Transcranial Magnetic Stimulation (TMS) Therapy for ASD
International Consensus Meeting May 9-10th, 2017
Scientific Discussion

Eleanor Cole wrote this report and each presenter reviewed their section.

Autism Spectrum Disorder (ASD) is the term used by the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) to describe a number of neurodevelopmental disorders, characterized by difficulties in social communication and restricted and repetitive behaviors (American Psychiatric Association, 2013). Approximately 1 in 59 children have a diagnosis of ASD, but currently there are no medications available which have shown to improve the core deficits of ASD effectively (Murphy et al., 2016). A number of behavioral interventions exist which aim to improve the social communication skills of individuals with ASD (LaGasse, 2017) but there is limited evidence to support their long-term effectiveness (Fernell, Eriksson, & Gillberg, 2013).

Repetitive transcranial magnetic stimulation (rTMS) may have the potential to alleviate difficulties experienced by individuals with ASD (Gómez et al., 2017). rTMS is a non-invasive brain stimulation technique which can be used to modulate brain activity and functional connectivity in targeted brain regions (Chervyakov, Chernyavsky, Sinitsyn, & Piradov, 2015). Brief magnetic pulses, emitted from a coil placed on the scalp, induce a transient electric current in the underlying brain region which can potentiate or disrupt ongoing brain activity. When rTMS pulses are delivered at a low-frequency (≤1Hz), rTMS results in reduced activation in the targeted brain region whereas high-frequency stimulation (≥5Hz) results in increased activation in the targeted brain area (Chervyakov et al., 2015). High-frequency rTMS delivered to the left dorsolateral prefrontal cortex (dlPFC) is an FDA-approved treatment for treatment-resistant unipolar depression (George, Taylor, & Short, 2013; Perera et al., 2016). rTMS protocols have been shown to be effective in treating other conditions including chronic pain, negative symptoms of schizophrenia and chronic motor stroke (Lefaucheur et al., 2014). Initial rTMS clinical trials in individuals with ASD have shown that rTMS can reduce social difficulties (Enticott et al., 2014; Enticott, Kennedy, Zangen, & Fitzgerald, 2011) and repetitive stereotyped behaviors (Casanova et al., 2014; Sokhadze et al., 2009; 2010).

A new form of rTMS known as theta burst stimulation (TBS) requires shorter durations of stimulation and lower stimulation intensities (Hong et al., 2015; Wu, Shahana, Huddleston, Lewis, & Gilbert, 2012). TBS involves administering TMS pulses in bursts of three, delivered at a frequency of 50Hz with an inter-burst interval of 200ms (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005; Oberman, Edwards, Eldaief, & Pascual-Leone, 2011). TBS can be delivered in a continuous fashion (cTBS), usually for 20 seconds or 40 seconds, to reduce activation in the underlying brain area. Alternatively, TBS can be applied intermittently (iTBS), usually involving twenty repeats of two seconds of TBS at a rate of 0.1 Hz, to increase activation in the targeted cortical region (Oberman et al., 2011). iTBS has shown to be more effective than traditional rTMS, producing equivalent antidepressant responses in 3 minutes compared to 37 minutes of traditional rTMS (Blumberger et al., 2015). Additionally, the optimal stimulation intensity for TBS is lower than the stimulation intensity used for traditional rTMS (Hong et al., 2015b). The

shorter duration of stimulation sessions, as well as the lower stimulation intensities, mean that TBS has the potential to be an advantageous therapeutic option for individuals with ASD.

The promising emerging evidence that rTMS (including TBS) may be an effective novel treatment method for the core symptoms of ASD has led leading experts in the field to gather annually, with the aim of establishing consensus on rTMS protocols for ASD therapy. The international consensus meeting held on the 9th and 10th May 2017 was organized and supported by the Clearly Present Foundation with additional support from Neuronetics and The Medical University of South Carolina. Dr. M. Frampton Gwynette was the first to give a presentation, outlining his findings using rTMS as a means potentially to alleviate both core symptoms and comorbid depressive symptoms in individuals with ASD. There is a high incidence of comorbid depression in ASD, with data suggesting as many as 70% of adults with ASD have experienced at least one major depressive episode (Lugnegård, Hallerbäck, & Gillberg, 2011). Traditional first-line treatments for depression (serotonin-selective re-uptake inhibitors) are less effective in individuals with ASD and can worsen core symptoms of ASD (Kolevzon, Mathewson, & Hollander, 2006; Williams, Brignell, Randall, Silove, & Hazell, 2013). Although rTMS is an effective treatment for depression (Gaynes et al., 2014; George et al., 2013), no previous studies have investigated the effectiveness of rTMS in treating comorbid depression in individuals with ASD. Dr. Gwynette and colleagues aim to investigate the effectiveness of daily (weekday) high-frequency (10Hz) rTMS applied to left dorsolateral prefrontal cortex (dlPFC) in alleviating comorbid depressive symptoms as well as core symptoms of ASD. A total of 25 stimulation sessions are administered over 5 weeks. The preliminary findings support the safety and tolerability of rTMS in adults with ASD. Reductions in both depressive symptoms and improvements in social functioning have been observed but, due to the current small sample size, these data are preliminary.

Scott Jackson then discussed the potential of the posterior superior temporal sulcus (pSTS) as a target for iTBS in autism and the use of multimodal measurements of social cognition to assess outcomes following iTBS. The pSTS is a cortical area which has been shown to play a role in various aspects of social cognition such as face processing, speech processing and theory of mind (Hein & Knight, 2008). Hypoactivation of the pSTS has been reported in ASD during face processing (Pierce, 2001), eye gaze processing (Pelphrey, Morris, & McCarthy, 2005) and mentalizing tasks (Castelli, Frith, Happé, & Frith, 2002). These data make pSTS a potential target for rTMS therapy aimed at improving social cognition deficits associated with ASD. Social cognition is usually measured using behavioral tasks (Pinkham et al., 2014). However, electroencephalography (EEG) and eye-tracking can provide implicit measures of social cognition and therefore could potentially provide more sensitive measures of rTMS-induced improvements in social cognition. The N170 and P300 elements of the EEG waveform are thought to reflect different elements of social-cognitive processing. The N170 is considered an index of early neural responses to social stimuli and the P300 is thought to indicate updating social information in response to changes in social context (Donchin & Coles, 1988; Gray, Ambady, Lowenthal, & Deldin, 2004; Meaux, Roux, & Batty, 2014) The N170 and P300 both have been shown to be atypical in individuals with ASD (Jeste & Nelson, 2009; Kang et al., 2017). Similarly, eye-tracking can provide an implicit measure of social processing as reduced duration of fixation on the eyes is characteristic of ASD (Dalton, Nacewicz, Alexander, & Davidson, 2007; Klin, Jones, Schultz, Volkmar, & Cohen, 2002) and thought to impair abilities to process socially relevant facial cues (Tanaka & Sung, 2016). Consequently, both fixation patterns and EEG measures could provide

more sensitive measures of rTMS-induced improvements in social functioning than behavioral social cognition assessments.

Measurements of social functioning were discussed further by Dr. Adam Naples who highlighted that the majority of neuroimaging studies use tasks that are passive rather than interactive like real-life social interactions. Dr. Naples and colleagues have investigated neural correlates of social functioning using interactive tasks. In the first study presented, EEG recordings were made when participants viewed faces which responded to their eye gaze (Naples, Wu, Mayes, & McPartland, 2017). Two event-related potentials (ERPs); N170 and P300, were largest when participants were engaged in reciprocal eye contact. The magnitude of these ERPs in response to reciprocal eye contact was inversely related to the level of participants' autistic traits. In another experiment, Dr. Naples and colleagues used EEG to measure the brain activity of pairs of subjects while they were playing a competitive game against each other, compared to when playing the same game against a computer (Rolison, Naples, Rutherford, & McPartland, 2017). EEG components reflecting reward processing were, overall, larger when participants were playing against a human competitor compared to a computer. However, individuals with higher levels of autistic traits showed reduced magnitude of these ERPs when interacting with a human competitor. These data demonstrate that EEG can provide objective, implicit measures of social brain functioning which vary according to the level of autistic traits displayed. The ERPs identified in these studies could be used as objective outcome measures of social functioning following rTMS alongside clinical assessments, which are subjective.

Professor Peter Enticott described his rTMS clinical trials in ASD. In the first trial, high- frequency stimulation (5Hz) was applied to the dorsomedial prefrontal cortex (dmPFC) bilaterally (Enticott et al., 2014). The dmPFC is considered a core region of the 'mentalizing system' which is a network of brain regions that display increased activation when inferring the internal states of others (Frith & Frith, 2006). Reduced dmPFC activation has been reported in individuals with ASD during mentalizing tasks (Castelli et al., 2002; Happé et al., 1996; Kana, Keller, Cherkassky, Minshew, & Just, 2009), although not consistently (Assaf et al., 2013; Kana, Libero, Hu, Deshpande, & Colburn, 2014; Kirkovski, Enticott, Hughes, Rossell, & Fitzgerald, 2016). In this trial, participants received 16 stimulation sessions across 4 weeks. Each stimulation session was 30 minutes long, composed of 60 trains of ten seconds of stimulation with twenty second intervals between each pulse train. Five stimulation sessions were received per week in the first two weeks (daily weekday sessions) and three sessions per week were given in the last two weeks (Monday, Wednesday, Friday). At the end of the stimulation course, the Social Responsiveness Scale (SRS) and the Ritvo Autism-Aspergers Scale Revised (RAADS-R) indicated significant improvements in social functioning which were sustained one month after completion (Enticott et al., 2014). However, scores on these clinical assessments three and six months after treatment did not significantly differ to baseline. It is possible that a stimulation course of longer duration or additional maintenance treatments are required to observe sustained improvements. Alternatively, different cortical targets may improve clinical outcomes. Professor Enticott outlined an ongoing clinical trial investigating the efficacy of both iTBS applied to right temporoparietal junction (rTPJ) and iTBS applied to dmPFC in reducing social communication difficulties associated with ASD. The TPJ is another core region of the mentalizing system and hypoactivation of the TPJ has also been reported in individuals with ASD (Kana et al., 2014; Murdaugh, Nadendla, & Kana, 2014; Pantelis, Byrge, Tyszka, Adolphs, & Kennedy, 2015).

Participants in this ongoing trial will receive iTBS to one of these cortical sites and after six months receive stimulation to the alternative cortical site.

Dr. Natalia Albein-Urios discussed the potential of high-definition transcranial direct current stimulation (HD-tDCS) to improve cognitive flexibility and emotion regulation in ASD. Impairments in cognitive flexibility are well documented in ASD, and are thought to contribute to key clinical features including repetitive behaviours, restricted interests, and difficulties in adapting to social contexts (Geurts et al., 2009). In addition, many of the symptoms of ASD are considered difficulties in emotional self-regulation which is described as the ability to control one's behaviour, particularly when experiencing intrusive thoughts and negative emotions, and is thus essential for adaptive social interactions and daily functioning (Mazefsky, 2015). Brain systems have been identified as allowing both cognitive flexibility and emotional self-regulation. Specifically, the ventrolateral prefrontal cortex has been shown to play an important role in these two abilities (Levy & Wagner, 2011; Morawetz et al., 2016). Dr. Albein-Urios is currently conducting a clinical trial using HD-tDCS over the ventrolateral prefrontal cortex to investigate potential improvements in cognitive flexibility and emotion regulation in an ASD population.

Dr. Nicolaas Puts outlined the role of ***γ***-aminobutyric acid (GABA) in processing sensory information, the potential role of GABA in autism and possible roles of TMS. 95% of parents with a child with autism report that their child shows abnormal sensory processing (Rogers & Ozonoff, 2005), with tactile difficulties being common. GABA plays an important role in shaping the neuronal response to tactile stimulation (Juliano, Whitsel, Tommerdahl, & Cheema, 1989; Whitsel et al., 1989) and several studies have shown that the GABA system may be different in ASD (Cellot & Cherubini, 2014; Coghlan et al., 2012; Enticott et al., 2013). Therefore, it is possible that differences in the GABA system give rise to altered tactile function in ASD, which in turn may lead to sensory, social, and communicative issues. Dr. Puts and colleagues have developed a battery of tasks to objectively measure tactile processing (Puts, Edden, Wodka, Mostofsky, & Tommerdahl, 2013; Zhang, Tannan, Holden, Dennis, & Tommerdahl, 2008) and have found abnormal tactile thresholds in children with ASD (Puts et al., 2016). The relationship between abnormal tactile processing and GABA levels were investigated using Magnetic Resonance Spectroscopy (Mullins et al., 2014). The abnormal tactile thresholds corresponded with reduced GABA levels in the sensorimotor cortex (Puts et al., 2016). These data link differences in GABA function to altered sensory function in ASD (Puts et al., 2016). TMS techniques could be used to 1) elucidate the specific GABA mechanisms underlying these abnormalities (e.g. using paired-pulse paradigms which are considered a measure of GABA mediated cortical inhibition) or, 2) rTMS could potentially be used as an intervention to modulate GABA function and therefore change tactile perception.

Dr. Ali Jannati discussed hyper-plasticity in individuals with ASD and factors which contribute to inter-individual differences in responses to TMS protocols. Previous studies have shown enhanced responses to TBS in individuals with ASD, indicating abnormal cortical plasticity (Oberman et al., 2012). However, there is considerable inter-individual variability in response to TMS protocols(Guerra, López-Alonso, Cheeran, & Suppa, 2017), including TBS (Vallence et al., 2015). Such variability can limit the use of TMS protocols. One approach to address this issue is to use data-driven methods such as cluster analysis to identify subgroups of individuals with distinct patterns of response (Jannati, Block, Oberman, Rotenberg, & Pascual-Leone, 2017). Comparing potential covariates between the subgroups can identify important predictors of

response, including active motor threshold and polymorphism in the brain-derived neurotrophic factor (BDNF) gene (Cheeran et al., 2008; Jannati et al., 2017). Dr. Jannati and colleagues found that after controlling for such factors, responses to cTBS could differentiate between individuals with and without ASD with high sensitivity and specificity. Identifying the demographic, genetic, and neurophysiological factors that influence the reproducibility of TBS responses could enhance the potential use of rTMS in ASD.

Hyperplasticity in ASD was discussed further by Dr. Meng-Chuan Lai who presented two studies taking place at the Centre of Addiction and Mental Health (CAMH) at the University of Toronto, Canada, that he collaborates on with Drs. Pushpal Desarkar and Stephanie Ameis. The first is an ongoing TMS-EEG study, led by Dr. Pushpal Desarkar at CAMH. The preliminary results from this work suggest that excessive cortical plasticity in adults with ASD is present in both motor cortex and dlPFC. The ongoing study examines whether a single session of 20Hz rTMS (6000 pulses) delivered to the motor cortex may improve plasticity. These data highlight cortical plasticity differences which should be taken into consideration when designing rTMS treatment protocols and that TMS may have a role in targeting/treating hyper-plasticity, which could serve as a potential biomarker in ASD. The second project discussed at the meeting is led by Dr. Stephanie Ameis at CAMH who recently completed recruitment for the largest randomized, double-blind clinical trial that has ever been undertaken using rTMS in autism (including 40 individuals with ASD). Her study examined the feasibility and therapeutic potential for using a 4-week high-frequency rTMS protocol to improve executive function deficits in 16-35 year olds with ASD. Recruitment for this study is complete and the study is currently being written up for publication early in 2019.

Professor Manual Casanova discussed the potential benefit of developing other neuromodulation techniques to overcome some of the limitations of rTMS. Professor Casanova described four different ways to modulate the activity of the brain: 1) the induction of electrical activity by a varying magnetic field (e.g. in rTMS), 2) passing an electric current through the brain, 3) training the brain by watching a real-time display of its activity, and 4) brainwave entrainment. Professor Casanova explained that a major problem of some of these techniques, including rTMS, is that they operate at an energy level that is several magnitudes higher than the physiologic activity of the brain. As a result, neuromodulation methods that use high amplitude stimulation (such as rTMS) may have effects that are nonlinear and non-physiological (Hanakawa et al., 2009). In comparison, transcranial direct current stimulation (tDCS) uses a low current and is thought to alter the resting neuronal membrane potentials, rather than cause neuronal firing by neuronal membrane depolarization (Pelletier & Cicchetti, 2015). However, inconsistent outcomes have been reported following tDCS (Kim et al., 2014; Ramaraju, Roula, & McCarthy, 2018). Small changes in electrode placement (Ramaraju et al., 2018) as well as the dimensions of the electrodes and the electrolyte-soaked sponges (Reinhart, Cosman, Fukuda, & Woodman, 2017) have been shown to alter the effects of tDCS. In addition, the effects of inter-individual neuroanatomical variability, such as gyrification, on tDCS outcomes have not been modelled (Berker, Bikson, & Bestmann, 2013). Professor Casanova argued that alternative methods for neuromodulation of brain activity are needed that work within the physiologic parameters of the brain. The potential benefit of further developing brain entrainment techniques, methods which entrain the activity of the brain to a periodic stimulus, were discussed (Huang & Charyton, 2008; Will & Berg, 2007). These periodic stimuli are usually acoustic or visual but electromagnetic radiation may also

provide a means of brain entrainment (Gherardini, Ciuti, Tognarelli, & Cinti, 2014; Mohammed, Fahmy, Radwan, & Elsayed, 2013).

Finally, Professor James McPartland presented the aims of the Autism Biomarkers Consortium for Clinical Trials (ABC-CT). The ABC-CT aims to evaluate possible biomarkers for social communication deficits in ASD to be used in clinical trials. Current biomarkers for social communication deficits show inconsistent results (Li, Karnath, & Xu, 2017; Papagiannopoulou, Chitty, Hermens, Hickie, & Lagopoulos, 2014; Walsh, Elsabbagh, Bolton, & Singh, 2011; Xu, Li, & Zhong, 2015). The inconsistent evidence likely stems from the small sample sizes and heterogeneous participant populations in ASD studies, as well as limited knowledge as to how these biomarkers vary within the typical population. Professor McPartland and colleagues are running a multi-site trial investigating biomarkers for social-communicative functioning in children with ASD using a range of methods including EEG, eye-tracking, and blood samples. Biomarkers will be assessed on their validity, reliability, sensitivity and feasibility. Data is being collected between October 2016 and May 2019. The hope is to identify reliable, reproducible biomarkers for social-communicative functioning which can be used to objectively measure social communicative outcomes in ASD clinical trials, including rTMS trials.

Protocol discussion

In the final part of the meeting, researchers considered possible rTMS protocols for ASD therapy. This discussion led to the conclusion that three potential stimulation sites, in particular, warranted further investigation for rTMS therapy in individuals with ASD. These stimulation sites were: the right inferior frontal gyrus (IFG), the right temporoparietal junction/posterior superior temporal sulcus (TPJ/pSTS) and the left dorsolateral prefrontal cortex (dlPFC). The TPJ and pSTS occupy very similar areas of the cortex and some studies have combined these areas into one region (Aichhorn, Perner, Kronbichler, Staffen, & Ladurner, 2006; Pantelis et al., 2015). Other studies have only referred to one of these sites but very similar coordinates have been reported for both areas across different studies (Lee & McCarthy, 2016; Schultz, Friston, O'Doherty, Wolpert, & Frith, 2005). Right TPJ and right pSTS are considered to play important roles in a variety of social tasks (Carter, Hodgins, & Rakison, 2011) including mentalizing tasks (Pantelis et al., 2015). Hypoactivation has been reported in both these areas in individuals with ASD (Ciaramidaro et al., 2015; Koldewyn, Whitney, & Rivera, 2011; Pantelis et al., 2015). Low-frequency (inhibitory) rTMS protocols applied to pSTS/TPJ in neurotypical individuals have resulted in disrupted mentalizing abilities and impaired action processing (Bardi, Six, & Brass, 2017; Grossman, Battelli, & Pascual-Leone, 2005; Schuwerk, Langguth, & Sommer, 2014; van Kemenade, Muggleton, Walsh, & Saygin, 2012). Consequently, it is predicted that high-frequency stimulation applied to the right TPJ/pSTS would improve mentalizing abilities and social functioning in individuals with ASD.

Low-frequency stimulation delivered to the right IFG would be predicted to reduce social functioning deficits and language processing difficulties in ASD. Neuroimaging studies have shown atypical structure, function and connectivity of right IFG with ASD (Cole, Barraclough & Enticott, 2018; Kosaka et al., 2010). Low-frequency rTMS over the right IFG has been used in stroke patients with non-fluent aphasia to improve naming skills (Naeser et al., 2012). Although ASD is associated with difficulties in higher-level language comprehension and communication, rather than naming skills (Groen, Zwiers, van der Gaag, & Buitelaar, 2008), it is thought that atypical development of the brain areas underlying basic language skills (e.g. naming) contribute

to these higher-level deficits (Fecteau, Agosta, Oberman, & Pascual-Leone, 2011). John Elder Robinson has written a book about improvements in social functioning he experienced following 1Hz stimulation to right IFG (Robinson, Pascual-Leone & Just, 2017). Additionally, the founder of the Clearly Present Foundation, Kim Hollingsworth Taylor, has reported the improved social functioning she observed in her son Nick after a specific type of rTMS, continuous theta burst stimulation (cTBS), to the right IFG (https://clearlypresent.org/tms-for-autism/). These individual cases highlight the potential of right IFG as an effective stimulation site for rTMS.

Lastly, high-frequency stimulation applied to the left dlPFC may improve executive functioning and alleviate comorbid depressive symptoms in ASD. Executive function deficits (Griebling et al., 2010; Sawa et al., 2013) and prefrontal cortex dysfunction (Courchesne et al., 2011; Gilbert, Bird, Brindley, Frith, & Burgess, 2008; Morgan et al., 2010, 2012) are well reported in ASD. High-frequency rTMS over left dlPFC is an FDA-approved treatment for treatment-resistant depression and has shown to improve executive functioning. The initial work of Dr. Gwynette and colleagues suggests that left dlPFC stimulation could be an effective method to alleviate both comorbid depressive symptoms and core symptoms of ASD. An additional rTMS clinical trial targeting left dlPFC is ongoing, investigating whether 20 Hz rTMS improves executive functioning deficits in ASD (Ameis et al., 2017). Somewhat paradoxically, low-frequency stimulation applied to left dlPFC has also been shown to improve behaviors and neural correlates associated with ASD, particularly reduced repetitive behaviors (Baruth et al., 2010; Carter & O'Reardon, 2014; Casanova et al., 2012; Sokhadze et al., 2009). Therefore, there may be clinical benefits to both low- and high-frequency stimulation applied to left dlPFC depending on the symptom profile of the individual.

Limitations for TMS in ASD

Although existing data from TMS studies in ASD are promising, larger clinical trials which are double-blind and sham-controlled are required in order to determine the efficacy of rTMS as a potential therapy for individuals with ASD. The existing rTMS studies in ASD have used relatively small sample sizes, the majority have not included a sham control condition and the clinical assessments used as outcome measures have usually not been conducted by blinded raters. The heterogeneous nature of ASD, with the lack of defined neurological subtypes, provides an additional barrier to rTMS development and studies to date have made minimal efforts to reduce heterogeneity in their participant samples. It is likely that the optimal stimulation site for rTMS therapy will differ depending on the behavioral characteristics displayed by the individual such as the presence or lack of repetitive behaviors, sensory hypersensitivies or hyposensitivities. In addition to the identification of the optimal stimulation site, the optimal stimulation parameters also need to be determined in order to maximize the clinical efficacy of rTMS therapy for ASD. The stimulation parameters include factors such as stimulation intensity, the number of magnetic pulses delivered and the inter-session interval (Daskalakis, 2014; George et al., 2014; Schulze et al., 2017). Stimulation parameters for rTMS therapies are selected to maximize the desired neuronal changes. The majority of data regarding neurophysiological changes induced by rTMS have been collected using neurotypical individuals (Chervyakov et al., 2015; Chung, Rogasch, Hoy, & Fitzgerald, 2015; Siebner, Hartwigsen, Kassuba, & Rothwell, 2009; Terao & Ugawa, 2002) and therapeutic rTMS parameters have mostly been refined for the treatment of depression (George et al., 2013; Perera et al., 2016). Individuals with ASD have been shown to exhibit aberrant cortical plasticity mechanisms (Oberman et al., 2010, 2012; Pedapati et al., 2016) and some studies have

reported reduced levels of cortical inhibition (Enticott, Rinehart, Tonge, Bradshaw, & Fitzgerald, 2010; Enticott et al., 2013; Gaetz et al., 2017). Consequently, the known neurophysiological effects induced by TMS protocols and the optimal treatment parameters developed for the treatment of depression may not apply to individuals with ASD. Further research is required in order to optimize stimulation parameters for the treatment of ASD.

Conclusion

Existing data from rTMS studies in ASD suggest that rTMS may be a promising method to alleviate both core symptoms of ASD as well as common comorbid conditions such as depression. The identification of reliable biomarkers of social functioning in ASD will aid outcome measures following rTMS therapy. The existing rTMS studies in ASD are limited by the small sample sizes, the minimal number of sham-controlled trials and the lack of double-blind clinical assessments. The heterogeneity of ASD adds further complexity to the development of rTMS therapy. Larger, double-blind, sham controlled trials in subgroups of individuals with ASD displaying certain behavioral or neural characteristics are required to determine the efficacy of rTMS therapy. TBS has the potential to be a preferable option to traditional rTMS for individuals with ASD due to the shorter duration of stimulation sessions and lower stimulation intensities required. However, further research investigating the optimal stimulation parameters for these TMS protocols for individuals with ASD is required to account for neural differences such as atypical cortical plasticity and cortical inhibition.

Attendees

Natalia Albein-Urios, PhD, Deakin University, Melbourne, Australia
Manuel Casanova, MD, University of South Carolina School of Medicine
Eleanor Cole, PhD, Stanford University
Glen Elliot, PhD, MD, Children's Health Council, Palo Alto, California
Peter Enticott, PhD, Deakin University, Melbourne, Australia
Sunday Francis, University of Minnesota
M. Frampton Gwynette, MD, Medical University of South Carolina
Kim Hollingsworth Taylor, Clearly Present Foundation
Scott Jackson, PhD, Yale University
Ali Jannati, MD, PhD, Harvard University
Meng-Chuan Lai, MD, PhD, University of Toronto, Canada
Jennifer Levitt, MD, University of California Los Angeles
James McPartland, PhD, Yale University
Stewart Mostofsky, MD, John Hopkins University
Adam Naples, PhD, Yale University
Lindsey Oberman, PhD, Uniformed Services University of the Health Sciences
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