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Editorial

# Transcranial Magnetic Stimulation, Neuroplasticity and Autism Spectrum Disorder

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Autism Spectrum Disorder (ASD) is a complex neuro developmental condition characterized by persistent deficits in social interaction and communication and stereotyped patterns of behaviour, interests and activities (DSM-5) [1]. Data from recent epidemiological research indicate that the prevalence of ASD is rising and the most recent fact that it was found in 1 in 88 children [2] does not only make ASD the most prevalent of developmental disorders, but also makes the condition more common than schizophrenia. Thus, the social, clinical and financial burden of ASD is astounding. Almost seven decades have elapsed since Leo Kanner's first description of this condition, yet the exact cause of ASD remains unknown and successful treatment remains elusive. Thus, there is an urgent need to explore novel and effective treatment options for ASD. Aberrant Neuroplasticity and Autism Spectrum Disorder

Neuroplasticity is the ability of neurons to alter and re-organize their anatomical and functional connectivity in response to environmental inputs. Long Term Potentiation (LTP) and Long Term Depression (LTD), two prototypes of neuroplasticity, involve increased and decreased synaptic efficacy, respectively [3]. Several lines of evidence have consistently indicated an abnormal neuroplasticity in ASD. Mutations in a number of genes involved in synaptic development and plasticity such as Neuroligin 3 and 4 (synaptogenesis) [4], CNTNAP2 (neural migration) [5]; SHANK3 (dendritic development) [5], c3orf58, NHE9, PCDH10 (critically involved in synaptic development) [6] have been linked with ASD. Several animal models of ASD with diverse measures have also demonstrated abnormally excessive neuroplasticity. For example, the valproic acid (VPA) rat model of autism demonstrated cellular hyper-plasticity indexed by significantly increased Long Term Potentiation (LTP) in VPA treated rats [7,8]. Further, it has been suggested that inhibition-excitation balance is the key determinant of adult neuroplasticity and an imbalance will create a state of aberrant neuroplasticity. In this regard, converging results indicate an increased excitation/inhibition ratio in ASD brain. It has been found that excitatory glutamate receptors (N-methyl-D-Aspartate or NMDA and metabotropic glutamate receptor 5) are over-expressed and expression of inhibitory Gamma Aminobutyric Acid A ($GABA_A$) and $GABA_B$ receptors are reduced in ASD brain [9].

Previous research suggested that aberrant neuroplasticity may play a critical role in the pathogenesis of ASD [10,11]. An optimum level of plasticity is necessary for optimal performance and this process essentially involves keeping excitability within a normal physiological range [12]. Despite findings in animal models, evidence of aberrant neuroplasticity in human subjects has been largely indirect and these mainly came from a handful of neuroimaging and neurophysiology studies [13]. More direct evidence of aberrant neuroplasticity in human ASD subjects recently came from Transcranial Magnetic Stimulation (TMS) studies.

## Transcranial magnetic stimulation and neuroplasticity in autism spectrum disorder

TMS has rapidly evolved to become a widely used, safe and non-invasive neuroscientific tool to investigate a variety of neurophysiological processes, including neuroplasticity. Theta-Burst Stimulation (TBS) is a safe and well-established non-invasive repetitive Transcranial Magnetic Stimulation (rTMS) paradigm to study neuroplasticity in humans [14]. TBS comprises of 2 well established paradigms: continuous (cTBS) or intermittent (iTBS). TBS paradigm involves the delivery of a burst of 3 pulses at 50Hz (i.e. 20 ms between stimuli) at intervals of 200 ms (i.e. 5 Hz) for a total number of pulses of 600. In cTBS, the delivery of these pulses is continuous for 40 sec. In iTBS paradigm, the delivery of these pulses is in 2 sec trains of TBS repeated every 10 sec for a total of 190 sec [14]. cTBS results in long lasting suppression of cortical activity that is analogous to LTD and iTBS results in long lasting enhancement that is analogous to LTP [13,15].

Asperger Disorder (AD) is a subtype of ASD that has been shown to be associated with aberrant neuroplasticity using TBS paradigms. One study found among 4 adult subjects with AD that both LTP- and LTD-like activities in the motor cortex (M1) were excessively enhanced in response to iTBS and cTBS, respectively, compared to controls [16]. A second study obtained similar results among 20 adult subjects with AD [13]. In a third study of 9 subjects using a different TMS-based paradigm to assess neuroplasticity, LTP-like activity was also shown to be aberrant in a group of adolescents and adults with AD [17].

## The future

Unlike schizophrenia, TMS research in Autism Spectrum Disorders is now at its infancy. However, the diagnostic and therapeutic potential of TMS in ASD is beginning to be explored by various researchers across the world. With regard to its application in neuroplasticity, the current focus is on assessing it at the motor cortex. In the near future, studies will also look at neuroplasticity in other key areas of ASD brain, e.g. dorsolateral prefrontal cortex, areas related to facial processing such as superior temporal sulcus, etc. As well, the combination of TMS with EEG (TMS-EEG) will offer researchers an exciting opportunity to gather a more direct measure


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of neuroplasticity. Ultimately, TMS-EEG will be combined with genetic research to understand the genetic underpinnings of aberrant neuroplasticity. Future research will also explore the therapeutic potential of novel rTMS protocols in ASD. rTMS affords researchers to explore and test various mechanism-driven methods aimed at rectifying aberrant neuroplasticity in ASD. It has been suggested that Gamma Aminobutyric Acid B ($GABA_B$) receptor mediated Cortical Inhibition (CI) is essential for the regulation of neuroplasticity and neuronal excitability and the therapeutic effects of rTMS are mediated by the induction of local changes in cortical inhibition (CI) and excitability [12]. Therefore, it is possible to establish rTMS protocols that can restore altered excitation/inhibition balance, and thus, neuroplasticity, through facilitating $GABA_B$ receptor mediated inhibitory neurotransmission in the stimulated area of brain. Finally, it can be hypothesized that the ultimate benefit of stabilizing aberrant neuroplasticity in ASD will be an improvement in cognitive and social performance.

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