Review

Biological Psychiatry

Impaired Tuning of Neural Ensembles and the Pathophysiology of Schizophrenia: A Translational and Computational Neuroscience Perspective

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ABSTRACT

The functional optimization of neural ensembles is central to human higher cognitive functions. When the functions through which neural activity is tuned fail to develop or break down, symptoms and cognitive impairments arise. This review considers ways in which disturbances in the balance of excitation and inhibition might develop and be expressed in cortical networks in association with schizophrenia. This presentation is framed within a developmental perspective that begins with disturbances in glutamate synaptic development in utero. It considers developmental correlates and consequences, including compensatory mechanisms that increase intrinsic excitability or reduce inhibitory tone. It also considers the possibility that these homeostatic increases in excitability have potential negative functional and structural consequences. These negative functional consequences of disinhibition may include reduced working memory–related cortical activity associated with the downslope of the "inverted-U" input–output curve, impaired spatial tuning of neural activity and impaired sparse coding of information, and deficits in the temporal tuning of neural activity and its implication for neural codes. The review concludes by considering the functional significance of noisy activity for neural network function. The presentation draws on computational neuroscience and pharmacologic and genetic studies in animals and humans, particularly those involving *N*-methyl-D-aspartate glutamate receptor antagonists, to illustrate principles of network regulation that give rise to features of neural dysfunction associated with schizophrenia. While this presentation focuses on schizophrenia, the general principles outlined in the review may have broad implications for considering disturbances in the regulation of neural ensembles in psychiatric disorders.

Keywords: Cognition, Computational psychiatry, Glutamate, Neural ensembles, Neurodevelopment, Schizophrenia

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Most cortical pathologies can be understood as a disturbance in the balance of glutamatergic excitation and gamma-aminobutyric acidergic (GABAergic) inhibition (E/I balance). Glutamate and GABA neurons account for most cortical synapses, and they are the main targets of other cortical modulators (1). As a result, changes in cortical network activity are expressed as a form of E/I imbalance, however transient.

This review considers three forms of E/I imbalance that may be relevant to psychiatry: disinhibition, reduction in the spatial and temporal tuning of neural activity, and noise. This presentation draws on studies of schizophrenia, the effects of pharmacologic agents in animals and healthy humans, and computational models of cortical microcircuits (2). While this discussion focuses on schizophrenia, the general principles reviewed may apply to other psychiatric disorders (3–5).

EXCITATORY SYNAPTIC DEFICITS

Schizophrenia, at its developmental core, is a disorder of E/I imbalance arising from deficient excitatory connectivity. The symptoms of schizophrenia, particularly the prominent cognitive and negative symptoms, are associated with reductions in cortical gray matter (6) and white matter (7) and with reduced task-related prefrontal cortical activation, although not universally so (8).

Deficits in glutamate synaptic structure and function are a component of the neurobiology of schizophrenia (9). For example, genes that code for the development, function, and elimination of glutamate synapses figure prominently among both the rare (10–14) and common (15,16) gene variants that contribute to the heritable risk for schizophrenia. In the frontal cortex, these genes are expressed prominently in utero or shortly after birth (17,18). Thus, it is likely that glutamatergic signaling deficits are among the earliest forms of pathology expressed in schizophrenia. Furthermore, primary deficits in *N*-methyl-D-aspartate receptor (NMDAR) glutamate synaptic signaling, particularly in layer 3 pyramidal neurons in prefrontal cortex (19), are thought to underlie impaired executive cognitive functions, including working memory deficits (20). These deficits are thought to undermine recurrent

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excitation and the maintenance of information in working memory (21).

Deficits in synaptic connectivity also may directly contribute to the development of delusions and hallucinations. For example, Hoffman (22) and Hoffman and McGlashan (23) suggested that synaptic deficits associated with schizophrenia create a propensity for cortical networks to settle into aberrant representations of thought or sensory experience. In the parlance of chaos theory, these aberrant states may constitute abnormal chaotic attractors; or in topological theory, parasitic foci.

IMPAIRED TUNING OF THE MAGNITUDE OF EXCITATION, ALLOSTATIC ADAPTATIONS, AND THE INVERTED U

There is also evidence of increased excitability or cortical disinhibition in schizophrenia, particularly early in the course of illness. For example, cortical levels of glutamate, glutamine, and GABA as measured by ^{1}H magnetic resonance spectroscopy are elevated in healthy individuals at high genetic risk or in patients early in their course of illness, with declining levels with advancing age to a point below that of healthy subjects (24–30). In addition, studies of covarying regional brain activity assessed with functional magnetic resonance imaging (MRI) at rest (i.e., resting cortical functional connectivity) reveal increases in high risk and unmedicated first episode patients and reductions in this trait over time during long-term treatment (31,32). Similarly, working memory–related fronto-parietal connectivity also appears to decline with illness progression (33). In addition, electrophysiological studies point to relative increases in excitability as reflected in functional connectivity and increased amplitude of the M100 and M170 evoked responses early in the course of schizophrenia that decline with illness progression (34,35).

The downregulation of cortical connectivity with age or duration of illness in schizophrenia may be exacerbated by increased cortical excitation and functional connectivity. For example, individuals at high risk for developing schizophrenia show increased energy metabolism rates in the CA1 and subiculum regions of the hippocampus. When followed through their transition to psychosis, the areas that had earlier shown hyperactivity now showed atrophy, as measured by volume loss on MRI (36). In this study, ketamine, an NMDAR antagonist that acutely disinhibits some cortical networks (37), was shown in mice to activate hippocampal subregions acutely but to produce atrophy in these activated regions with long-term administration. Similarly, when followed over time, the degree of cortical functional hyperactivity in unmedicated schizophrenia patients in their first episode was correlated with the decline in functional connectivity over time (32). Together, these studies suggest that hyperactivation triggers functional and perhaps structural synaptic downregulation.

As outlined in Figure 1 (38), it is possible that the increased rate of decline in cortical structural and functional indices in schizophrenia compared with healthy comparison subjects is a consequence of homeostatic processes intended to adapt to increased cortical excitation (2). The mechanisms of synaptic homeostasis enable neurons to have stable functional characteristics despite growth-related alterations and changing strength of neural inputs (39). In the presence of the

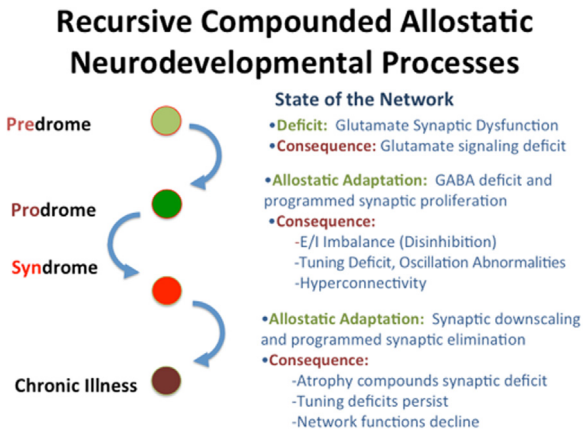

Figure 1. Phases in the development of schizophrenia may be expressed, in part, through the accumulation of successive homeostatic neuroadaptations that serve to reduce glutamatergic excitation and gamma-aminobutyric acidergic (GABAergic) inhibition (E/I) imbalances but come at a cost with regard to network integrity and function. In this way, the adaptations are viewed as allostatic rather than homeostatic. [Reproduced from (38).]

persistence of increased excitation, both pre- and postsynaptic mechanisms are engaged in homeostatic downscaling of functional and structural connectivity (40–42). In this way, homeostatic plasticity contrasts with Hebbian plasticity, which in the presence of increased excitation would be predicted to increase both functional and structural connectivity (42).

How might disinhibition emerge? First, as suggested in Figure 1, the preponderance of genetic information so far points toward primary deficits in glutamate synaptic connectivity. However, there may also be mutations associated with schizophrenia that might directly increase cortical excitability. For example, alterations in several genes implicated in schizophrenia risk, including reductions in transcription factor 4 (43), 15q13.3 microdeletion (44), and increases in *hERG* (45) or *CACNA1c* (46), might contribute to schizophrenia risk by increasing cortical excitability. Second, pyramidal neurons may compensate for deficits in glutamatergic input by upregulating their excitability. For example, when the GluN1 subunit of NMDAR is selectively eliminated from cortical pyramidal neurons in mice, perhaps mimicking deficits in NMDAR signaling that might be associated with schizophrenia, pyramidal neurons adapt by increasing their excitability via reductions in G protein–regulated inward rectifier potassium channel 2 (47,48).

However, increased excitation also might emerge as a consequence of allostatic deficits in GABA signaling, that is, a homeostatic reduction of basal E/I imbalance that compromises functions attributable to interneurons (2). Abnormalities have been described in several GABA neuronal populations in schizophrenia (49). The best-characterized deficits are in the parvalbumin (PV)-containing GABA cells, including chandelier cells, which synapse on the initial axonal segment of pyramidal neurons and gate output (50), and the basket cells, which synapse on the soma and proximal dendrites and which shape the timing of neuronal activity at high frequencies (γ oscillations) (19). In addition, deficits are reported in cholecystokinin (CCK)-containing basket cells, which express cannabinoid (CB_1) receptors and temporally tune