial magnetic stimulation in autism spectrum disorder: Challenges, promise, and roadmap for future research

Lindsay M. Oberman, **Peter G. Enticott**, **Manuel F. Casanova**, **Alexander Rotenberg**, **Alvaro Pascual-Leone**, **James T. McCracken**, and **the TMS in ASD Consensus Group**

Abstract

Autism Spectrum Disorder (ASD) is a behaviorally defined complex neurodevelopmental syndrome characterized by impairments in social communication, by the presence of restricted and repetitive behaviors, interests and activities, and by abnormalities in sensory reactivity. Transcranial magnetic stimulation (TMS) is a promising, emerging tool for the study and potential treatment of ASD. Recent studies suggest that TMS measures provide rapid and noninvasive pathophysiological ASD biomarkers. Furthermore, repetitive TMS (rTMS) may represent a novel treatment strategy for reducing some of the core and associated ASD symptoms. However, the available literature on the TMS use in ASD is preliminary, composed of studies with methodological limitations. Thus, off-label clinical rTMS use for therapeutic interventions in ASD without an investigational device exemption and outside of an IRB approved research trial is premature pending further, adequately powered and controlled trials. Leaders in this field have gathered annually for a two-day conference (prior to the 2014 and 2015 International Meeting for Autism Research, IMFAR) to share recent progress, promote collaboration across laboratories, and establish consensus on protocols. Here we review the literature in the use of TMS in ASD in the context of the unique challenges required for the study and exploration of treatment strategies in this population. We also suggest future directions for this field of investigations. While its true potential in ASD has yet to be delineated, TMS represents an innovative research tool and a novel, possibly transformative approach to the treatment of neurodevelopmental disorders.

Keywords

autism spectrum disorder; transcranial magnetic stimulation; consensus; review; treatment

Introduction

Autism Spectrum Disorder (ASD) is a behaviorally defined complex neurodevelopmental syndrome. Core ASD symptoms include impairments in social communication, restricted and repetitive behaviors, interests and activities [American Psychiatric Association, 2013]. The diagnosis of ASD is based on observations and assessments of behavior using Diagnostic and Statistical Manual of Mental Disorders (DSM)) or International

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Classification of Diseases (ICD) criteria, however, postmortem, genetic and neuroimaging data indicate that the behavioral ASD phenotype is the product of atypical brain development [Ameis & Catani, 2015]. Despite many years of research, our understanding of this atypical neurodevelopment is limited. The brain networks responsible for the high-level skills that are impaired as part of the core ASD features are complex and require efficient integration of multiple, distributed brain regions. Thus, ASD pathophysiology likely is not limited to dysfunction of a single brain region, but rather a breakdown in the functioning and integration of long-range neural circuits.

Over the past quarter century, neuroscience techniques have been developed and applied to ASD to study brain structure and function. Additionally, clinical trials of therapeutic inteventions aimed at modulating brain functioning have also been evaluated. In this article, we will discuss one neuroscientific technique, namely transcranial magnetic stimulation (TMS) that has been used both to study the neural mechanisms of ASD as well as to therapeutically target the predicted dysfunction.

TMS is a method for noninvasive focal brain stimulation, where localized intracranial electrical currents, large enough to depolarize a small population of neurons, are generated by rapidly changing extracranial magnetic fields [Wagner, Valero-Cabre, & Pascual-Leone, 2007]. TMS can be applied in single pulses, pairs of pulses, or repeated trains of pulses (rTMS). Following standardized guidelines and procedures, human studies with adults and children have demonstrated TMS procedures to be safe and well tolerated [Croarkin, Wall, & Lee, 2011; Garvey & Gilbert, 2004; Hong et al., 2015; Rajapakse & Kirton, 2013; Rossi, Hallett, Rossini, Pascual-Leone, & Safety of T.M.S. Consensus Group, 2009].

When single pulse TMS is applied in primary motor cortex (M1) at suprathreshold intensities, it activates corticospinal outputs, producing a twitch in a peripheral muscle (a motor evoked potential (MEP)), which can be used as an index of corticospinal excitability [Barker, Jalinous, & Freeston, 1985]. Early TMS studies discovered that the evoked responses are primarily reflective of functioning of intracortical circuits (rather than the corticospinal projection neurons themselves) [Day et al., 1989]. Thus, protocols to probe intracortical inhibitory and facilitatory processes using paired pulse stimulation protocols have also been developed [Claus, Weis, Jahnke, Plewe, & Brunholzl, 1992; Kujirai et al., 1993; Valls-Sole, Pascual-Leone, Wassermann, & Hallett, 1992; Ziemann, 1999]. Finally, trains of repeated TMS pulses (rTMS) at various stimulation frequencies and patterns can induce a lasting modification of activity in the targeted brain region, which can outlast the effects of the stimulation itself. The after effects of rTMS are thought to relate to activity-dependent changes in the effectiveness of synaptic connections between cortical neurons, reflecting cortical plasticity mechanisms [Fitzgerald, Fountain, & Daskalakis, 2006; Hoogendam, Ramakers, & Di Lazzaro 2010; Thickbroom, 2007; Ziemann, et al., 2008]. Single and paired pulse TMS protocols are exclusively used for investigational purposes, while rTMS protocols can be used both in investigational and therapeutic applications.

Given the current data emphasizing circuit-level dysfunction as well as aberrant synaptic plasticity and excitation/inhibition ratio in ASD (see [Ameis & Catani, 2015; Casanova, Buxhoeveden, & Gomez, 2003; Oberman, Rotenberg, & Pascual-Leone, 2014; Rubenstein

& Merzenich, 2003] for reviews) and the capacity of TMS to both investigate and modulate cortical excitability and plasticity [see Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Huerta & Volpe, 2009; Thickbroom, 2007; Ziemann, 2004], the potential for TMS in the field of autism research is beginning to be explored in a number of laboratories world-wide.

The inaugural "Transcranial Magnetic Stimulation (TMS) Therapy for Autism Consensus Conference" was held in May of 2014 with a second conference held in May of 2015. The purpose of these conferences was to gather TMS and autism researchers and clinicians to share recent progress in the field, promote collaboration across laboratories and disciplines, and establish consensus on TMS parameters that may be useful for the study of pathophysiology and the potential treatment of ASD. This article benefitted from the combined expertise and discussions of those present at these conferences. This is an evolving area of research with great promise, but also many open questions that have yet to be explored. In this article, we review the current data related to the use of TMS both as an investigational and a therapeutic tool, discuss the challenges inherent in this type of research, and propose a roadmap for future research in this area.

Published Reports of TMS in ASD

TMS as an Investigative Tool

Different TMS paradigms have been developed to probe cortical excitability, inhibitory control, and plasticity respectively, and have been used to explore the neurophysiology of ASD, generally among individuals without intellectual disability (findings summarized in Table 1).

Single pulse TMS

In ASD, single pulse TMS has been used to probe baseline levels of corticospinal excitability and modulation of corticospinal excitability in response to visually presented stimuli. Six independent studies have shown no difference in either motor threshold (the lowest intensity of stimulation required to induce a MEP) or size of MEP in response to a suprathreshold pulse of TMS between individuals with ASD and neurotypical individuals [Enticott, Kennedy, Rinehart, Bradshaw, et al., 2013; Enticott, Kennedy, Rinehart, Tonge, et al., 2013; Enticott, Rinehart, Tonge, Bradshaw, & Fitzgerald, 2010; Minio-Paluello, Baron-Cohen, Avenanti, Walsh, & Aglioti, 2009; Oberman et al., 2012; Theoret et al., 2005]. These published data suggest that baseline M1 excitability is not affected in ASD.

Several other studies [Enticott, Kennedy, Rinehart, Bradshaw, et al., 2013; Enticott, Kennedy, et al., 2012; Minio-Paluello et al., 2009; Theoret et al., 2005] assessed modulation of M1 excitability in individuals with ASD as measured by single pulse TMS during the observation of another person's actions. In neurotypical individuals the observation of another person's actions results in a simultaneous activation of the observer's sensorimotor system. This phenomenon is referred to as interpersonal motor resonance (IMR) and is considered a putative index of mirror neuron system activity [Uithol, van Rooij, Bekkering, & Haselager, 2011]. Studies evaluating IMR in individuals with ASD have reported mixed results that appear to be dependent on the properties of the stimuli such as the presentation

from egocentric or allocentric perspectives, transitive versus intransitive actions, or the social or emotional content of the stimulus. These findings suggest that the aberrant IMR responses may be a result of differences in visual processing or attention to certain stimuli, but typical responses to other stimuli in ASD [Enticott, Kennedy, Rinehart, Bradshaw, et al., 2013].

Paired Pulse TMS

In the conventional paired pulse TMS protocol, two consecutive magnetic pulses are applied through the same TMS coil in rapid succession over primary motor cortex at various interpulse intervals. The outcome measure is the degree of effect of the first pulse "conditioning stimulus" (CS) on the second pulse "test stimulus" (TS) [Claus et al., 1992; Kujirai et al., 1993; Valls-Sole et al., 1992; Ziemann, 1999].

When the interpulse interval between a subthreshold CS and suprathreshold TS is 1–6 msec, the resulting MEP suppression is thought to reflect GABAA receptor mediated short-interval intracortical inhibition (SICI) [Kujirai et al., 1993; Ziemann et al., 2015]. When the interpulse interval is increased to 10–25 msec, the net result is facilitatory, making this paired pulse paradigm a putative index of intracortical facilitation (ICF), which is thought to be mediated by a combination of receptor types including n-methyl-d-aspartate (NMDA) glutamate receptors [Ziemann, Tergau, Wischer, Hildebrandt, & Paulus, 1998], GABAA receptors [Inghilleri, Berardelli, Marchetti, & Manfredi, 1996; Mohammadi, et al., 2006; Ziemann, Lonnecker, Steinhoff, & Paulus, 1996], and noradrenaline (NA) receptors [Boroojerdi, Battaglia, Muellbacher, & Cohen, 2001; Gilbert et al., 2006; Herwig, Brauer, Connemann, Spitzer, & Schonfeldt-Lecuona, 2002; Kirschner et al., 2003; Moll, Heinrich, & Rothenberger, 2003; Plewnia, Bartels, Cohen, & Gerloff, 2001; Plewnia et al., 2002]. Two suprathreshold pulses delivered at an interpulse interval of 50–200 msec is used to evaluate GABA mediated long interval intracortical inhibition (LICI) [McDonnell, Orekhov, & Ziemann, 2006; Pierantozzi et al., 2004; Valls-Sole et al., 1992; Werhahn, Kunesch, Noachtar, Benecke, & Classen, 1999; Hsieh et al., 2012].

A number of studies have been conducted using these paradigms to probe intracortical inhibition and facilitation in ASD. Two studies report no significant difference in response to the SICI paradigm between ASD and neurotypical individuals [Jung et al., 2013; Theoret et al., 2005]. Three studies employed the ICF paradigm and found no significant difference between ASD and neurotypical controls [Enticott, Kennedy, Rinehart, Tonge, et al., 2013; Enticott et al., 2010; Theoret et al., 2005]. Three studies have reported mixed results with some ASD individuals showing impaired intracortical inhibition and others showing typical responses [Enticott, Kennedy, Rinehart, Tonge, et al., 2013; Enticott et al., 2010; Oberman et al., 2010]. Thus, abnormal intracortical inhibition may be present in a subgroup, but this alteration of cortical physiology does not appear to be consistently demonstrable in all individuals with ASD.

rTMS

The effects of single and paired pulses are short lasting (on the order of milliseconds), however, when pulses are applied in repeated trains, such as in the case of rTMS, there is the

potential to affect cortical excitability for several minutes following a single session, or several days to months following a series of daily sessions. Thus, rTMS can be used to provide a measure of cortical plasticity (the degree to which the excitability of the cortex changes following these rTMS trains) [Pascual-Leone et al., 2011]. Depending on the parameters of stimulation, focal cortical excitability can be either facilitated or suppressed [Pascual-Leone, Valls-Sole, Wassermann, & Hallett, 1994]. The degree and direction of the effect of rTMS, both at the level of the brain and behavior, depends on factors such as location of stimulation, intensity of stimulation, frequency of stimulation, number of sessions, and frequency of sessions, as well as individual symptom pathophysiology [Rotenberg, Horvath, & Pascual-Leone, 2014]. Some protocols appear to induce suppression or facilitation through Hebbian mechanisms of long-term depression (LTD) and long-term potentiation (LTP) across populations of neurons [Ahmed & Wieraszko, 2006; Cardenas-Morales, Gron, & Kammer, 2011; Thickbroom, 2007]. While others may induce these changes by modulating activity in GABAergic interneurons [Funke & Benali, 2010; Trippe, Mix, Aydin-Abidin, Funke, & Benali, 2009]. The prominent role of inhibitory interneurons in rTMS-induced modulation of cortical excitation is of importance in autism as the GABAergic system has repeatedly been implicated in this disorder.

One rTMS protocol developed specifically to probe NMDA dependent Hebbian plasticity mechanisms is refererred to as Paired associated stimulation (PAS) [Stefan, Kunesch, Cohen, Benecke, & Classen, 2000; Ziemann, 2004] This protocol involves applying pairs of electrical median nerve stimulation combined with single pulses of TMS to primary motor cortex repeatedly for 90 pairings with 20 sec between the pairings (for approximately 30 min). In neurotypical individuals, when the peripheral median nerve stimulation and TMS stimulation are timed such that the afferent signal coming from the peripheral nerve stimulation to the motor cortex arrives at the same time as the TMS pulse is applied over the primary motor cortex (25 msec interstimulus interval), an LTP-like facilitation of cortical excitability, lasting up to an hour after the end of the protocol, is induced [Classen et al., 2004]. Jung et al. [2013] recently published a study reporting abnormally reduced LTP-like facilitation of MEPs following the PAS paradigm in individuals with ASD, suggesting an impairment in Hebbian plasticity mechanisms.

Another common rTMS paradigm, theta burst stimulation (TBS), has been developed to investigate nonHebbian plasticity mediated by changes in GABAergic tone [Benali et al., 2011; Stagg et al., 2009]. TBS involves application of 3 bursts of 50-Hz rTMS repeated every 200 msec either continuously (cTBS) for a total of 40 sec or intermittently (iTBS) (every 8 sec) for about 3 min [Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Huang, Rothwell, Edwards, & Chen, 2008]. When applied to the motor cortex, cTBS and iTBS tend to result in lasting suppression or facilitation, respectively, of cortical excitability for approximately 20–40 min in neurotypical individuals [Huang et al., 2005]. Oberman and coworkers recently published a series of studies where high functioning adults with ASD showed an increased duration of response to the TBS paradigm [Oberman et al., 2012; Oberman et al., 2010; Oberman & Pascual-Leone, 2014]. The authors interpreted this increased duration to represent hyperplasticity (seemingly counter to the impaired plasticity response reported by Jung et al. [2013]). An additional study where TBS was applied to children with ASD demonstrated an increase in the duration of response across childhood

and revealed a subgroup of children who showed paradoxical facilitation to the typically suppressive cTBS paradigm [Oberman, Rotenberg, et al., 2014]. The authors suggested that their findings may reflect abnormalities in GABAergic inhibitory control in those individuals who showed paradoxical facilitation.

Although both PAS and TBS paradigms suggest abnormalities in cortical plasticity in ASD, initial studies have yielded conflicting findings, with PAS showing impaired and TBS showing enhanced plasticity. These differences may reflect the small sample sizes of the studies, etiologic heterogeneity of the population, or paradigmatic differences (Hebbian vs. non-Hebbian mechanisms) and highlight the need for larger-scale studies that include phenotypic and if possible genotypic characterization of the samples [Enticott & Oberman, 2013].

Summary of TMS as an Investigational Tool in ASD

In summary, the findings from the above mentioned literature using TMS as an investigational device partially support the theories suggesting excitation/inhibition imbalance and aberrant plasticity mechanisms in ASD. However, what the studies above reveal most clearly is the variability of the findings. Other than no abnormality in baseline corticospinal excitability, all other indexes of response to TMS vary both within and across studies. One should note that the sample sizes in the studies are relatively small (ranging from 5 to 36) and represent a small subgroup of the overall ASD population. Specifically, (1) the aforementioned studies either did not document or did not exclude individuals on psychoactive medications; (2) all studies excluded individuals with intellectual disability; and, (3) all studies excluded individuals with a history of seizures or abnormal electroencephaolography (EEG) findings.

A number of unanswered questions related to the use of TMS as an investigative device in ASD remain—Are aberrant physiological findings causal or a consequence of ASD pathology? What is the impact of age or development on these measures? Are the effects consistent across the spectrum (verbal and nonverbal, with and without comorbidities or intellectual disability)? And what underlying mechanisms are driving the observed heterogeneity in the population? Future research efforts should acquire larger, well-powered samples and attempt to stratify or enrich ASD samples according to clinical, genetic, or neurocognitive attributes. Additionally, researchers should strive to adopt consistent experimental procedures including standardized pulse sequences, outcome measures, and side-effect monitoring. There is intrasubject and intersubject variability in response to rTMS even when the parameters are kept constant, the variability of effects will be even larger when publications vary on other experimental procedures. Despite the limitations of the studies to date, results suggest that TMS-measures of brain physiology may have the potential to serve as biomarkers to guide the search for ASD subtypes.

TMS as a Therapeutic Intervention

rTMS has been studied as a therapeutic intervention for a number of neurological and psychiatric conditions [Kobayashi & Pascual-Leone, 2003]. These include medication-

refractory major depressive disorder [Gaynes et al., 2014] where two different TMS devices are cleared by the Food and Drug Administration, stroke rehabilitation [Pinter & Brainin, 2013], chronic pain [Galhardoni et al., 2015] Parkinson's disease [Kimura et al., 2011], Alzheimer's disease [Freitas, Mondragon-Llorca, & Pascual-Leone, 2011], and epilepsy [Sun et al., 2012].

A number of recent studies [Baruth et al., 2010; Casanova et al., 2012; Casanova et al., 2014; Enticott et al., 2014; Enticott, Rinehart, Tonge, Bradshaw, & Fitzgerald, 2012; Fecteau, Agosta, Oberman, & Pascual-Leone, 2011; Panerai et al., 2013; Sokhadze et al., 2010; Sokhadze et al., 2012; Sokhadze et al., 2009; Sokhadze, El-Baz, Sears, Opris, & Casanova, 2014; Sokhadze, El-Baz, Tasman, et al., 2014] and case reports [Cristancho, Akkineni, Constantino, Carter, & O'Reardon, 2014; Enticott, Kennedy, Zangen, & Fitzgerald, 2011; Niederhofer, 2012] have reported on the efficacy of both high and low frequency rTMS protocols in ASD (findings summarized in Table 2). A variety of brain regions and symptom domains have been targeted including: dorsal lateral prefrontal cortex (DLPFC) to improve irritability, repetitive behaviors, and executive functioning, supplementary and primary motor cortices to improve motor behavior, medial prefrontal cortex to improve mentalizing, and premotor cortex to improve speech production and eye-hand coordination. Of importance to note, it is unlikely that therapeutic TMS would reverse multiple aspects of the ASD phenotype, rather, it may improve specific core or associated symptoms related to an alteration in the functioning of a specific cortical region or circuit.

Low Frequency Stimulation

The earliest and majority of the published studies on therapeutic use of rTMS in ASD have been conducted by Manuel Casanova and et al. [2003], who have employed low-frequency, subthreshold rTMS to dorsolateral prefrontal cortex (DLPFC) (left or sequential bilateral) to suppress excitability in ASD. This paradigm was chosen to address the hypothesized cortical inhibition deficits resulting from suspected minicolumnar abnormalities in individuals with ASD. Statistically significant improvements in irritability and repetitive behaviors [Baruth et al., 2010; Casanova et al., 2012; Casanova et al., 2014; Sokhadze, El-Baz, Sears, et al., 2014; Sokhadze, El-Baz, Tasman, et al., 2014], normalization of (EEG) components related to target detection and error monitoring [Baruth et al., 2010; Casanova et al., 2012; Sokhadze et al., 2010, 2012, 2009; Sokhadze, El-Baz, Sears, et al., 2014] and enhanced autonomic balance [Casanova et al., 2014] have been reported following this protocol. These results have been further corroborated and improved on in a pilot trial using EEG neurofeedback in combination with rTMS [Sokhadze, El-Baz, Tasman, et al., 2014]. Though the effect sizes were large in these studies (d=0.7–1.2), the trial designs were all open-label (with a waitlist control group), thus results may be confounded by placebo effects or adaptation to the environment and protocol.

Additional studies have applied low-frequency rTMS to other regions of prefrontal cortex to modulate functioning of different cortical circuits. Fecteau et al. [Fecteau et al., 2011] discovered that 1 Hz rTMS to individuals with ASD enhanced object naming when applied to left pars triangularis, but reduced object naming when applied to left pars opercularis. Enticott et al. [2012] reported changes in movement-related EEG cortical potentials

(MRCPs) that are involved in preparation and execution of movements. Following a single session of 1 Hz rTMS to supplementary motor area and M1 (relative to M1 sham) ASD participants showed increases in these components, indicating increased activity in supplementary motor cortex during movement preparation. There were, however, no observable changes in motor behavior.

High Frequency Stimulation

Other investigators have employed high-frequency rTMS protocols in an attempt to enhance excitability within presumably underactive cortical regions and associated networks in ASD. Enticott et al. [2014] applied either active or sham high-frequency (5 Hz) rTMS to bilateral medial prefrontal cortex among adults with ASD in a double-blind randomized sham-controlled trial. This study was designed to have an excitatory effect on networks devoted to mentalizing, which have shown reduced activation in ASD in neuroimaging studies [Di Martino et al., 2009]. The authors reported a significant improvement in the Social Relatedness Subscale of the Ritvo Autism Asperger Diagnostic Scale (RAADS) with a medium effect size, but no effect on other behavioral scales including the Autism Spectrum Quotient (AQ), Interpersonal Reactivity Index (IRI), or experimental measures of mentalizing (reading the mind in the eyes test and animations mentalizing test). In another trial, Panerai et al. [2013] applied high frequency (8 Hz) rTMS to left premotor cortex in children with ASD with intellectual disability. The authors report significant improvements in eye-hand coordination that were accentuated when paired with behavioral eye-hand integration training. Notably, this is the only study in the published literature that included participants with intellectual disability.

Summary of TMS as a Therapeutic Intervention in ASD

Although an emerging literature, the aforementioned trials collectively provide preliminary support for further exploration of the potential efficacy of rTMS for ASD. However, no study published thus far has followed strict clinical trial protocols (e.g., randomization, identification of clear and objective primary endpoints, double-blinding with appropriate sham conditions, sufficient power, etc.), thus the generalizability to clinical settings is unclear.

A publication [Lefaucheur et al., 2014] recently established guidelines for evaluating the therapeutic efficacy of rTMS in a number of indications. Four classes of studies were described: A Class I study is an adequately data-supported, prospective, randomized, placebo-controlled clinical trial with masked outcome assessment in a representative population ($n \geq 25$ patients receiving active treatment) and includes (a) randomization concealment; (b) clearly defined primary outcomes; (c) clearly defined exclusion/inclusion criteria; (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias, and (e) relevant baseline characteristics substantially equivalent among treatment groups or appropriate statistical adjustment for differences. A Class II study is a randomized, placebo-controlled trial performed with a smaller sample size ($n < 25$) or that lacks at least one of the criteria listed above. Class III studies include all other controlled trials. Class IV studies are uncontrolled studies, case series, and case

reports. There have been 15 studies and case reports published assessing rTMS as a therapeutic intervention in ASD, however, most would be characterized as Class III or IV. Thus, therapeutic use of rTMS in ASD would likely be classified as Level C: "possibly effective" according to these guidelines [Lefaucheur et al., 2014].

As with the use of TMS as an investigational tool, there remain several gaps in knowledge with regard to the use of TMS for ASD treatment—What is an adequate "dose"? What are optimal stimulus parameters and application sites? What are the clinical targets that TMS may be considered for? On what basis should participants be selected? Are there predictors of treatment response? There are currently a small number (N = 4) of recently completed or ongoing clinical trials using rTMS as an intervention for multiple symptom targets in ASD, three of which are using a randomized, double-blind, sham-controlled approach (e.g., ClinicalTrials.gov ID: NCT02311751, NCT01388179, and NCT00808782). It is the consensus of the authors that off-label clinical use of rTMS for therapeutic interventions in ASD without an investigational device exemption and outside of an IRB approved research trial is currently premature pending further, properly powered and well-controlled trials.

Development of a Roadmap for the Use of TMS in ASD Research

As with any investigational or therapeutic device, application of TMS poses both practical and ethical challenges that need to be addressed (see Table 3 for a summary of challenges and recommendations). Among challenges to consider when determining the research utility and clinical efficacy of TMS in any population are: (1) establishment of experimental guidelines that should be kept uniform across studies, and how to ensure adherence to such guidelines and (2) study design, analysis, and measurement strategies to ensure treatment and assessment blinding. This second challenge is necessary to protect against placebo effects, thus yielding valid and reliable data across studies. These more general challenges apply across clinical populations and have been specifically addressed in recent white papers [Brunoni & Fregni, 2011; Canadian Agency for Drugs and Technologies in Health, 2014; Klein et al., 2015; Lefaucheur et al., 2014; Nielson, McKnight, Patel, Kalnin, & Mysiw, 2015]. The TMS in ASD literature would greatly benefit from applying the knowledge that has been gleaned by TMS researchers working in other clinical applications to future studies. For ASD there are additional challenges to manage including: (1) the known behavioral, functional, and neurological heterogeneity of the population and (2) safety, tolerability and ethical concerns related to potentially increased risk of side effects, tolerability of these procedures, as well as developmental considerations related to applying TMS to children.

Experimental Guidelines, Oversight, and Regulatory Concerns

A decade ago, there were only a handful of widely used TMS protocols and a small number of laboratories and clinics using this technology. However, the field has grown exponentially leading to alternative experimental and clinical paradigms being introduced into the literature and a growing number of researchers and clinicians utilizing this technology. This growth has produced a rich, yet discordant literature. Given the known variability in effect that can be seen with even small changes to TMS parameters (location of stimulation, coil

orientation, interpulse interval, etc.), studies must begin to utilize consistent paradigms to eliminate this potential source of variability across studies.

From a regulatory standpoint, there is also a safety concern with the growth of the field both in numbers and in novel paradigms whose safety profile (especially in clinical populations) has not been fully established. Previously, TMS was only available in labs or clinics affiliated with hospitals. However, access to these devices has recently become more widespread and TMS is being applied in doctor's offices and even by patients themselves in the home (e.g., Spring TMS, eNeura Inc., Baltimore, MD). Compared to drugs, brain stimulation is often perceived as a deceivingly simple and a more specific way to modify brain activity. Indeed, another brain stimulation technology (direct current stimulation) has already gained popularity in the "do-it yourself," "DIY" movement resulting in a number of researchers and clinicians voicing ethical concerns (Fitz & Reiner, 2015). However, the most recent TMS safety guidelines [Rossi et al., 2009] dictate that the principal investigator on any TMS protocol "should be an expert in TMS with knowledge about principles, physiology and potential side effects of the technique" and "appropriate emergency medical attention for possible TMS complications should be planned for. A licensed physician that is intimately familiar with the study protocol, the risks of TMS, the treatment of any of its possible complications and side effects, and the condition of any patients undergoing TMS, should be involved in the design and conduct of study protocols." Thus, consistent with these guidelines, any application of TMS in ASD should involve oversight and regulation at institutional and/or federal levels and be conducted by a trained expert to ensure safe and ethical applications of this technology.

Study Design and Placebo Effect Concerns

The studies that have been published thus far using TMS in ASD had a number of limitations. First, there has been little effort to reduce the biological or clinical heterogeneity of the samples. The inclusion criteria for most studies have simply been either a clinical diagnosis of ASD or at best a "high-functioning" sample (based largely on IQ score). This is especially concerning given the small sample sizes of many of the studies. This sampling method has likely contributed to the null or conflicting findings both in research and clinical use. Second, these studies have not been designed using strict clinical trial designs with clear and objective primary clinical endpoints. The clinical outcome measures that have been utilized are often subjective self- or observer- based reports. Self or observer-based reports are often highly influenced by placebo effects, which threaten to mask or undermine assessment of change [King et al., 2001]. Furthermore, when physiological outcome measures have been evaluated, the relationship between the physiological outcome measures (e.g., ERPs) and the clinical outcome measures has not been clearly established. The lack of blinding or true sham control conditions employed in the majority of extant studies further compounds these concerns. This is likely a result of the limited availability of "true sham" TMS coils and the small sample sizes employed by the studies thus far. While some management of expectancy bias can be achieved through the use of blinded, independent raters, further efforts are needed to identify additional objective outcome measures, whether behavioral or biological. Ideally, such study endpoints should be grounded by other

information which demonstrates their association to the targeted pathophysiology being studied.

Heterogeneity

One ubiquitous challenge in autism research is the considerable heterogeneity both in the severity and quality of the core and comorbid symptoms in ASD. This is a challenge for all researchers aiming to study and treat individuals with ASD. Two individuals could meet DSM or ICD criteria for ASD but present with vastly different behavioral phenotypes as well as variable psychiatric and medical challenges. Subjects diagnosed with ASD share core symptoms in the areas of social communication as well as restricted, repetitive, and stereotyped patterns of behavior, interests and activities [American Psychiatric Associaiton, 2013] that can be evaluated using DSM or ICD criteria. However, the severity of ASD symptoms, the presence of comorbid symptoms (including intellectual disability, epilepsy, sleep disturbance, gastrointestinal conditions, and others), and the underlying cause and pathophysiology differs markedly across individuals on the “spectrum” of ASD. With regard to behavior alone, individuals with ASD are well known to suffer from common comorbid psychiatric symptoms, including anxiety, attention deficits, hyperactivity, depression, and irritability. These co-occurring psychiatric symptoms lead to a widespread use of psychotropic medication in ASD, a phenomenon that can likely generate confounding effects in both basic physiological research and clinical TMS studies.

Though TMS studies thus far have largely limited enrollment to high functioning, verbal individuals, future applications of TMS both as investigational probes of physiology and as potential therapeutic interventions need to carefully evaluate subject selection, and seek to identify more homogeneous subject populations to avoid the possible masking of TMS effects due to intrinsic subject differences. In future studies, rigorous behavioral phenotyping by research reliable assessors using standardized measures to assess both ASD symptoms (such as the Autism Diagnostic Observation Scheduled (ADOS) and Autism Diagnostic Interview-Revised (ADI-R)) as well as other comorbid behavioral and psychiatric symptoms (such as Aberrant Behavior Checklist (ABC), and Vineland Adaptive Behavior Scales, Second Edition (VABS-II), etc.) would allow for improved sample characterization, stratification, and enrichment and less variability in baseline and outcome measures. Researchers using rTMS are also encouraged to stratify their sample based on objective brain-based measures. Recently, a number of such putative brain-based measures that significantly correlate with ASD behavioral measures have been evaluated including proton magnetic resonance spectroscopy [Baruth, Wall, Patterson, & Port, 2013], EEG [Wang et al., 2013], and resting state functional magnetic resonance imaging (rsfMRI) [Plitt, Barnes, & Martin, 2015].

Furthermore, in keeping with modern clinical trial design, studies must declare clearly formulated, primary hypotheses to be tested, which are grounded on well-articulated understanding of pathophysiology, with an effort to identify mechanisms of change, if benefits are found. For example, if the aims of a therapeutic trial are to enhance self-regulation and behavioral control (e.g., reduce hyperactivity), a reasonable approach would be that individuals with prominent deficits in behavioral control would exhibit insufficient

cortical inhibitory control in a defined neural network, based on TMS, perhaps combined with other neuroimaging or neurocognitive measures. The hypothesis to be tested would be that active rTMS aimed at increasing inhibitory control in that network would be associated with greater improvement in clinical measures of behavioral inhibition versus sham treatment. Moreover, the true test of proof-of-principle would require demonstration that the specific behavioral effects are indeed related to changes in network inhibition.

Safety, Tolerability, and Ethical Concerns

As noted above, TMS is considered quite safe, even in pediatric populations, if applied within current safety guidelines [Garvey & Gilbert, 2004; Rajapakse & Kirton, 2013]. TMS does, however, pose some risk for adverse side effects [Rossi et al., 2009]. Thus, factors including medications and medical history need to be assessed and the risk–benefit ratio of the procedure should be carefully considered before the patients undergo TMS. The most serious possible TMS-related adverse event is induction of a seizure. To date, 16 cases of rTMS induced seizures have been reported out of tens of thousands of individuals who have received rTMS over the past 25 years. Overall the risk of seizure is considered to be less than 0.01% across all patients and all paradigms [Rossi et al., 2009], however, the risk varies based on factors including interpulse interval, intensity of stimulation, and risk factors in the participants. For example, no seizures have been reported during single or paired-pulse TMS paradigms in neurologically healthy individuals. 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 neuropsychiatric disorder. A gap in the preliminary studies of TMS in ASD (as well as other conditions), is the lack of a systematic effort to identify, track, and report adverse events in study publications. As a result, it is possible that even though TMS appears to show a large safety margin, the risk of overall adverse event burden from TMS may be underestimated, especially in a vulnerable population as in individuals with ASD.

There are currently no identified ASD-specific risk factors for TMS-induced adverse effects. Individuals with ASD may, however, may present added concern regarding relative risk of seizure due to the frequent prescribing of psychotropic medications in individuals with ASD [Murray et al., 2014] and the increased prevalence of epilepsy in the population [Spence & Schneider, 2009]. Though relatively few patients with ASD have participated in TMS protocols (<500), no seizures have been reported in any individual with ASD and the frequency and quality of side-effects reported thus far approximates that seen in the general population [Oberman, Rotenberg, & Pascual-Leone, 2015].

There are also concerns regarding the tolerability of TMS across the autism spectrum. With the exception of a single study [Panerai et al., 2013] all other studies have excluded individuals with intellectual disability. Individuals with ASD often display hyperreactivity to sensory input (1) and comorbid hyperactivity, anxiety and impulsive behavior. The feasibility and tolerability of these procedures in these individuals, especially those protocols that require long or repeated sessions has yet to be fully established. Some individuals may require additional aids including a “mock” stimulator (similar to what is used in MRI

studies), or other interventions to reduce the stress of the procedure (weighted blanket, soothing music, electronic device, etc.) to increase tolerability.

In addition to safety and tolerability concerns, there are also ethical concerns that have been voiced when considering the application of rTMS in a clinical population, particularly a vulnerable population such as ASD, and especially so when considering exposure in children. One ethical concern is whether modulation in excitability in one direction for one brain region may result in a compensatory modulation in another area in the opposite direction. Under this model, any improvement in behavior in one domain may be matched with a relative decrement in skills in another domain (see [Brem, Fried, Horvath, Robertson, & Pascual-Leone, 2014] for a review of this argument). There is also potential for symptom worsening in the target domain as the pathophysiology underlying the behavioral phenotype of ASD is likely a result of a complex balance within and across multiple brain regions and networks. Thus, it is important to systematically and broadly assess a range of behavioral and cognitive outcomes and side-effects of the stimulation. Also, both investigational and therapeutic studies should have data safety monitoring boards to monitor side effects and adverse events and clear stopping rules in the event of a serious or unexpected adverse event.

Another ethical concern relates to the application of rTMS in a pediatric brain that is still undergoing development. It is increasingly being recognized that the brain of a child is not simply a smaller version of an adult brain and that therapeutic interventions such as rTMS may have distinct, unpredictable, and potentially long-lasting effects on neurodevelopment [George et al., 2007]. These effects may be the target of the treatment or may be an unexpected side-effect. A recent meta-analysis [Rajapakse & Kirton, 2013] reviewed the studies to date involving all rTMS protocols in children (approximately 1000 children have been studied across all rTMS protocols to date) and concluded “Its minimal risk, excellent tolerability and increasingly sophisticated ability to interrogate neurophysiology and plasticity make it an enviable technology for use in pediatric research with future extension into therapeutic trials.” However, there is some evidence suggesting that the effects of stimulation change across development [Geinisman, deToledo-Morrell, & Morrell, 1994; Oberman, Pascual-Leone, & Rotenberg, 2014] and few studies involve long-term follow up to evaluate effects of stimulation weeks or months after the final session. Follow up assessments of pediatric subjects well beyond the end of TMS exposure may be able to track how stimulation paradigms interact with the moving target of developmental neural plasticity.

Conclusion

Though all of the scientific and practical limitations have yet to be fully addressed, the application of TMS in autism research and treatment holds significant promise as both an investigational and therapeutic tool. Though the existing literature has some limitations, the concerns and challenges raised here are all addressable in future studies and many are certainly not unique to this population or this intervention. Through collaboration across disciplines and across labs, researchers and clinicians can begin to develop valid and reliable uses of TMS to both study the pathophysiology and develop novel treatments for ASD. This type of collaborative effort is underway through the establishment of the “TMS in ASD

Consensus Group." This group of researchers, clinicians, regulatory affairs officers, and community partners meets annually prior to the International Meeting for Autism Research (IMFAR) and convenes periodically throughout the year through teleconference to facilitate ongoing discussion, establish consensus on investigative and therapeutic protocols and encourage collaboration across centers.

Using the "Fast-Fail Drug Trials" and "Research Domain Criteria" initiatives put forward by the NIMH, rTMS trials can begin to quickly identify protocols that reliably modulate a specific brain circuit and in turn measurably alter a clearly defined and objective behavioral endpoint. As highlighted above, attention will need to be paid to guidelines previously established for the use of TMS in other clinical populations, but also take into consideration the specific concerns related to ASD. Namely, how these protocols approach the issues inherent in studying younger, developing populations to evaluate the safety and ethics of applying these protocols across the age-span. These trials, especially in such a clinically and physiologically heterogeneous population, will require large samples of individuals (hundreds) across the age-span and across levels of functioning to test the validity and reliability of these measures. Further, it would be advisable to attempt to stratify the sample based on reliable, objective biomarkers to match treatment to individual differences in underlying biology. While its true potential in ASD has yet to be delineated, TMS represents an innovative research tool and a novel, possibly transformative approach to the treatment of neurodevelopmental disorders.

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Table 1

Published Reports of Investigational Use of TMS in ASD

Paper	Diagnosis	Intellectual Disability	*n* (ASD)	Mean age (years)	Gender	Medication	Site	Frequency	Intensity
Theoret et al. [2005], Current Biology	ASD	None	10	Age Range: 23–58	M/F	–	L M1	Single Pulse and Paired Pulse (1, 2, 3, 6, 9, 12, 15 msec ISI)	Single Pulse590%, 100%, 105%, 110%, 115%, 120%, 130%, 140%, 150%, 160% RMT; Paired Pulse = 80% and 120% RMT
Minio-Paluello et al. [2009], Biological Psychiatry	AS	None	16	28	M	–	L M1	Single Pulse	120% RMT
Oberman et al. [2010], Frontiers in Synaptic Neuroscience	AS	None	5	41	M/F	–	L M1	TBS	80% AMT
Enticott et al. [2010], Developmental Medicine and Child Neurology	ASD (11 HFA, 14 AS)	None	25	16.67	M/F	clomipramine, risperidone, quetiapine, venlafaxine, fluoxetine, valproate	L and R M1	Single Pulse and Paired Pulse (2 and 15 msec ISI)	Single Pulse=115% RMT; Paired Pulse=90% and 115% RMT
Jung et al. [2012], Developmental Medicine and Child Neurology	ASD (7 HFA, 6 AS, 2 PDD-NOS)	None	15	18	M/F	None	R M1 (PAS)	PAS, Single Pulse and Paired Pulse (2 and 3 msec ISI)	Lowest intensity producing average 1 mV motor-evoked potential
Oberman et al. [2012], European Journal of Neuroscience	AS	None	35 (cTBS), of which 9 also iTBS	36	M/F	–	L M1	TBS	80% AMT
Enticott et al. [2012], Biological Psychiatry	ASD	None	34	26	M/F	SSRI, atypical antipsychotic, benzodiazapine, antidepressant	L M1	Single Pulse	120% RMT
Enticott et al. [2013], Frontiers in Human Neuroscience	ASD	None	32	25	M/F	SSRI, atypical antipsychotic, benzodiazapine, antidepressant	L M1	Single Pulse	120% RMT
Enticott et al. [2013], Neuropharmacology	ASD	None	36	26	M/F	fluoxetine, citalopram, sertraline, lorazepam, olanzapine, venlafaxine, risperidone, mirtazapine, quetiapine	L and R M1	Single Pulse and Paired Pulse (2, 15 and 100 msec ISI)	Single Pulse=115% and 130% RMT; 115% and 130% AMT; Paired

Paper	Diagnosis	Intellectual Disability	*n* (ASD)	Mean age (years)	Gender	Medication	Site	Frequency	Intensity
									Pulse=90% RMT and 120% RMT
Oberman et al. [2014], Frontiers in Human Neuroscience	ASD	None	19	12	M	citalopram, atomoxetine, buspirone, sertraline, methylphenidate, risperidone, guanfacine	L M1	TBS	80% AMT
Oberman et al., [2014], Medical Hypotheses	ASD	None	35	36	M/F	–	L M1	TBS	80% AMT

Paper	Duration	Trains	Pulses Delivered	Sessions	Blinding	Assessment Times	Reported Effects	Side Effects
Theoret et al. [2005], Current Biology	n/a	n/a	264	1	None	Online	No group difference in RMT or response to ppTMS. Impaired corticospinal facilitation in response to finger movements viewed from the egocetnric point of view in the ASD group.	Not Indicated
Minio-Paluello et al. [2009], Biological Psychiatry	n/a	n/a	72	1	None	Online	No modulation of corticospinal excitability in response to the observation of painful stimuli affecting another individual in the Asperger's Group.	Not Indicated
Oberman et al. [2010], Frontiers in Synaptic Neuroscience	190 s (iTBS), 47 s (cTBS)	iTBS: 20 × 2 s, 10 s ISI; cTBS 1 train of 47 s	600	2 (1 cTBS, 1 iTBS)	None	Before, 5, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120 min after cTBS	Longer lasting facilitation (enhanced MEP) following iTBS in ASD Longer lasting inhibition (suppressed MEP) following cTBS in ASD No effect the following day using opposite protocol for ASD (suggesting enhanced metaplasticity)	None
Enticott et al. [2010], Developmental Medicine and Child Neurology	n/a	n/a	120	1	None	Online	Reduced intracortical inhibition in the HFA group as compared to the AS or control group	Not Indicated
Jung et al. [2012], Developmental Medicine and Child Neurology	13.3 min (PAS)	n/a	200	1	None	Before, after, 30 min after, 60 min after PAS	No LTP-like MEP facilitation in ASD (group difference significant at 60 min). No group difference in response to ppTMS.	–
Oberman et al. [2012], European Journal of Neuroscience	190 s (iTBS), 40 s (cTBS)	iTBS: 20 × 2 s, 10 s ISI; cTBS 1 train of 40 s	600	1 or 2	Data analysis (patient group)	Before, 5, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120 min after cTBS	Longer lasting facilitation (enhanced MEP) following iTBS in ASD Longer lasting inhibition (suppressed MEP) following TBS in ASD	None
Enticott et al. [2012], Biological Psychiatry	n/a	n/a	50	1	None	Online	No group difference in degree of corticospinal excitability in response to observation of single static hand stimuli. Impaired corticospinal	Not Indicated

Paper	Duration	Trains	Pulses Delivered	Sessions	Blinding	Assessment Times	Reported Effects	Side Effects
							facilitaiton in response to single hand transitive hand actions in the ASD group.	
Enticott et al. [2013], Frontiers in Human Neuroscience	n/a	n/a	50	1	None	Online	No group difference in degree of corticospinal excitability in response to single static hand stimuli or two person interactive hands.	Not Indicated
Enticott et al. [2013], Neuropharmacology	n/a	n/a	170	1	None	Online	No group difference in RMT. Heterogeneous response to paired pulse TMS in the ASD group.	Not Indicated
Oberman et al. [2014], Frontiers in Human Neuroscience	40 s cTBS	1 train of 40 s	600	1	Data analysis (patient group)	Before, 5, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120 min after cTBS	Positive linear relationship between age and duration of modulation of TBS after effects in children and adolescents with ASD. A subgroup of the ASD participants showed paradoxical facilitation.	mild headache, mild fatigue.
Oberman et al., [2014], Medical Hypotheses	40 s cTBS	1 train of 40 s	600	1	Data analysis (patient group)	Before, 5, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120 min after cTBS	Longer lasting inhibition (suppressed MEP) and greater degree of inhibition (area under the curve) following TBS in ASD. Age did not significantly contribute to the model.	None

All studies used TMS-evoked MEP amplitude as outcome measures. All Studies used Figure of 8 coils. ASD, Autism Spectrum Disorder; HFA, High Functioning Autism; PDD-NOS, Pervasive Developmental Disorder, Not Otherwise Specified; AS, Asperger's Syndrome; M1, Primary Motor Cortex; Fo8, Figure of 8 coil; ISI, Interstimulus Interval; ppTMS, Paired Pulse TMS; rTMS, Repetitive Transcranial Magnetic Stimulation; PAS, Paired Associative Stimulation; iTBS, Intermittant Theta Burst Stimulation; cTBS, Continuous Theta Burst Stimulation; RMT, Resting Motor Threshold; AMT, Active Motor Threshold; MEP, Motor Evoked Potential; LTP, Long Term Potentiation; SSRI, Selective Serotonin Reuptake Inhibitor.

Table 2

Published Reports of Therapeutic Use of TMS in ASD

Paper	Diagnosis	Intellectual Disability	*n* (ASD)	Mean age (years)	Gender	Medication	Site	Coil	Frequency	Intensity	Duration
Sokhadze et al. [2009], Journal of Autism and Developmental Disorders (RCT with waitlist control)	Autism	None	13 (8rTMS, 5 waitlist)	17	M	–	L dlPFC (5cm anterior to M1)	Fo8	0.5 Hz	90% RMT	10 min
Baruth et al. [2010], Journal of Neurotherapy (RCT with waitlist control)	ASD	2	25 (16rTMS, 9 waitlist)	14	M/F	–	L & R dlPFC (5cm anterior to M1)	Fo8	1 Hz	90% RMT	10 min
Sokhadze et al. [2010], Applied Psychophysiology and Biofeedback (Clinical trial with no control)	Autism	None	13	16	M/F	–	L dlPFC (5cm anterior to M1)	Fo8	0.5 Hz	90% RMT	10 min
Enticott et al. [2011], Journal of ECT (Single case study)	AS	None	1	20	F	None	Bilateral dmPFC (7cm anterior to M1)	H-coil	5 Hz	100% RMT	15 min
Fecteau et al. [2011], European Journal of Neuroscience (Crossover trial with sham control)	AS	None	10	37	M/F	None	L & R pars opercularis, L & R par triangularis (MRIneuronavigation), sham (central lobe midline)	Fo8	1 Hz	70% of stimulator output	30 min
Casanova et al. [2012], Translational Neuroscience (RCT with waitlist control)	ASD	None	45 (25 rTMS, 20 waitlist)	13	M/F	-	L & R dlPFC (5cm anterior to M1)	Fo8	1 Hz	90% RMT	10 min
Enticott et al. [2012], Brain Stimulation (Crossover trial with sham control)	ASD (6 HFA, 5 AS)	None	11	18	M/F	-	SMA (15%of nasion to inion anterior to Cz), L M1, Sham (M1)	Fo8	1 Hz	100% RMT	15 min
Niederhofer [2012], Clinical Neuropsychiatry (Single case study with placebo)	Autism	Not reported	1	42	F	None	M1	–	1 Hz	–	1 hr
Sokhadze et al. [2012], Applied Psychophysiology and Biofeedback (RCT with waitlist control)	ASD (36 HFA, 4 AS)	None	40 (20 rTMS, 20 waitlist)	14	M/F	–	L & R dlPFC (5cm anterior to M1)	Fo8	1 Hz	90% RMT	10 min

Paper	Diagnosis	Intellectual Disability	*n* (ASD)	Mean age (years)	Gender	Medication	Site	Coil	Frequency	Intensity	Duration
Panerai et al. [2013], Autism ((i) Crossover trial with sham; (ii) RCT with sham; (iii) crossover trial with sham iv) RCT (TMS, EHI training, TMS + EHI training))	Autism	Severe to profound	(i) 9 (ii) 17 (iii) 4 (iv) 13	(i) 14 (ii) 13 (iii) 16 (iv) 13	M	–	(i) left and right PrMC (2.5 cm anterior to M1) (ii), (iii), iv) left PrMC	Fo8	(i) 8 Hz, 1 Hz (ii) 8 Hz, 1 Hz (iii), (iv) 8 Hz	90% RMT	8 Hz 30 min, 1 Hz 15 min;
Enticott et al. [2014], Brain Stimulation (RCT with sham control)	ASD (4 HFA, 24 AS)	None	28 (15active, 13 sham)	33	M/F	Yes (39%)	dmPFC (7cm anterior to M1)	H-coil	5 Hz	100% RMT	15 min
Cristancho et al. [2014], Journal of ECT (Single case study)	Autism, Depression	Not reported	1	15	M	olanzapine, fluoxetine, guanfacine, clonazepam	(i) R DLPFC (6cm anterior to M1), (ii) L DLPFC (6cm anterior to M1)	Fo8	1 Hz	0% RMT	Variable (between 5 to 25 min)
Casanova et al. [2014], Frontiers in Human Neuroscience (Proof of feasibility study, no control)	ASD	None	18	13	M/F	–	L & R dlPFC (5cm anterior to M1)	Fo8	5 Hz	90% RMT	10 min
Sokhadze et al. [2014a], Frontiers in Systems Neuroscience (RCL with waitlist control)	ASD	None	27	14.5	M/F	–	L & R dlPFC (5cm anterior to M1)	Fo8	1 Hz	90% RMT	10 min
Sokhadze et al. [2014b], Appl Psychophysiol Biofeedback (Clinical trial with waitlist control)	ASD	None	42	14.5	M/F	–	L & R dlPFC (5cm anterior to M1)	Fo8	1 Hz	90% RMT	10 min

Paper	Trains	Pulses Delivered	Sessions	Blinding	Measures	Assessment Times	Reported Effects	Side Effects
Sokhadze et al. [2009], Journal of Autism and Developmental Disorders	15 × 10 sec, 20–30 sec ISI	150	6	None	EEG Gamma power Accuracy, RT (Kanizsa), Abberant Behavior Checklist (ABC), Social Responsiveness Scale (SRS) (Caregiver-report), Repetitive Behavior Scale-Revised (RBS-R)	Before and two weeks after treatment course	Decreased frontal EEG P3a amplitude to non-targets following TMS Decreased centro-parietal latency EEG P3b to nontarget and non-Kanizsa following TMS Decrease in gamma power for non-target and non-Kanizsa following TMS Reduced repetitive behavior (RBS-R) following TMS	–
Baruth et al. [2010], Journal of Neurotherapy	15 × 10 sec, 20–30 s ISI	150	12 (6 L, 6 R)	None	EEG Gamma power Accuracy, RT (Kanizsa), Abberant Behavior Checklist (ABC), Social Responsiveness Scale (SRS) (Caregiver-report),	Before and two weeks after treatment course	Increased EEG gamma power to targets, decrease to nontargets Reduced repetitive behavior (RBS-R) Reduced irritability (ABC)	Itching sensation at nose (5) Mild headache (1)

Paper	Trains	Pulses Delivered	Sessions	Blinding	Measures	Assessment Times	Reported Effects	Side Effects
					Repetitive Behavior Scale-Revised (RBS-R)			
Sokhadze et al. [2010], Applied Psychophysiology and Biofeedback	15 × 10 sec, 20–30 sec ISI	150	6	None	EEG event-related potentials (visual oddball) Accuracy, RT (Kanizsa) Abberant Behavior Checklist (ABC) Social Responsiveness Scale (SRS) (Caregiver-report) Repetitive Behavior Scale-Revised (RBS-R)	Before and two weeks after treatment course	Reduced error rate Increased frontal EEG P50 amplitude to targets Increased frontal EEG P50 latency to targets Decreased frontal EEG N200 latency to novel distractors Decreased parieto-occipital EEG P50 to novel distractor Increased centro-parietal EEG P50 to targets and decreased to standard distractor Centro-parietal EEG P3b amplitude increase to targets and decrease to standard distractors Centro-parietal EEG P200 increased latency to targets Reduced repetitive behaviors (RBS-R)	–
Enticott et al. [2011], Journal of ECT	30 × 10 sec, 20 sec ISI	1500	10	Double	IRI, AQ, RAADS	Before, after, and one-month after treatment course	Reduction on all measures Anecdotal reports of improvement from patient and relatives	None
Fecteau et al. [2011], European Journal of Neuroscience	1	1800	1 per site	Double	Response latency on Boston Naming Test	Before and after TMS	Increased response latency after L pars opercularis Decreased response latency after L pars triangularis	Many reported, including: Sleepy, Trouble concentrating, Improved mood, Headache, Dizziness
Casanova et al. [2012], Translational Neuroscience	15 × 10 sec, 20–30 sec ISI	150	12 (6 L, 6 R)	None	EEG event-related potentials (ERP) Accuracy, RT (Kanizsa), Abberant Behavior Checklist (ABC), Social Responsiveness Scale (SRS) (Caregiver-report), Repetitive Behavior Scale - Revised (RBS-R)	Before and two weeks after treatment course	Reduced error rate Increased frontal EEG N200 to targets Reduced frontal EEG N200 latency Increased frontal RHEEG P300 to targets Increased parietal EEG N200 to targets, Reduced repetitive behavior (RBS) Reduced irritability (ABC)	–
Enticott et al. [2012], Brain Stimulation	1	900	1 per site	Single	EEG movement-related cortical potentials Motor response time	Before and after TMS	SMA: increased early EEG component PMC: increased EEG negative slope	–
Niederhofer [2012], Clinical Neuropsychiatry	1	1200	5	Single	Abberant Behavior Checklist (ABC)	Before and after treatment course	ABC Irritability: Active 40 to 33, Sham 39 to 35, ABC Sterotypy: Active 18 to 12, Sham 16 to 15	–

Paper	Trains	Pulses Delivered	Sessions	Blinding	Measures	Assessment Times	Reported Effects	Side Effects
Sokhadze et al. [2012], Applied Psychophysiology and Biofeedback	15 × 10 sec, 20–30 sec ISI	150	12 (6 L, 6 R)	None	EEG event-related potentials (ERPs) RT Accuracy (Kanizsa)	Before and after treatment course	Reduced omission error rates Increased EEG ERN amplitude Reduced EEG ERN latency	–
Panerai et al. [2013], Autism	8 Hz 30 × 3.6 sec, 56.4 sec ISI	900	i) 3; ii) 10; iii) 5 active, 5 sham, 5 active, 5 sham; iv) 10	Double	(i), (ii), (iii), (iv) Psychoeducational Profile-Revised (PEP-R) eye-hand coordination;	Before and after treatment course	(i), (ii), (iii) improved eye-hand coordination score following lPrMC HF TMS iv) Improved eye-hand coordination score following combined TMS + EHI training compared to each technique alone	–
Enticott et al. [2014], Brain Stimulation	30 × 10 sec, 20 sec ISI	1500	10	Double	Interpersonal Reactivity Index (IRI) Autism Spectrum Quotient (AQ) Ritvo Autism-Aspergers Diagnostic Scale (RAADS) Reading the Mind in the Eyes Test (RMET) Mentalizing Animations Task	Before, after, and one-month after treatment course	Reduced social relatedness (RAADS) Reduced personal distress (IRI)	1. “light-headedness” 2. facial discomfort during rTMS
Cristancho et al. [2014], Journal of ECT	(i) 15 × 10 sec, 10–30 sec ISI (week 1), 30 × 10 sec, 10–30 sec ISI (week 2), (ii) 30–60 × 10 sec, 10–15 sec ISI	(i) 150–300, (ii) 300–600	(i) 10, (ii) 26	None	Mental status examination	Before and after treatment course	Anecdotal reports of improve mood, eye contact, interpersonal communication, verbal expression, focus, activity	Mild headaches, jaw twiching, transient dizziness
Casanova et al. [2014], Frontiers in Human Neuroscience	8 × 10 sec, 20 sec ISI	160	18	None	Aberrant Behavior Checklist, restricted Behavior Pattern, Time- domain measures of HRV (R-R interval, SDNN, RMSSD, pNN50), Frequency –domain measures of HRV (LV and HF of HRV, LF/HF ratio index), SCL	Before and 2 weeks after treatment	Increase in R-R interval, SDNN, and HF power. Significant decrease in the LF/HF ratio and SCL. Significant improvements in RBS-R and ABC rating scores.	None
Sokhadze et al. [2014a], Frontiers in Systems Neuroscience	9 × 20 sec, 20–30 sec ISI	180	18	None	Aberrant Behavior Checklist (ABC), Repetitive Behavior Scale (RBS-R), EEG event related potentials (ERPs), RT and post-error RT	Before and after	Decreased irritability and hyperactivity on the Aberrant Behavior Checklist (ABC), and decreased stereotypic behaviors on the Repetitive Behavior Scale (RBS-R). Decreased amplitude and pro-	None

Paper	Trains	Pulses Delivered	Sessions	Blinding	Measures	Assessment Times	Reported Effects	Side Effects
							longed latency in the frontal and fronto-central N100, N200, and P300 (P3a) ERPs to non-targets. Increased amplitude of P2d (P2a to targets minus P2a to non-targets) and centro-parietal P100 and P300 (P3b) to targets. Decrease in latency and increase in negativity of ERN during commission errors.	
Sokhadze et al. [2014b], Appl Psychophysiol Biofeedback	9 × 20 sec, 20–30 sec ISI	180	18	None	Aberrant Behavior Checklist, Repetitive Behavior Scale-Revised, EEG Gamma power, Theta/Beta ratio, RT and Accuracy, Post-error RT, EEG event related potentials (ERPs)	Before and after	Integrated TMS-NFB treatment enhanced the process of target recognition. Significant improvements in RBS-R and ABC rating scores. Improvement in both early and later stage ERP indices.	None

ASD, Autism Spectrum Disorder; HFA, High Functioning Autism; AS, Asperger's Syndrome; M1, Primary Motor Cortex; dlPFC, Dorsolateral Prefrontal Cortex; dmPFC, Dorsomedial Prefrontal Cortex; Fo8, Figure of 8 coil; ISI, Interstimulus Interval; rTMS, Repetitive Transcranial Magnetic Stimulation; RMT, Resting Motor Threshold.

Table 3

A summary of the challenges and recommendations for TMS research in ASD

Challenges	Recommendations
Experimental Guidelines, Oversight and Regulatory Concerns	Consensus should be achieved on consistent paradigms to be utilized across studies
	Data should be made available to others in the field to enable metaanalysis of results across studies and across centers.
	Studies should be conducted by a trained expert, and involve institutional and governmental oversight and regulation
Study Design and Placebo Effect Concerns	Researchers should adhere to gold-standard clinical trial designs including: • Use of double blind, sham-controlled designs • Use of objective primary outcome measures (behavioral or biological) • Obtainment of data on a sample large enough to achieve adequate power to test the hypothesis • Development of hypotheses based on current understanding of pathophysiology
Heterogeneity	Rigorous behavioral phenotyping of participants by reliable clinicians using standardized measures should be employed
	Samples should be stratified based on objective measures
Safety, Tolerability, and Ethical Concerns	Medication, medical history, and risk-benefit ratio should be assessed to determine the safety of the TMS protocol.
	Feasibility and tolerability of TMS procedures in younger and lower-functioning individuals should be established.
	A broad range of side effects and behavioral/cognitive outcomes should be consistently assessed.
	Side effects and behavioral/cognitive outcomes should be assessed both immediately following the TMS session and at periodic intervals to evaluate long-term effects that may not be evident immediately following the TMS administration.

ASD, Autism Spectrum Disorder; TMS, Transcranial Magnetic Stimulation.