Aberrant Neuroplasticity In Autism Spectrum Disorder

Jayaraman, Anusha
Center for Child Development and Disabilities, 202, Sackhumvit House, New Bel Road, Bangalore – 560054 Karnataka, India

Mundkur, Nandini
Center for Child Development and Disabilities, 202, Sackhumvit House, New Bel Road, Bangalore – 560054 Karnataka, India

ABSTRACT Autism spectrum disorder (ASD) prevalence has been increasing at an alarming rate in recent decades. The underlying causal 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. Neurromodulatory 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 building new ones. In infants, the brain is making and pruning connections at a very high rate. The more children receive as much stimulation and repetition as possible, the more 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 Beutetisch, 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 (Ismael 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.

References
1. American Psychiatric Association. (2013). Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) Washington, DC.
2. Baroncelli, L., Branci, C., Spolidoro, M., Begennisic, T., Maifei, L., & Sale, A. (2011). Brain plasticity and disease: a matter of inhibition. Neural Plasticity, 2011, 286073.
3. Beutefisch, C. M. (2015). Role of the centralgesial hemisphere in post-stroke recovery of upper extremity motor function. Frontiers in Neurology, 6, 214.
4. Bourgueron, T. (2015). From the genetic architecture to synaptic plasticity in autism spectrum disorder. Nature Reviews Neuroscience, 16(9), 551-563.
5. Bozdagi, O., Tavassoli, T., & Buxbaum, J. D. (2013). Insulin-like growth factor-1 rescues synaptic and motor deficits in a mouse model of autism and developmental delay. Molecular Autism, 4(1), 9.
6. Christensen, D. L., Bai, J., Van Naarden Braun, K., Bilder, D., Charles, J., Constantino, J. N., et al. (2016). Prevalence and characteristics of autism spectrum disorder among children aged 8 years – Autism and developmental disabilities monitoring network, 11 sites, United States, 2012. Morbidity and Mortality Weekly Report. Surveillance Summary, 65(3), 1-23.
7. Desarkar, P., Rajji, T. K., Amies, S. H., & Daskalakis ZJ. (2015) Assessing and stabilizing aberrant neuroplasticity in autism spectrum disorder: The potential role of transcranial magnetic stimulation. Frontiers in Psychiatry, 6, 124.
8. Fatemi, S. H., Stary, J. M., Halt, A. R., & Realmuto, G. R. (2001). Dysregulation of Reelin and Bcl-2 proteins in autistic cerebellum. Journal of Autism and Developmental Disorders, 31(6), 529-535.
9. Fatemi, S. H. (2005). Reelin glycoprotein in autism and schizophrenia. International Review of Neurobiology, 71,179-187.
10. Fatemi, S. H., Folson, T. D., Reutiman, T. J., & Thruss, P. D. (2009). Expression of GABA(B) receptors is altered in brains of subjects with autism. Cerebellum, 8(1), 64-69.
11. Fitzgerald, P. B., Maller, J. J., Hoy, K., Farzan, F., & Daskalakis, Z. J. (2009). GABA and cortical inhibition in motor and non-motor regions using combined TMS-EEG: a time analysis. Clinical Neurophysiology, 120(9), 1706-1710.
12. Hazlett, H. C., Poe, M. D., Gerig, G., Styner, M., Chappell, C., Smith, R. G., Vachet, C., & Piven, J. (2011). Early brain overgrowth in autism associated with an increase in cortical surface area before age 2 years. Archives of General Psychiatry, 68(5), 407-476.
13. Huang, Z. Y., Edwards, M. J., Rounis, E., Bhatia, K. P., & Rothwell, J. C. (2005). Theta burst stimulation of the human cortex. Neuron, 45(2), 201-206.
14. Huerta, P. T., & Volpe, B. T. (2009). Transcranial magnetic stimulation, synaptic plasticity and network oscillations. Journal of Neuroengineering and Rehabilitation, 6, 7.
15. Ismael, F. Y., Fatemi, A., & Johnston, M. V. (2016). Cerebral plasticity: Windows of opportunity in the developing brain. European Journal of Paediatric Neurology, Aug 9 [Epub ahead of print].
16. Jablonka, E., & Raz, G. (2009). Transgenerational epigenetic inheritance: prevalence, mechanisms, and implications for the study of heredity and evolution. The Quarterly Review of Biology, 84(2), 131-176.
17. Jung, N. H., Janzarik, W. G., Delvendahl, I., Munchau, A., Biscaldi, M., Mainberger, F., Baumer, T., Rauh, R., & Mall, V. (2013). Impaired induction of long-term potentiation-like plasticity in patients with high-functioning autism and Asperger syndrome. Developmental Medicine and Child Neurology, 55(1), 83-89.
18. Kinney, D. K., Munir, K. M., Crowley, D. J., & Miller, A. M. (2008). Prenatal stress and risk for autism. Neuroscience and Biobehavioral Reviews, 32(8), 1519-1532.
19. Kolevzon, A., Bush, I., Wang, A. T., Halpern, D., Frank, Y., Grodberg, D., Rapaport, R., Tavassoli, T., Chaplin, W., Soorya, L., & Buxbaum, J. D. (2014). A pilot controlled trial of insulin-like growth factor-1 in children with Phelan-McDermid syndrome. Molecular Autism, 5(1), 54.
20. Lee, Y. A., Yamaguchi, Y., & Goto, Y. (2015). Neurodevelopmental plasticity in pre- and postnatal environmental interactions: Implications for psychiatric disorders from an evolutionary perspective. Neural Plasticity, 2015:291476.
21. Luscher, C., & Huber, K. M. (2010). Group 1 mGluR-dependent synaptic long-term depression: mechanisms and implications for circuitry and disease. *Neuron*, 65(4), 445-459.

22. Mercier, F., Kwon, Y. C., & Douet, V. (2012). Hippocampus/amygdala alterations, loss of heparan sulfates, fractones and ventricle wall reduction in adult BTRR T+tf/J mice, animal model for autism. *Neuroscience Letters*, 50(6), 208-213.

23. Nudo, R. J. (2013). Recovery after brain injury: mechanisms and principles. *Frontiers of Human Neuroscience*, 7, 887.

24. Oberman, L., Ifert-Miller, F., Najib, U., Bashir, S., Woolacott, L., Gonzalez-Heydrich, J., Picker, J., Rotenberg, A., & Pascual-Leone, A. (2010). Transcranial magnetic stimulation provides means to assess cortical plasticity and excitability in humans with fragile X syndrome and autism spectrum disorder. *Frontiers in Synaptic Neuroscience*, 2, 26.

25. Oberman, L. M., & Pascual-Leone, A. (2014). Hyperplasticity in autism spectrum disorder confers protection from Alzheimer’s disease. *Medical Hypotheses*, 83(3), 337-342.

26. Pantazopoulos, H., Berretta, S. (2016). In sickness and in health: Perineuronal nets and synaptic plasticity in psychiatric disorders. *Neural Plasticity*, 2016, 9847696.

27. Pearson, B. L., Corley, M. J., Vasconcellos, A., Blanchard, D. C., & Blanchard, R. J. (2013). Heparan sulfate deficiency in autistic postmortem brain tissue from the subventricular zone of the lateral ventricles. *Behavioral Brain Research*, 243, 138-145.

28. Persico, A. M., D’Agruma, L., Maiorano, N., Totaro, A., Militerni, R., Bravaccio, C., et al. (2001). Reelin gene alleles and haplotypes as a factor predisposing to autistic disorder. *Molecular Psychiatry*, 6(2), 150-159.

29. Richetto, J., & Riva, M. A. (2014). Prenatal maternal factors in the development of cognitive impairments in the offspring. *Journal of Reproductive Immunology*, 104-105, 20-25.

30. Ronald, A., Pennell, C. E., & Whitehouse, A. J. (2011). Prenatal maternal stress associated with ADHD and autistic traits in early childhood. *Frontiers in Psychology*, 1, 223.

31. Rubenstein, J. L, & Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes Brain and Behavior*, 2(5), 255-267.

32. Santini, E., Huynh, T. N., MacAskill, A. F., Carter, A. G., Pierre, P., Ruggero, D., Kaphzan, H., & Klann, E. (2013). Exaggerated translation causes synaptic and behavioural aberrations associated with autism. *Nature*, 493(7432), 411-415.

33. Stankiewicz, A. M., Swiergiel, A. H., & Lisowski, P. (2013). Epigenetics of stress adaptations in the brain. *Brain Research Bulletin*, 98, 76-92.

34. Wagner, T., Valero-Cabre, A., & Pascual-Leone, A. (2007). Noninvasive human brain stimulation. *Annual Review of Biomedical Engineering*, 9, 527-565.

35. Weinstock, M. (2008). The long-term behavioural consequences of prenatal stress. *Neuroscience and Biobehavioral Reviews*, 32(6), 1073-1086.

36. [www.cdc.gov/ncbddd/autism/data.html](http://www.cdc.gov/ncbddd/autism/data.html). Date accessed: 15 September 2016.