Overview: Neuroplasticity and synaptic function in neuropsychiatric disorders

As our understanding of the cellular and molecular mechanisms underlying neurodevelopmental and neuropsychiatric disorders deepens, it is has become clear that many if not most can be described as synaptopathies, disorders of synaptic function and plasticity. This view is probably more established with respect to monogenic syndromic forms of autisms spectrum disorders (ASDs) than for non-syndromic forms of ASDs or neuropsychiatric conditions such as schizophrenia and bipolar disorder (Ebrahimi-Fakhari & Sahin, 2015). It is therefore timely to consider whether all neurodevelopmental and psychiatric disorders are caused by synaptic defects, and to examine the genetics underlying these defects. This was the topic of a symposium organised by the Neuroscience & Mental Health Research Institute at Cardiff University in April 2017.

Genome-wide association studies (GWAS) have identified a large number of single-nucleotid polymorphism (SNPs) and copy number variants (CNVs) that increase the risk of schizophrenia (Giegling *et al.*, 2017), bipolar disorder (Craddock & Sklar, 2013); (Ikeda *et al.*, 2018) and ASDs (Kirov, 2015); (Ramaswami & Geschwind, 2018); (Miles, 2011). However, the vast majority of those are of low penetrance, and therefore do not lend themselves well to an exploration of the neurophysiological mechanisms that would link a genetic defect to a disease phenotype. Conversely, there are a small number of much rarer mutations which contribute to neurodevelopmental and neuropsychiatric conditions with high penetrance, and these are the focus of most of the ongoing research and of the symposium at Cardiff.

The reviews by Tropea et al. and Michaelsen-Preusse et al. deal with two of the genes whose products are best known for their involvement in schizophrenia and autism, respectively, namely Disrupted-In-Schizophrenia 1 (DISC1) and Fragile X Mental Retardation Protein (FMRP).

Disrupted-In-Schizophrenia 1 (DISC1) is a strong candidate susceptibility gene notably for schizophrenia, but also bipolar disorder and depression. The human DISC1 gene is located on chromosome 1 and is directly disrupted by translocation in schizophrenia. Interacting with a large number of synaptic and cytoskeletal molecules, DISC1 is involved in a wide range of processes such as neuronal axon and dendrite outgrowth, cell proliferation, differentiation and migration as well as in synaptic plasticity. A recent study by (Greenhill *et al.*, 2015) demonstrated a key role for DISC1 in a 'meta' critical period, a time very early in life during which the potential for experience dependent plasticity later in life is established. Here, Tropea et al. review what is known about the mechanisms by which mutations in different loci disrupt synaptic plasticity. Mutations that impair the binding of Phosphodiesterase 4B (PDE4B) to the N-terminal domain of DISC1 affect synaptic plasticity through downstream effects on CREB activation and phosphorylation of the AMPA receptor subunit GluA1. Moreover, DISC1 is a component of the postsynaptic density (PSD) of excitatory synapses and interacts with a number of proteins including Kalarin-7 which via Ras-Related C3 Botulinum Toxin Substrate 1 (Rac1) plays an important role in the control of spine morphology. In contrast, mutations of the highly conserved C-terminal domain impair intracellular trafficking and thereby affect cytoskeletal development such as spine maturation. Tropea et al. propose that N-terminal and C-terminal interactions make up the two main branches of the effects of DSIC1 on synaptic plasticity and dendritic spine stability.

Fragile X Syndrome (FXS) is the most common known single-gene cause of ASD, accounting for about 2-3% of all cases. Abnormal expansion of a CGG repeat in the FMR1 gene results in loss of FMRP. Although the diverse functions of FMRP have not been fully characterised it has been implicated in synaptic plasticity due to its role as an inhibitor of RNA translation. FMRP is an RNA-binding protein that has been shown to repress the translation of target mRNAs at synapses. FMRP-mediated control of translation in turn is regulated by Group 1 metabotropic glutamate receptor (mGluR) signalling which has led to the mGluR theory of Fragile X (Bear *et al.*, 2004). Several studies have shown dendritic spine abnormalities in the *fmr1* KO mouse model of Fragile X (although evidence is at times conflicting), including increased spine density on both layer 2/3 and layer 5 pyramidal neurons, changes in spine shape and size and delayed stabilisation (He & Portera-Cailliau, 2013) which may in turn account for abnormal structural and functional synaptic plasticity. The review by Michaelsen-Preusse et al. focuses on the role of FMRP in the regulation of actin dynamics; given that active is the major cytoskeletal component of the spine abnormal actin dynamics are likely to be reflected in altered dendritic spine morphology. Michaelsen-Preusse et al. conclude that dysregulation of the actin cytoskeleton might emerge as a central element in mediating aberrant spine phenotypes in FXS and perhaps in ASD in general. They point out that while several studies link altered spine morphology phenotype in FXS to a role of FMRP in activity-dependent mRNA transport and local translation, only little is known about direct interactions between actin-binding protein mRNAs and FMRP (Reeve *et al.*); (Michaelsen-Preusse *et al.*, 2016). Moreover, both pre- and postsynaptic changes could account for impaired spine structure and function.

It is interesting to note that both the research into DISC1 and FMRP reviewed here highlight the importance of the role of the cytoskeleton in spine structure and function and, by extension, in synaptic plasticity. This convergence also lends further support to the view that ASDs, schizophrenia and bipolar disorder can be placed on a gradient of neurodevelopmental and affective pathology (Craddock & Owen, 2010).

References

Bear MF, Huber KM & Warren ST. (2004). The mGluR theory of fragile X mental retardation. *Trends in Neurosciences* **27,** 370-377.

Craddock N & Owen MJ. (2010). The Kraepelinian dichotomy - going, going... but still not gone. *The British Journal of Psychiatry* **196,** 92-95.

Craddock N & Sklar P. (2013). Genetics of bipolar disorder. *The Lancet* **381,** 1654-1662.

Ebrahimi-Fakhari D & Sahin M. (2015). Autism and the synapse: emerging mechanisms and mechanism-based therapies. *Current Opinion in Neurology* **28,** 91-102.

Giegling I, Hosak L, Mössner R, Serretti A, Bellivier F, Claes S, Collier DA, Corrales A, DeLisi LE, Gallo C, Gill M, Kennedy JL, Leboyer M, Maier W, Marquez M, Massat I, Mors O, Muglia P, Nöthen MM, Ospina-Duque J, Owen MJ, Propping P, Shi Y, St Clair D, Thibaut F, Cichon S, Mendlewicz J, O'Donovan MC & Rujescu D. (2017). Genetics of schizophrenia: A consensus

paper of the WFSBP Task Force on Genetics. *The World Journal of Biological Psychiatry* **18,** 492-505.

Greenhill SD, Juczewski K, de Haan AM, Seaton G, Fox K & Hardingham NR. (2015). Adult cortical plasticity depends on an early postnatal critical period. *Science* **349,** 424-427.

He CX & Portera-Cailliau C. (2013). The trouble with spines in fragile X syndrome: density, maturity and plasticity. *Neuroscience* **251,** 120-128.

Ikeda M, Saito T, Kondo K & Iwata N. (2018). Genome-wide association studies of bipolar disorder: A systematic review of recent findings and their clinical implications. *Psychiatry and Clinical Neurosciences* **72,** 52-63.

Kirov G. (2015). CNVs in neuropsychiatric disorders. *Human Molecular Genetics* **24,** R45-R49.

Michaelsen-Preusse K, Zessin S, Grigoryan G, Scharkowski F, Feuge J, Remus A & Korte M. (2016). Neuronal profilins in health and disease: Relevance for spine plasticity and Fragile X syndrome. *Proceedings of the National Academy of Sciences* **113,** 3365-3370.

Miles JH. (2011). Autism spectrum disorders—A genetics review. *Genetics In Medicine* **13,** 278.

Ramaswami G & Geschwind DH. (2018). Chapter 21 - Genetics of autism spectrum disorder. In *Handbook of Clinical Neurology*, ed. Geschwind DH, Paulson HL & Klein C, pp. 321-329. Elsevier.

Reeve SP, Bassetto L, Genova GK, Kleyner Y, Leyssen M, Jackson FR & Hassan BA. The Drosophila Fragile X Mental Retardation Protein Controls Actin Dynamics by Directly Regulating Profilin in the Brain. *Current Biology* **15,** 1156-1163.