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Guest Editorial

Neuroplasticity and dysplasticity processes in schizophrenia

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Schizophrenia and other psychotic disorders are now understood to be pathologies of brain neural circuit function, in which representational and computational processes generated within neuronal architecture and supported by neural oscillatory coupling are distorted. Neural oscillatory activity spans a broad range of physiologic processes, extending from interneuron-pyramidal neuron microcircuits with their millisecond cycles, to flows of information over hundreds of milliseconds in columnar mesocircuits, to long-range brain macrocircuit interactions over seconds that support higher order cognitions and actions (Mathalon and Sohal, 2015). While distortions in all of these processes have been well-studied in psychotic disorders, there is often an unfortunate tendency to (implicitly) conceptualize and study these various circuit distortions as if they were static. And yet, neural activity arises from, and interacts with, a neuronal-glial scaffold whose intrinsic property is plasticity— both developmental and experiential.

Indeed, brain circuits represent, store, update, and act upon information (and execute computations) by relying on plasticity in their synaptic strength, membrane conductance, topology, and structural architecture (Sejnowski and Paulsen, 2006). It follows then, that impairments in normal plasticity operations – and/or maladaptive compensatory plasticity processes that attempt to adapt to other underlying circuit pathology – are an important focus of study in schizophrenia and related disorders. It also follows that a deeper understanding of these processes could lead to novel approaches for illness prevention and treatment. We are excited – in this Special Issue of *Schizophrenia Research* – to bring you a broad array of data-driven perspectives on how such plasticity and "dysplasticity" mechanisms could play a role in the expression and treatment of psychotic disorders.

1. Mechanistic insight into plasticity and dysplasticity

The first three papers in this special issue present basic science findings that provide a mechanistic framework at the molecular and circuit level implicating dysplasticity processes in the pathophysiology of schizophrenia.

Voss et al. (2019–in this issue) provide an overview of the mechanisms regulating cortical plasticity across the lifespan, with an emphasis on experiments done in the auditory system. They discuss how the early sensory processing impairments observed in schizophrenia might arise from a dysregulation of plasticity regulators, resulting in either reduced plasticity or excessive unregulated plasticity, that ultimately contribute to disturbances in higher-order cognitive processes.

Smith et al. (2019–in this issue) apply an unbiased transcriptome-based bioinformatics approach based on the developmental trajectory of cortical plasticity, and examine to what extent it is disrupted in schizophrenia and bipolar disorder. They match the transcriptome signature of the critical period for human visual cortex plasticity – a well-studied model of cortical critical periods – with publically available transcriptome data from postmortem tissues. They find that the majority of psychotic cases show either hyper- or hypo-plasticity phenotypes at the transcriptome level.

These two manuscripts focused on cortical systems are followed by an article that examines the hippocampal system. O'Reilly et al. (2019–in this issue) discuss two related yet separable functions of synaptic plasticity, the operations of item memory and process memory carried out by the hippocampal learning system. They demonstrate how these memories are differentially dysregulated in neurodevelopmental rodent models relevant for psychiatric disorders, and they discuss how dysplasticity factors may contribute to adult outcomes following early cognitive experience.

Collectively, these three reports provide support for the role of developmental dysplasticity processes (both hyper-plasticity and hypo-plasticity) that may underlie the pathophysiology of schizophrenia at the molecular and circuit level.

2. Dysplasticity in schizophrenia

The following section presents three studies that investigate to what extent dysplasticity processes are evident in schizophrenia and at-risk populations. These studies apply various means to induce (direct electric stimulation, perceptual, and behavioral tasks) and assess (electrophysiological, behavioral) various types of plasticity processes (motor, sensory, multimodal) at different timescales (seconds to minutes).

Mehta et al. (2019–in this issue) perform a systematic quantification of motor cortical plasticity in schizophrenia through a meta-analysis of motor evoked potential upon Transcranial Magnetic and Direct Current Stimulation. They report that individuals with schizophrenia demonstrate diminished LTP- and LTD-like motor cortical plasticity. This study encourages the use of perturbation-based biomarkers to characterize disease trajectories in larger samples in future studies.

Thakkar et al. (2019–in this issue) assess rapid adaptive plastic perceptual changes in people with schizotypal features, using sensory adaptation tasks in the visual system. They find that increased schizotypal traits are related to reduced adaptation (e.g. reduced orientation aftereffect strength, a greater proportion of mixed perception during binocular rivalry), suggesting that short-term plasticity in the visual system can provide important information about the disease mechanisms of schizophrenia.

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Benson and Park (2019–in this issue) assess plasticity of multisensory bodily self-experience in individuals at-risk for schizophrenia. Self-disturbances such as altered perception of one's own body boundary are frequently reported in people with schizophrenia. By using a multisensory paradigm known as the Pinocchio Illusion task (that engenders the feeling that one's nose is changing), they found this form of rapid plastic change in self-perception was enhanced in the clinical high risk group, but with no change in tactile sensitivity. These results highlight the negative consequence of excessive plasticity in individuals with attenuated schizophrenia spectrum symptoms.

Collectively, these studies suggest that individuals with schizophrenia and at clinical high risk are characterized by various forms of dysplasticity processes from hypo- to hyper-plasticity, which is in line with the molecular and circuit changes discussed in the prior section.

3. Targeting plasticity for therapeutic intervention

The last three articles explore ways in which emerging basic science knowledge related to neuroplasticity – especially with regards to NMDA-receptor function – might inform new therapeutic approaches to schizophrenia.

Panizzutti et al. (2019–in this issue) examine the effects of intensive targeted cognitive training of the auditory system on serum D-serine levels. D-Serine is a key co-agonist of the NMDA receptor, and in animal experiments, brain D-serine has been shown to increase after intense cognitive activity and learning. In people with schizophrenia, serum levels are often lowered; this is felt to possibly reflect impaired NMDA receptor (NMDAR) activity. Panizzutti et al. found a significant correlation between increases in serum D-serine induced by intensive auditory training and increases in cognitive outcome measures, while no such correlation was found in a computer games control condition. They suggest that such changes may reflect the neurophysiologic effects of intensive training on NMDAR functioning, and may indicate that D-serine co-agonism could be a useful therapeutic target to enhance the neuroplastic effects of training.

In keeping with this finding, Kantrowitz (2019–in this issue) provides a thoughtful review of the potential usefulness of NMDAR modulators as cognitive enhancers in schizophrenia, with a focus on auditory system plasticity. Interestingly, he provides evidence to indicate that a strategy of intermittently targeting NMDAR modulation in schizophrenia (rather than providing ongoing daily treatment) – when combined with training paradigms – may provide the highest likelihood of addressing plasticity deficits and driving meaningful behavioral gains. This finding illustrates that “correcting” neuroplasticity impairments in a heterogeneous neurodevelopmental disorder such as schizophrenia, where multiple compensatory and homeostatic processes are at play, is likely to require complex multimodal and asynchronous approaches.

Finally, we conclude this special issue by with the review by Guercio et al. (2019–in this issue) who examine the evidence for altered neuroplasticity in schizophrenia, and the potential role of dopaminergic, glutamatergic, cholinergic, and oxytocinergic systems in addressing these alterations. Guercio et al. provide a succinct rationale for how pharmacologic enhancement of these systems, when combined with behavioral interventions such as cognitive training, may have the greatest success for driving functional change. They remind us of pioneering work that is emerging with such combinations in other areas of psychiatry, and highlight the importance of targeting both lower level (perceptual) and higher level (executive functions, social cognition) deficits in order to maximize outcomes for patients.

We hope that the readers will enjoy reading the various reports in this Special Issue, and – like you – we look forward to future research that will provide us with a deeper understanding of normal and abnormal neuroplasticity mechanisms and help us to unravel the mysteries and complexities of the schizophrenia syndrome.

Conflict of interest

None.

Contributors

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