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Aberrant Neuroplasticity In Autism Spectrum Disorder

Medical Science

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ABSTRACT

Autism spectrum disorder (ASD) prevalence has been increasing at an alarming rate in recent decades. The underlying causative mechanisms of ASD are still unclear. Aberrant neuroplasticity has been suggested to contribute to the development of ASD. Here, we review the role of neuroplasticity in ASD, factors implicated in aberrant neuroplasticity, and possible interventions. Given the importance of neuroplasticity in healthy and diseased brain, we intend to emphasize the need for interventions, especially for ASD, at a very early stage when the plasticity of the brain is high. Current literature highlights the connection between aberrant neuroplasticity resulting from various genetic and environmental factors and ASD. Neuromodulatory interventions are promising tools to regulate aberrant neuroplasticity and as potential therapies for ASD although further studies are required. Modulation of neuroplasticity at an early developmental stage through behavioral therapy might be a useful strategy to adopt at clinical settings for children with ASD.

Introduction

The key characteristics of autism spectrum disorder (ASD), a complex neurodevelopmental disorder, include persistent impairment in social communication and interaction, repetitive behaviors, and limited interests and activities (American Psychiatric Association, 2013). Recent years have seen an exponential rise in the estimated prevalence of ASD leading to severe socio-economic burden (www.cdc.gov/ncbddd/autism/data.html). Moreover, ASD is significantly more prevalent among boys than girls (Christensen *et al.,* 2016). Recent research has shown that aberrant/atypical neuroplasticity may be one of the mechanisms contributing to autism spectrum disorder (ASD). Neuroimaging studies have shown brain overgrowth in ASD, especially in the frontal and temporal regions of the brain, which are associated with learning (Hazlett *et al.,* 2011). Moreover, mutations in ASD have been linked to genes involved in neuroplasticity (Bourgeron, 2015). Taken together, evidence suggests the need for early intervention in ASD when the brain plasticity is high. However, the exact connection between aberrant neuroplasticity and ASD symptoms remains largely unclear. In the next sections, we review the importance of neuroplasticity during early development, abnormal neuroplasticity in neurodevelopmental disorders, specifically the autism spectrum disorder (ASD), along with discussion of risk factors and potential interventions.

Neuroplasticity

Neuroplasticity refers to the lifelong process the brain's ability to form new connections and reorganize itself (Ismail *et al.,* 2015). It helps our brain to adjust to the changes around us and respond appropriately and to recover from/compensate for injuries and diseases. For example, when you want to develop a good habit or quit a bad habit, you can alter your behavior with practice because your brain has neuroplasticity. Everything we do, feel, or think influences our brain wiring, by making old connections stronger or by building new ones. In infants, the brain is making and breaking new connections all the time. It is important that little children receive as much stimulation and repetition as possible, for these new connections to stabilize. The more the connections, the more the child learns and remembers, making him/her smarter. The environment plays a very important role in brain plasticity, along with genetic factors.

The significance of neuroplasticity is profound in cases of brain injury or disorder. For example, in a stroke patient who has lost the use of a limb, the size of the motor area in the brain corresponding to the use of that limb reduces over time. On the other hand, since the use of the unaffected limb increases considerably, the size of the motor area corresponding to the unaffected limb increases (Nudo, 2013 and Beutefisch, 2015). In the same way, it is suggested that the brain rewires itself in order to compensate and replace functions/behaviors lost in the case of several injuries/diseases.

Risk factors for aberrant neuroplasticity

Stress

One of the major causes of neuroplasticity deficit is stress. Several epidemiological studies have shown that maternal exposure to stress during pregnancy increases the risk of psychiatric disorders including ASD (Kinney *et al.,* 2008 and Ronald *et al.,* 2011). Stress can induce behavioral and genetic changes through epigenetic mechanisms, which are inheritable through parental gametes (Stankiewicz *et al.,* 2013, Jablonka and Raz, 2009 and Lee *et al.,* 2015). In accordance with epidemiological evidence, several animal studies have shown the relationship between maternal exposure to stress and neurodevelopmental deficits in the offspring (Weinstock, 2008 and Richetto and Riva, 2014).

Similarly, viral infections and malnutrition during pregnancy also increases the risk of psychiatric disorders including ASD (Kinney *et al.,* 2008 and Ronald *et al.,* 2011).

Changes in protein synthesis

Protein synthesis and degradation play a role in synaptic plasticity. Changes in protein synthesis or degradation at the synapses have been considered to affect synaptic plasticity. For example, aberrant synthesis of proteins involved in mGluR-mediated long-term depression (mGluR-LTD), leading to a deficit in mGluR-LTD, has been demonstrated in mouse models of ASD and other cognitive disorders (Luscher and Huber, 2010 and Santini *et al.,* 2013). Therefore, a balance between protein synthesis and degradation is important for proper synaptic functioning and neurodevelopment.

Altered gene expression

Several evidences implicate that abnormalities in the extracellular matrix (ECM) are associated with ASD. Numerous genome-wide association studies (GWAS) on autism have implicated several molecules that regulate ECM and peri-

neuronal nets (Pnn) (Pantazopoulos and Berretta, 2016). Especially, the altered expression Reelin has been observed in various brain regions in autism and reduced blood levels of Reelin have been shown in subjects with autism Persico *et al*, 2001 and Fatemi, 2005). In addition, a transgenic mouse with mutations in the Reelin gene shows neurodevelopmental impairment similar to that of autism (Fatemi *et al*., 2001). Another candidate implicated in the pathophysiology of autism is heparin sulfate proteoglycans. An animal model of autism shows altered HSPG expression (Pearson *et al*., 2013 and Mercier *et al*., 2012).

Excitation-inhibition imbalance

Excitation-inhibition balance is important for proper neurotransmission. An imbalance in this ratio has been suggested as one of the reasons for aberrant neuroplasticity leading to ASD (Rubenstein and Merzenich, 2003). In particular, a deficit in inhibitory neurotransmission has been implicated in ASD (Baroncelli *et al*., 2011). A study involving patients with ASD showed that the expression of excitatory neurotransmitter receptors was increased and that of the inhibitory neurotransmitter receptors were decreased in their brains (Fatemi *et al*., 2009). These may be responsible for the abnormal increase of neuroplasticity in ASD.

Neuromodulatory interventions

The concept of critical and sensitive periods during development where there is increased plasticity and the various patterns of plasticity are very important to understand to facilitate neuromodulatory interventions for neurodevelopmental disabilities (Ismail *et al*., 2016). In this regard, transcranial magnetic stimulation (TMS) is a new, emerging noninvasive tool for focal brain stimulation (Wagner *et al*., 2007 and Desarkar *et al*., 2015). One variation of TMS developed to investigate NMDA-dependent Hebbian plasticity is the paired associated stimulation (PAS). TMS can be used for investigation and modulation of cortical plasticity (Huang et al., 2005 and Huerta and Volpe, 2009), thus making it a promising therapeutic approach in autism research. In fact, some studies have already been conducted where TMS and PAS has been used to assess cortical plasticity in ASD (Oberman *et al*., 2010, Jung *et al*., 2013 and Oberman *et al*., 2014). TMS has also been used to investigate the excitation-inhibition imbalance. It is said to specifically target cortical inhibition to regulate neuroplasticity (Fitzgerald et al., 2009). Although the results are varied, the results from these studies somewhat support the aberrant plasticity hypothesis of ASD and show that TMS can be a significant investigational and therapeutic tool in the field of pediatric neurodevelopment.

In studies with Shank3-deficient mice, a model for ASD, insulin-like growth factor-1 (IGF-1) has been shown to reverse plasticity and behavioral deficits (Bozdagi *et al*., 2013). A recent pilot study in children with Phelan-McDermid syndrome (PMS), which causes a monogenic form of ASD, IGF-1 treatment has been shown to significantly improve behavioral parameters as compared to placebo treatment, suggesting the possibility of IGF-1 treatment in ASD (Kolevzon *et al*., 2014).

Conclusion

This review highlights the connection between aberrant neuroplasticity resulting from various genetic and environmental factors and ASD. Future research and use of new technologies such as transcranial magnetic stimulation could help us resolve this connection and provide a therapeutic solution toward repairing atypical neuroplasticity and improving the cognitive ability in ASD. Modulation of neuroplasticity at an early developmental stage through behavioral therapy might be a key strategy that needs to be adopted at clinical settings for children with ASD.

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