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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 will consider ways that disturbances in the balance of excitation and inhibition might develop and be expressed in cortical networks in association with schizophrenia. This presentation will be framed within a developmental perspective that begins with disturbances in glutamate synaptic development *in utero*. It will consider developmental correlates and consequences including compensatory mechanisms that increase intrinsic excitability or reduce inhibitory tone. It will also consider 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, deficits in the temporal tuning of neural activity and its implication for neural codes, and conclude by considering the functional significance of noisy activity for neural network function. This presentation will draw on computational neuroscience and pharmacologic and genetic studies in animals and humans, particularly those involving NMDA glutamate receptor antagonists, to

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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 this review may have broad implications for considering disturbances in the regulation of neural ensembles in psychiatric disorders.

Keywords

computational psychiatry; schizophrenia; glutamate; cognition; neurodevelopment; neural ensembles

Most cortical pathology can be understood as a disturbance in the balance of glutamatergic excitation and 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 will draw on studies of schizophrenia, the effects of pharmacologic agents in animals and healthy humans, and computational models of cortical microcircuits (2). While this discussion will focus on schizophrenia, the general principals reviewed may apply to other psychiatric disorders (3)(4)(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 (6) and white matter (7) and to 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. Further, primary deficits in NMDA receptor (NMDA-R) 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 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. Hoffman, for example, suggested that synaptic deficits associated with schizophrenia create a propensity for cortical networks to settle into aberrant representations of thought or sensory experience (22, 23). 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)(25–30). Also, studies of covarying regional brain activity assessed with fMRI 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 NMDA-R 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 chronic 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, it is possible that the increased rate of decline in cortical structural and functional indices in schizophrenia compared to 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 face of the 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 face 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) or 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 NMDA-R is selectively eliminated from cortical pyramidal neurons in mice, perhaps mimicking deficits in NMDA-R 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, i.e., 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-containing (PV) GABA cells including chandelier cells, which synapse on to 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-containing (CCK) basket cells, which express cannabinoid (CB1) receptors and temporally tune pyramidal neurons in a manner distinct from PV basket cells (including θ oscillations) (51), and somatostatin-containing (SST) interneurons, which gate the excitability of distal dendrites in an input-specific manner and which are vulnerable to stress (52). Recent data suggests that deficits in GABA neuronal function associated with schizophrenia arise as a consequence of deficient excitatory input (53) or responsivity to this input (54) and serve to reduce inhibition in cortical microcircuits in ways that compensate for reduced excitatory connectivity (55). The notion that reduced excitatory drive to interneurons would disinhibit cortical microcircuits would be consistent with evidence that NMDA-R antagonists reduce GABA neuronal activity (56), disinhibit activity in deep cortical layers in primates (20), increase extracellular glutamate in animals (57), raise voxel glutamate levels in humans (58), and increase high frequency activity in animals (59) and humans (60). Also, genetic ablation of the GluN1 subunit on parvalbumin neurons increases network excitability, increases resting gamma oscillations, and produces cognitive impairments in animals (48, 61).

Disinhibition in cortical networks may contribute to cortical network dysfunction and impairments in cognition and behavior. The impairment in neural function with increased activation is sometimes referred to as the “inverted-U” phenomenon because increasing input (arousal (62), working memory load (63), dopaminergic activation (64), thalamic activity (65), etc.) increases cortical output up to a particular level of output, beyond which, further increases in input produce declining benefit and if increased further, decreases in output. Grossberg (66, 67) hypothesized that in networks characterized by “gated opponent processes”, i.e., networks in which neurons mutually excite and indirectly (via interneurons) inhibit each other, maintenance of E/I balance supports network output up to the point of

optimal network activation. Beyond that level, elevated inhibitory tone recruited balance basal excitation at rest may reduce the ability of subsequent task-related input to activate the network; contributing to the downslope of the inverted-U curve. This hypothesis is consistent with evidence from schizophrenia (32, 34, 68) and ketamine effects in healthy subjects (69, 70) that resting hyperactivity and reduced task-related cortical activation are related. The integrity of the inverted-U in schizophrenia suggests that despite deficits, sufficient residual GABA tone remains to grossly balance E/I. This situation contrasts with autism, where some of the same genetic mechanisms are implicated, but where nearly a third of patients exhibit seizures (71). This observation suggests that autism may be associated with more profound disruptions of E/I balance than schizophrenia. However, it is evident that the inverted-U pattern is only one of several potential relationships between input and out in working memory networks. There appear to be specific properties (whether recurrent inhibition dominates recurrent excitation, whether excitation is dominated by AMPA-R or NMDA-R, etc.) that influence the relationship between basal and task-related activation within working memory networks (72).

Another inverted-U curve describes the relationship between dopamine signaling and working memory-related neural activity (see figure 2). Under optimal conditions, D1-R stimulation promotes persisting neural activity that supports working memory (73) and enables working memory networks to effectively sculpt through inhibition the pattern of neural activity to precisely represent spatial information in memory (74). However, if D1-R stimulation is too low as may be the case in schizophrenia (75), network activity becomes disinhibited and spatial information cannot be effectively encoded. In this context D1 agonists might be prescribed to promote inhibitory tuning of cortical activity. In contrast, if D1-R stimulation is too great, then activity in these networks is suppressed and mnemonic function is impaired (76). The inverted-U relationships describing the relationships between glutamatergic and dopaminergic function appear inter-related suggesting that they interact at an intracellular or network level. For example, within individual human subjects, the same dose of amphetamine that impairs working memory reduces working memory deficits produced by ketamine (77).

There may be treatment implications of cortical disinhibition in schizophrenia. First, if cognitive deficits are a response to basal cortical activation, then reductions in cortical excitation might reduce symptoms and improve cognitive function. This approach is consistent with the symptomatic efficacy of drugs that reduce glutamate release, like lamotrigine (78, 79) and the metabotropic glutamate receptor-2 (mGluR2) agonist pro-drug, pomaglumetad methionil (80). It also may be consistent with the efficacy of low frequency repetitive transcranial magnetic stimulation for suppressing medication-resistant auditory hallucinations (81). However, neither lamotrigine (82) nor pomaglumetad (83–85) showed widespread efficacy for schizophrenia. This limited efficacy in heterogeneous patient populations may be because, as noted, hyperactivity appears to be a feature most prominent early in the course of schizophrenia (2). Consistent with this hypothesis, pomaglumetad was efficacious for schizophrenia patients early in their illness, but in patients with long-standing illness it either had no efficacy or made them worse (86). Thus, inhibitory treatments might be the first illness phase-specific treatments for this disorder.

Deficits in spatial tuning of cortical activity and impairments in sparse coding

The representation of information by the cortex requires fine-grained tuning of the spatial dispersion of excitation within a localized area. Within the primate prefrontal cortex, the representation of particular spatial locations within spatial working memory depends on the selective activation of particular layer 3 neurons and their associated microcolumns as well as the interneuron-mediated inhibition of neighboring neurons and microcolumns representing competing locations (87, 88). The restriction of activity to a small minority of potential neurons is called sparse coding (89) and its integrity depends on inhibition (90). The interneurons mediating the spatial dispersion of pyramidal neuron activitation are specific to cell type and layer. Computational models suggest that several interneuron subtypes cooperate in spatial tuning including parvalbumin (PV), calretinin (predominately VIP-containing), and somatostatin-containing (SST) interneurons (91, 92). Among layer 5 pyramidal neurons, the activation of subcortically projecting pyramidal neurons seems to be gated prominently by parvalbumin (PV) neurons, while callosally projecting pyramidal neurons are inhibited by somatostatin-containing (SST) neurons (93). In the hippocampus, SST neurons regulate the spatial extent of neural activation associated with mnemonic encoding (94).

In the case of working memory, sparse coding conveys several important functions: 1) the ability to simultaneously maintain multiple mnemonic cell assemblies, i.e., larger working memory buffer size, 2) better perceptual and mnemonic precision, and 3) protection of memories from distortion by distractors (89, 95–98). A bump attractor computational model, which implements working memory through self-sustained persistent neural activity, sheds light on how reduced lateral inhibition compromises memory (see figure 3). Reductions in lateral inhibition produce dispersion of the neural representation of spatial information within memory, contamination of spatial representations by nearby distractors, and increases in signal variance (noise) (95). Disruption of sparse coding also may contribute to the formation of memories that are distorted by distracting stimuli, contributing to the formation of false memories, as has been shown in flies (96). In humans, NMDA receptor antagonists produce many stigmata of impaired spatial tuning of memory networks including smaller working memory buffer size, decreased precision of mnemonic encoding, and the production of “false alarms” in working memory (95, 99). Extreme hyperconnectivity also has been predicted (22) to contribute to hallucinations, delusions, loose associations, and other forms of thought disorder. Further, impairments in top-down control of cortical representations may increase dependence upon bottom-up sensory processes that are also distorted; further undermining the environmental fidelity of cortical mnemonic representations (100, 101).

Schizophrenia patients show signs of reduced spatial tuning of cortical activation that may be related to features of the disorder. Resting state fMRI studies in patients show evidence of functional hyperconnectivity, as noted earlier (31, 102). Schizophrenia appears to be associated with an “inverted-U” working memory load-dependent pattern of prefrontal activation; with increased magnitude and spatial extent of activation under conditions of low demand and activation deficits with higher working memory load (8, 103–105).

Schizophrenia patients also show reduced working memory span (buffer size) and precision (104, 106, 107), but perhaps not universally (108). The reduction in working memory precision is, in itself, one form of distortion in the mnemonic representation of information. Further, the reduction in mnemonic precision would be predicted to render memories more vulnerable to distortion or contamination (104), i.e., the generation of false memories, distorted beliefs, or delusions (109–111). As a result, pharmacotherapies that reduce glutamate release, such as mGluR2 agonists, might improve working memory function (95, 112) and treat psychosis (80). However, some hyperactivity might be recruited as compensation for connectivity deficiencies (105). In these cases, glutamate release inhibiting medications might worsen symptoms by exacerbating connectivity deficits rather than providing relief.

Deficits in temporal tuning of cortical activity: ensembles, oscillations, and codes

The neural representation of information is a property of the coordinated activity of assemblies (97, 113). Exactly how the brain accomplishes this task is somewhat of a mystery. A focus on individual cortical neurons has provided critical insights into working memory and other cognitive functions (114). However, it is likely that functional connectivity within ensembles is reflected in higher order properties of neural networks, such as oscillations in network activity, since the activity of individual ensemble elements are linked by feedforward and feedback excitation and inhibition, essentially, waves of activity (97). From studies of spatial memory, it appears that the timing of the activation of particular hippocampal cells and their contributions to neural oscillations have higher order functional properties, such as their organization into sequences that serve as a code for spatial information in the environment (97).

Schizophrenia is associated with disturbances in cortical oscillations. There has been particular interest in high frequency cortical oscillations, as they are generated by fast-spiking PV neurons (115) that appear to be compromised in post-mortem studies (19). In schizophrenia, there is a small increase in resting γ oscillations (116) and reductions in γ oscillations induced by cognitive tasks or evoked by 40 Hz click trains (117, 118). Surprisingly, the increases in spontaneous γ oscillations in schizophrenia contrast with the impact of optogenetic inactivation of PV neurons, where spontaneous γ oscillations are reduced (115). However, they are similar to the effects of ketamine, which increases resting γ oscillations in animals and humans, despite inhibiting some subpopulations of GABA neurons (56, 60, 119).

Some confusion related to interneuron dysfunction might be explained by concurrent impairments in SST and PV neurons (91, 92) in the context of residual fast-spiking neuronal function (figure 4). SST neurons may be more sensitive than PV to deficits in NMDA-R signaling. Fast-spiking neurons have higher AMPA/NMDA ratios and reduced sensitivity to the effects of NMDA-R antagonists than pyramidal neurons (120) or regular-spiking or low threshold-spiking interneurons (121, 122), i.e., firing patterns characteristic of SST interneurons (123). In visual cortex, layer IV SST neurons inhibit PV neurons while PV

neurons do not prominently inhibit other interneuron populations (124, 125). As a result, SST inhibition by NMDA-R antagonists would increase PV activity and thereby increase γ oscillations. SST neurons also target distal dendrites of pyramidal neurons (126, 127), so their inhibition would increase pyramidal neuron excitability. Lastly, SST neurons provide input-specific inhibitory filtering (126, 127), so reduced SST activity might produce hyperconnectivity, as seen with schizophrenia (31) and ketamine effects in healthy individuals (69). Thus, impairments in SST neurons might help to explain three consequences of NMDA-R signaling deficits for schizophrenia patients early in their course of illness (figure 4): 1) increased resting excitation, 2) increased functional connectivity, and 3) increased resting γ oscillations.

Studies of cross-frequency coupling of oscillation amplitude may provide clues into codes used by the brain for aspects of the neural representation of information (97, 128). In cross-frequency coupling, the phase of the lower frequency oscillation is related to the amplitude of the higher frequency oscillation. The synchrony of θ and γ oscillations is related to the efficacy of network functions, such as memory encoding (129, 130). In the hippocampus, the firing of particular place cells in the γ frequency range occurs at a particular phase of the θ cycle when the animal is at a particular location (97, 128). As an animal explores its environment, the phase of θ where that place cell fires advances or precesses (131). The orderly sequence of the firing of individual place cells activated as the animal explores its space, for example as it walks down a track, constitutes a neural code that represents the spatial properties of its environment. There is growing evidence that synaptic signaling mechanisms implicated in schizophrenia may profoundly alter the integrity of the neural codes so generated. For example, θ and γ power in the EEG signal in area CA1 are less sensitive to the effects of an NMDA-R antagonist than the precession of γ on θ (132). However, this type of drug disrupts the experience-dependent modifications in hippocampal CA1 place fields and so disrupts the capacity to flexibly encode the evolving environmental cues during exploration. Consistent with this observation, selective blockade of NMDA-R activity in the intrinsic circuitry of the rodent hippocampus (i.e., upstream area CA3) results in reduced feed-forward activation of interneurons along with a somewhat inflexible internally-driven neural representation of the external space in CA1 (133). While there are tantalizing early studies of cross-frequency coupling in schizophrenia (134–136), these studies have not yet produced clear implications for pathophysiology, symptoms and functional impairment, or treatment.

Ultimately, we want to understand the neural codes that the brain uses to generate complex behavior and how disturbances in these codes account for symptoms and functional impairment. This level of detail may be required to correct the pathology in neural signaling associated with schizophrenia. The integrity of the adaptability of the interplay between fast-spiking and non-fast-spiking interneurons may be important for these neural codes. Cannabinoids stimulate CB1 receptors, which in the hippocampus, are most densely localized to the terminals of CCK interneurons (137), where they inhibit GABA release by these neurons. Thus cannabinoid effects in the hippocampus shed light on the role of CCK basket cells in shaping hippocampal spatial codes. For example, the effects of Δ-9 tetrohydrocannabinol (THC) on the population firing rates of pyramidal neurons and interneurons in the hippocampus are subtle and the location-dependent firing of CA1 place

cells remains largely intact (138, 139). However, CB1 agonists reduce neural oscillations across several frequencies, decrease the theta phase precession of place cell activity, make neural representations unstable, and profoundly disrupt the temporal coordination of cell assemblies (138–140). In essence, compromised CCK cell function impairs memory by disrupting hippocampal neural codes even though firing is largely intact (see figure 5).

It would be interesting to know whether the disarray in these neural codes is related to the schizophrenia symptoms, such as delusions or formal thought disorder.

Tuning Deficits, Signals, and Noise

Tuning deficits associated with schizophrenia reduce the ability of neural assemblies to represent information, i.e., to generate signals. This review considered the impact of deficiencies in several forms of the tuning of neural activity among cortical network functions, i.e., activation level, spatial extent of activation, and the timing of activation. Each of these deficits contributed to reductions in signal integrity. Consistent with the inverted-U input-output relationship (figure 2), increases in resting activation would be predicted to reduce the task related signal by recruiting inhibition (66), consistent with findings with ketamine effects in healthy humans and studies of schizophrenia patients (31, 104, 105, 142, 143). Further, the hyperactivity of networks may recruit homeostatic adaptations that downregulate synaptic functional connectivity (figure 1), further impairing the capacity of networks to generate signals. The impairment in the spatial tuning of neural activity may reduce the capacity to efficiently encode information, i.e., it would reduce signals in memory and decrease memory precision (figure 3). The impairment in spatial tuning also may contribute to hyperconnectivity and the homeostatic downregulation of functional connectivity. Lastly, the impairments in temporal tuning may give rise to deficits in the recruitment of neural ensembles when performing cognitive operations, aberrant cross frequency coupling, and disarray of higher order neural codes (figure 5), contributing to cognitive and behavioral impairments.

However, it is possible that tuning deficits also produce dysfunction through the failure to suppress noise. Noise could be understood as a type of neural activity that degrades signal, i.e., reduces the signal-to-noise ratio. It also could be a source of aberrant signal. This point is illustrated by reductions in the tuning of the spatial extent of cortical activity. The bump attractor model (see figure 3) predicts that reductions in spatial tuning could generate two types of noise. The first is the random “background” noise that would be expected to degrade signal through reduced storage capacity or reduced precision of representations. The second type of noise might itself constitute aberrant signals. The bump attractor model suggests that the presence of nearby distractors actually distorts the spatial representation of the “target” stimulus encoded initially, creating one form of false memory. Second, the loss of precision in the representation of the memory for the target location can lead to false attributions, i.e., the identification of the off-target probe as existing within the target location. Similarly, the disruption of cross-frequency coupling and disrupted neural codes could also generate aberrant signals.

There is evidence of increased levels of both forms of noise in schizophrenia. With regards to background noise, fMRI studies have identified elevated cortical global functional connectivity (31, 102), the failure to suppress default mode activity during the activation of the executive control network (143), reductions in hierarchical organization of activity giving rise to increased connectivity at lower levels of organization (spoke-to-spoke rather than spoke-hub) (144, 145), and increased cortical signal variance (146) among other potential forms of noisy neural activity. With regards to the EEG signal, the increase in γ oscillations at rest (118) or during sustained auditory stimulation (147) may be forms of a more general increase in high frequency background EEG noise associated with schizophrenia (148). There are other ways that schizophrenia might be associated with the accumulation of aberrant signals through the failure to suppress noise. A form of long-range tuning, corollary discharge, appears to be deficient in schizophrenia (149). Deficits in this form of cortico-cortical inhibition has been implicated in the failure of psychotic individuals to recognize their own thoughts, speech, and perhaps other actions as internally generated. Sleep spindles are also reduced in schizophrenia (150, 151). Sleep spindles, may serve to enhance memory consolidation and to depotentiate synaptic connectivity in the service of eliminating “mnemonic background noise” (152, 153). From this perspective, deficient sleep spindles in schizophrenia may both impede learning (154) but also clutter mnemonic stores. Unfortunately, studies of cross-frequency coupling are limited and there are not yet intracranial recording studies that would inform questions of sequences in schizophrenia.

Implications

Disturbances in the signal representation and information processing properties of the cerebral cortex appear to be a proximal cause of symptoms and functional impairments associated with schizophrenia and perhaps other forms of psychopathology. This review highlighted ways that impairments in the tuning properties of cortical networks related to E/I imbalances could arise from signaling abnormalities within cortical microcircuits and then contribute to disturbances in the functional outputs of these circuits. This perspective may lead us to maintain a focus on the output properties of networks when attempting to fix disturbances in specific synapses within these networks when developing novel therapies. For example, it may be important for us to appreciate that inhibitory treatments that reduce disinhibition within cortical microcircuits may also exacerbate long-range functional connectivity deficits associated with schizophrenia. This broader perspective may help the field to move beyond the current problems in medication development for this disorder.

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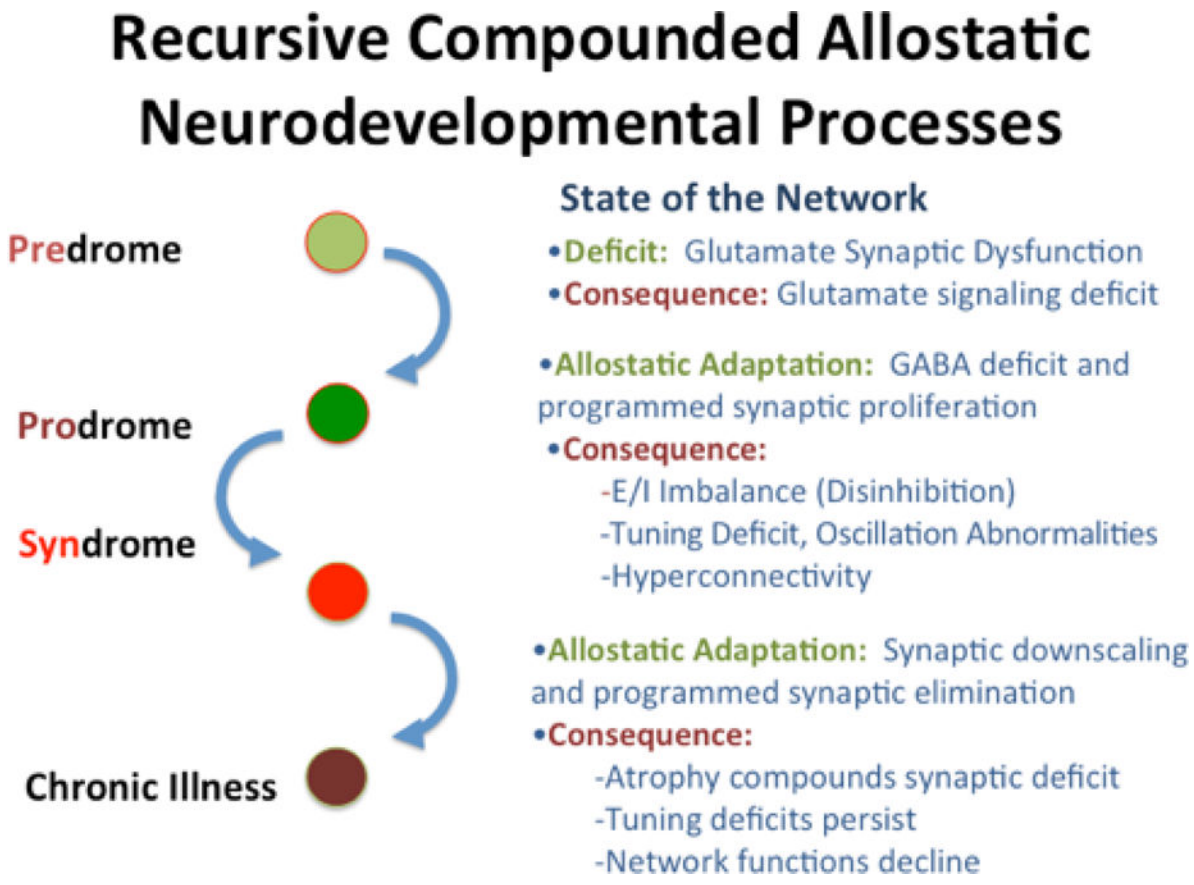

Figure 1.

Phases in the development of schizophrenia may be expressed, in part, through the accumulation of successive homeostatic neuroadaptations that serve to reduce E/I imbalances but come at a cost with regards to network integrity and function. In this way, the adaptations are viewed as allostatic rather than homeostatic. From (38)

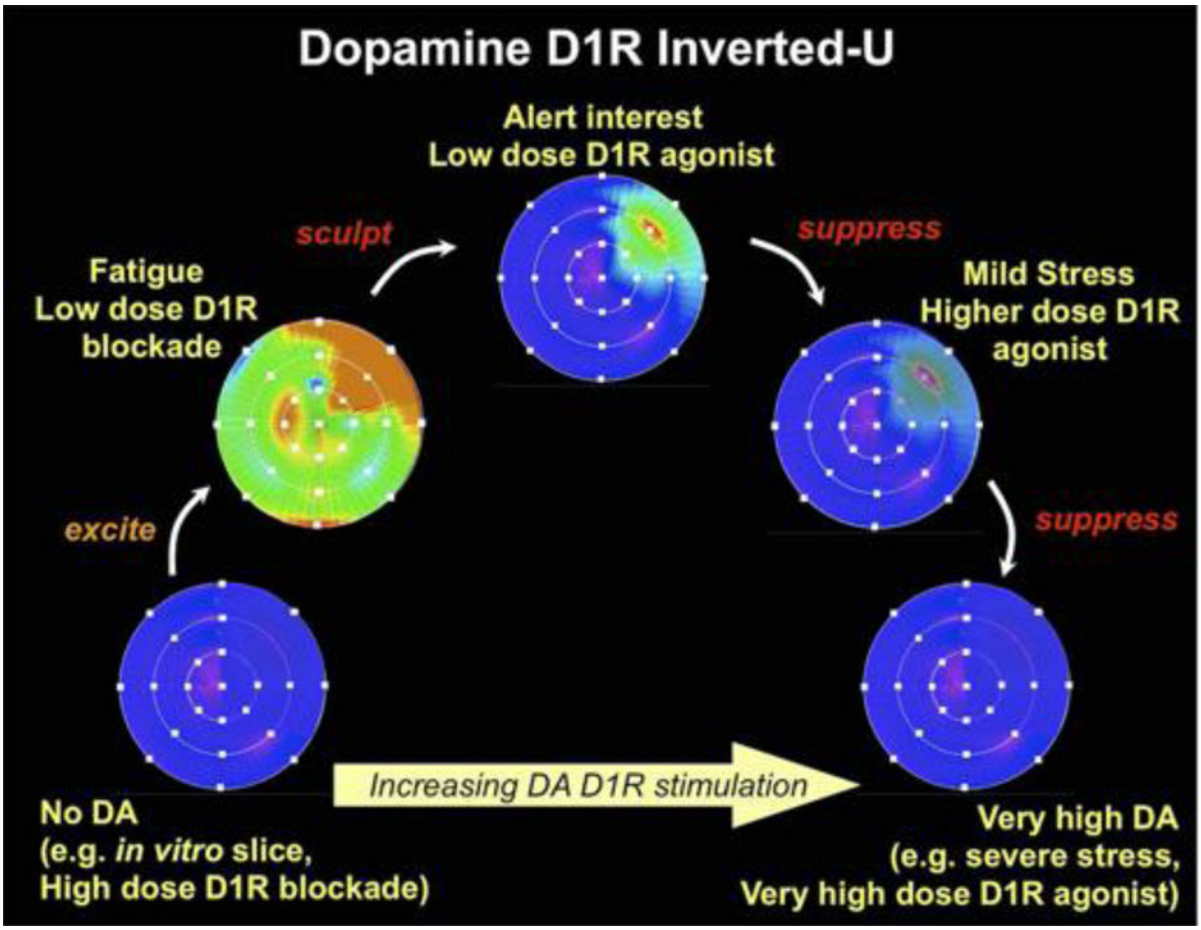

Figure 2.

A schematic illustration of the D1-R inverted-U influence on the "memory fields" of dorsolateral PFC Delay cells. Under optimal arousal conditions, Delay cells generate persistent representations of visual space, displaying high rates of firing (orange-red) to the memory of one spatial location and low rates of firing (blue) to the memory of all other spatial locations. Low levels of D1-R stimulation appear to be excitatory, e.g., phosphorylating NMDAR to increase their trafficking into the synapse. This can produce noisy firing for all directions, as represented by the generalized green-orange coloring of the memory field. With optimal levels of D1-R stimulation, there are additional sculpting actions, gating out "noise." This may involve opening of HCN channels on dendritic spines of layer III pyramidal neurons, enhancement of lateral inhibition by recruitment of interneurons, and selective reductions in glutamate release. At still higher levels of D1R stimulation as occurs during stress, neuronal firing is generally suppressed, and the neuron is unable to generate persistent representations of visual space (modified from (74)).

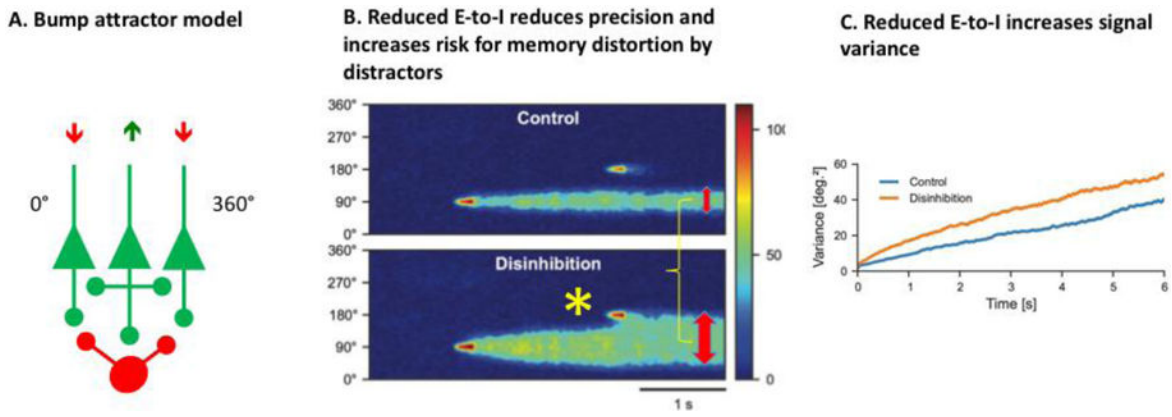

Figure 3.

Figure 3A. The bump attractor model provides for lateral inhibition of pyramidal neurons in a local circuit that maintains working memory through persisting neural firing, yielding the capacity to spatially focus activity. In this case, it allows for a center neuron to be activated (green arrow) but for surrounding neurons to be inhibited (red arrows) by local interneurons (red neuron). The properties of computational models elaborating on this simple circuit are presented in figure 3B. When recurrent inhibition is intact (top panel), the mnemonic representation of a stimulus is precise (small bidirectional red arrow) and there is no interference by neighboring stimuli (yellow arrow). However, when recurrent inhibition is reduced (bottom panel), the spatial extent of the memory becomes less precise (larger bidirectional arrow) and the same distracting stimulus now contaminates the mnemonic representation. Figure 3C. Reductions in recurrent inhibition in this model also increase signal variance (noise). From (95).

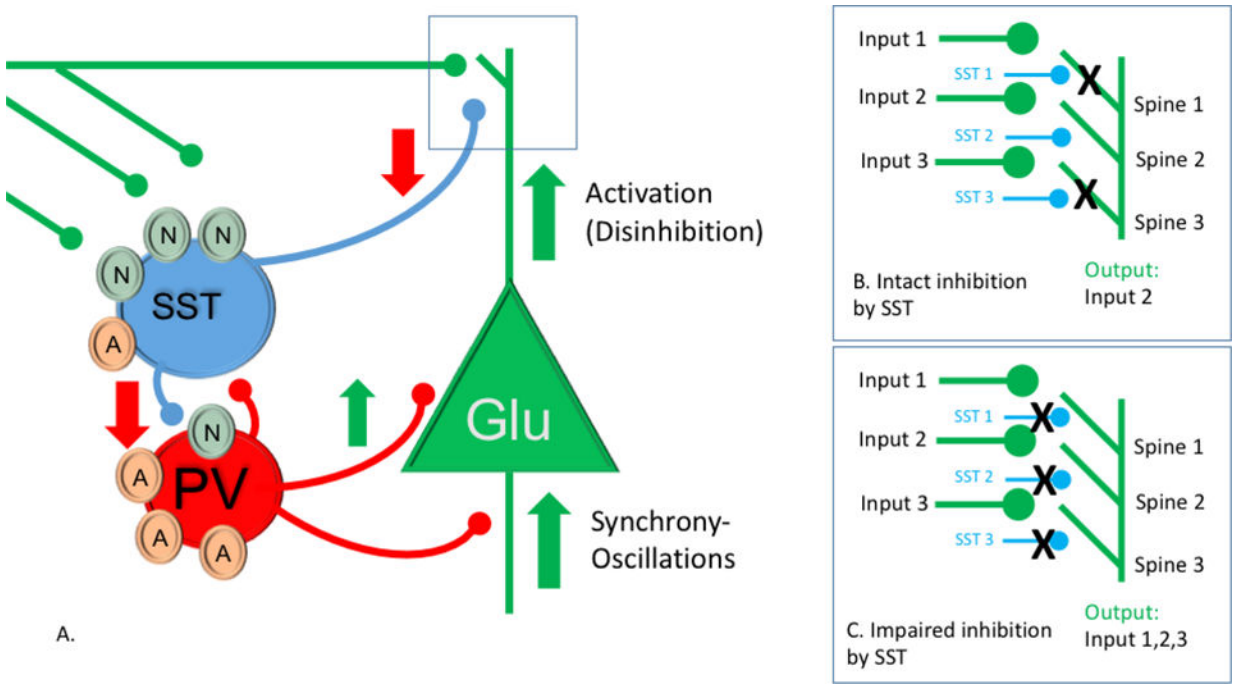

Figure 4.

Possible contributions of deficits in somotostatin (SST) interneurons to microcircuit dysfunction in schizophrenia. Figure 4A. SST neurons appear to have relatively greater dependence on NMDA-R (N) than parvalbumin (PV) neurons, which show relatively greater dependence on AMPA-R (A) stimulation (see text for citatinos). Reductions in SST inhibition of pyramidal neurons renders them hyperexcitable. Reductions in SST inhibition of PV neurons disinhibits them, increasing γ oscillations. Figure 4B enlarges the interplay of excitatory and SST inputs on to dendritic spines. Normally, SST neurons filter inputs yielding selective functional connectivity. Figure 4C highlights the potential for deficits in SST neuronal function to reduce input selectivity, giving rise to pathological (noisy) functional hyperconnectivity. References are presented in the text.

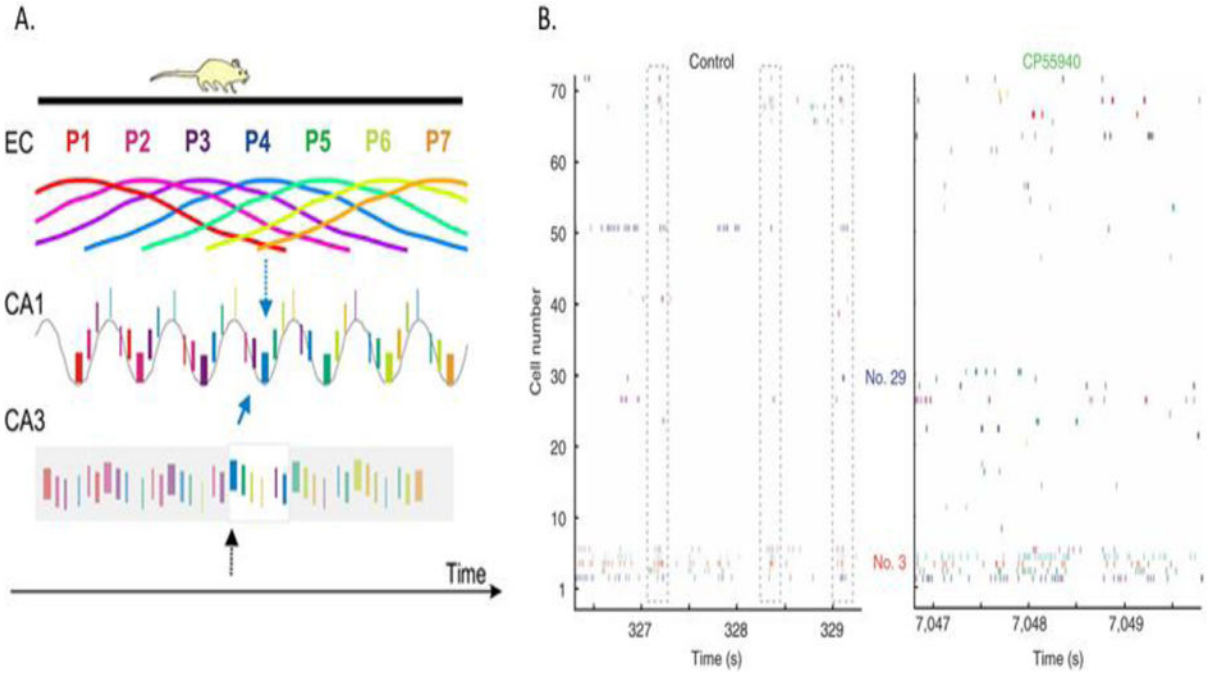

Figure 5.

Illustration of the relationship between sequences of hippocampal place cell neural firing and theta oscillation in the hippocampal encoding of spatial and temporal context (5A) and the disruption of this hippocampal coding by administration of a CB1 agonist (5B). Figure 5A. Illustration of a hippocampal CA1 place cell sequence and simultaneous theta sequences of activity during exploration of a linear environment. Each spatial position on a track (shown as Gaussian-shaped CA1 place cells, P1-P7) is defined by the most active cell assembly firing at the trough of the theta cycle (i.e., place cell P4-blue assembly). The width of the bars indicates assembly firing rates, while the temporal offset in firing curves between assemblies reflects the difference in their spatial representation (i.e., distance). Because each assembly contributes to multiple spatial representations, multiple assemblies are activated in each theta cycle. As a result, any particular assembly will be activated within a temporal context of prior and subsequent representations. The CA3 and CA1 representations correspond to the predicted (blue solid arrow) and updated (blue dotted arrow) by the entorhinal cortex (EC, activity not shown), respectively. One position is indicated in the boxed area. The black dotted arrow indicates the hypothesized initiation of sequence recall. Note reduced theta modulation as well as earlier activation of CA3 cell assemblies compared to CA1. Figure 5B presents evidence that stimulation of CB1 receptors undermines the integrity of the functional organization of hippocampal cell assemblies, i.e., scrambles the mnemonic codes. It presents representative raster plots of 71 simultaneously recorded CA1 cells in a control condition (Figure 5B, left figure) and after the administration of the CB1 agonist CP55940 0.3 mg/kg (Figure 5B, right figure). The number of spikes is not altered by the CB1 agonists (271 versus 270 spikes). Framed areas show synchronous discharges that are very clear in the control condition (5B left figure), but disorganized after the CB1 agonist (5B, right figure). From (139, 141).