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Transcranial magnetic stimulation (TMS) therapy for autism: an international consensus conference held in conjunction with the international meeting for autism research on May 13th and 14th, 2014

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The Centers for Disease Control and Prevention currently estimate the prevalence of Autism Spectrum Disorder (ASD) in the U.S. at 1:68 children (Baio, 2014). Despite decades of research across multiple levels of analysis, we currently lack a reliable biomarker that may facilitate diagnosis, illuminate pathophysiology, or guide treatment. The development of novel treatment strategies for ASD will require efforts for better clinical characterization, identification of more homogeneous subgroups for studies, and improved understanding of underlying pathophysiology. There is growing support for early intensive interventions in this population (Reichow, 2012). Pharmacological treatments have been shown to be effective in treating some of the common secondary and comorbid features of ASD (Hampson et al., 2012), but there is currently no pharmacotherapy conclusively shown to improve the core symptoms (Oberman, 2012).

Recently a number of investigators have begun to explore the use of transcranial magnetic stimulation (TMS) as a tool to characterize ASD pathophysiology, and to test its therapeutic potential. TMS is a safe and well-tolerated method for non-invasive focal cortical stimulation where small intracranial electrical currents are generated by a rapidly fluctuating extracranial magnetic field. In an effort to share recent progress in the use of TMS in ASD, promote collaboration across laboratories, and establish consensus on parameters that may be useful for the study of pathophysiology and the potential treatment of ASD, leading experts in the field gathered in Atlanta, GA on May 13th and 14th 2014 for the “Transcranial Magnetic Stimulation (TMS) Therapy for Autism Consensus Conference” organized and supported by the Clearly Autism Foundation with additional support from Neuronetics, Inc. and Autism Speaks.

Alvaro Pascual-Leone began the conference by discussing the basic mechanisms and safety of TMS in clinical populations. TMS can be applied in single pulses to investigate corticospinal excitability, pairs of pulses to study intracortical inhibition and facilitation, and repeated trains of TMS (rTMS) to both to study and therapeutically modulate excitability and plasticity in a number of neurological and psychiatric conditions (Kobayashi and Pascual-Leone, 2003). The effects of rTMS can be expected to differ considerably by virtue of varying parameters of stimulation and knowledge of underlying symptom pathophysiology. TMS is considered quite safe if applied within current safety guidelines; however, it does pose some risk for adverse side-effects (Rossi et al., 2009). Though relatively few patients with ASD have participated in TMS protocols, the frequency and quality of side-effects shown thus far approximates that seen in the general population (Oberman et al., 2013). As with any other condition, factors including medications and medical history need to be assessed when determining risk for an individual. There are currently no identified ASD-specific risk factors for TMS-induced adverse effects. Even though ASD can be associated with an increased risk for seizures, in TMS studies to date, there is no evidence of increased epileptogenic risk in ASD when safety guidelines and recommendations are followed.

Manuel Casanova then provided a targeted review of the literature on the pathophysiology of ASD. Postmortem studies have shown evidence of abnormalities of neuronal migration in the brains of individuals with ASD (Bailey et al., 1998), which include displaced neurons manifesting as focal cortical dysplasias in a majority of individuals with ASD (Casanova...
et al., 2013). Morphometric analysis of
cells within the malformed cortex has sug-
gested a reduced number of interneurons
(Casanova et al., 2013). This is consistent
with previous reports of abnormalities in
ASD within the peripheral cortical mini-
column neuropil space, the compartment
where most inhibitory cells are located
(Casanova et al., 2002). Both EEG and
vibrotactile studies corroborate a deficit
of cortical lateral inhibition (Keita et al.,
2011; Puts et al., 2014). He proposed that
this deficit could account for the seizures
and sensory abnormalities often reported
in ASD.

Lindsay Oberman discussed the use
of TMS as an investigative device to
study cortical excitability and plasticity in
ASD. These studies show that a num-
ber of basic mechanisms and circuits are
atypical while other measures appear to
be normal (see Oberman et al., 2013).
Specifically, motor thresholds and base-
line motor-cortical excitability measures
appear to be normal. There is hetero-
genesis in the response to paired-pulse
paradigms with impaired inhibition in
some individuals, typical response in oth-
ers, and paradoxical facilitation in another
subgroup. Studies exploring corticospinal
plasticity mechanics, using two different
rTMS protocols [theta burst stimula-
tion (TBS) and paired associative stimula-
tion (PAS)], have shown abnormalities.
However, the direction of the abnormal-
ity is unclear with TBS studies showing
enhanced response (Oberman et al., 2012)
and PAS showing reduced response (Jung
et al., 2013). There are a number of open
questions related to the use of TMS as
an investigative device in ASD includ-
ing developmental effects, effects related
to intellectual disability and functioning,
and what underlying mechanisms are driv-
ing the observed heterogeneity in the
population.

Peter Enticott discussed the efficacy
of rTMS as a therapeutic intervention
in ASD. A number of studies using low-
frequency rTMS in an effort to en-
hance cortical inhibitory tone in dor-
solateral prefrontal cortex have resulted in
improvements in EEG indices of
attention, information processing, and
error monitoring as well as behavioral
improvements in repetitive behaviors
and irritability (Sokhadze et al., 2014).

Low-frequency stimulation to left pars
triangularis resulted in improved object
naming in a single session study (Fecteau
et al., 2011). High-frequency stimula-
tion, designed to enhance excitability, has
suggested improvements in self-reported
social relating and social anxiety follow-
ing medial prefrontal cortex stimulation
(Enticott et al., 2014) and significant
improvements in eye-hand coordina-
tion following premotor stimulation
(Panerai et al., 2013). Although an emerg-
ing literature, these studies collectively
provide support for the potential effi-
cacy of rTMS in ASD (Oberman et al.,
2013). However, the small study samples,
lack of blind assessments, and limited
use of control or comparison conditions
limit the interpretation of these early
investigations.

James McCracken concluded the con-
ference by discussing key factors to con-
sider when designing clinical trials for
ASD. These factors included identification
of valid and reliable endpoints, incorpora-
tion of blind assessments, need for cred-
able control conditions, establishment of
effective stimulation parameters, need to
relate changes in electrophysiologic end-
points to functional change, and identi-
fication of biomarkers that can be used to
reduce the heterogeneity of the sam-
pal and stratify participants to treatment
strategies that are best matched to their
underlying pathophysiology. To this end,
those present discussed the utility of de-
veloping functional imaging and TMS indices
as potential standardized biomarkers and
the need for larger, multisite trials to
establish validity of these measures across
development and levels of functioning
and reliability of these measures across
centers.

At the conclusion of the conference,
there was enthusiasm for the potential use
of TMS in ASD. Further work is nec-
essary to achieve consensus on the key
factors discussed by Dr. McCracken, but
the expertise and commitment is present
in the research and clinical community
to work toward the end goal of design-
ing and implementing large-scale, double
blind, multisite clinical trials of rTMS for
ASD in the near future. Those present
committed to collaborate across labora-
tories to establish mutually agreed upon
protocols and to meet again within 1 year.

AUTHOR CONTRIBUTIONS
Lindsay M. Oberman, Peter G.
Enticott, Manuel F. Casanova, Alvaro
Pascual-Leone, and James T. McCracken
contributed to the organization of the
conference, were invited speakers to the
conference, and lead the discussion dur-
ing the conference. Alexander Rotenberg
contributed to the organization of the
conference, and the discussion during the
conference. All authors contributed to the
writing of the manuscript.

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Conflict of Interest Statement: Alvaro Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Axilum Robotics, Magstim, Neuroelectrics, and Neosync; and is listed as an inventor on several issued and pending patents on the real-time integration of transcranial magnetic stimulation (TMS) with electroencephalography (EEG) and magnetic resonance imaging (MRI). Alexander Rotenberg is listed as an inventor on a patent for apparatus and method of use of TMS in epilepsy. He is a co-founder of Neuromotion Inc. This conference was supported by the Clearly Present Foundation, Autism Speaks, and Neuronetics, Inc. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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