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Excitation, inhibition, local oscillations, or large-scale loops: what causes the symptoms of schizophrenia?

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Abstract

What causes the positive, negative, and cognitive symptoms of schizophrenia? The importance of circuits is underscored by the finding that no single gene contributes strongly to the disease. Thus, some circuit abnormality to which many proteins can contribute is the likely cause. There are several major hypotheses regarding the circuitry involved: 1) a change in the balance of excitation/inhibition in the PFC; 2) abnormal EEG oscillations in the gamma range; 3) an increase in theta/delta EEG power related to changes in the thalamus (particularly midline nuclei); 4) hyperactivity in the hippocampus and consequent dopamine hyperfunction; or 5) deficits in corollary discharge. Evidence for these hypotheses will be reviewed.

Schizophrenia (SZ) involves delusions and hallucinations that collectively have been termed positive symptoms. The disease also has cognitive symptoms (e.g., memory processes and executive control), negative symptoms (e.g., anhedonia), and sensory deficits. Efforts are being made to develop physiological models that explain some or all of these symptoms and that are constrained by key findings bearing on the physiological basis of the disease. Among these findings are: 1) Disinhibition is suspected because of the reduction in the GABA-synthesizing enzyme, GAD-67, observed in postmortem tissue [1]. 2) Abnormalities in brain oscillations are observed, notably in the gamma and delta frequency bands [2,3]. 3) The most effective treatment of SZ is by drugs with D2 antagonism, suggesting dopamine hyperfunction [4]. 4) NMDAR antagonist, when given to normal subjects, produces many of the symptoms of SZ, suggesting that the disease involves NMDAR hypofunction [5,6]. Although no physiological model yet provides a clear explanation for all these findings, models with substantial explanatory power have been developed. These will now be reviewed.

Balance of excitation and inhibition in the prefrontal cortex

The prefrontal cortex (PFC) is implicated in SZ because of its involvement in executive and working memory functions that are abnormal in SZ. Furthermore, functional imaging indicates reduced activation of the PFC during cognitive tests of PFC function [7]. One basis for these abnormalities could be a change in the balance of excitation and inhibition. Disinhibition is suggested by the finding that GAD-67 is reduced in SZ, a reduction that would be expected to reduce inhibition [1]. This inference was tested in an animal model

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with reduced GAD-67 in parvalbumin-containing neurons of the PFC [8]. As expected, there was a reduction in functional inhibition, as indicated by the smaller size and lower frequency of mIPSCs. The reduction of GAD-67 (and other changes in gene expression) appears to be triggered by the reduction in Ca^{2+} entry through the NMDAR [**9]. This entry may be the mechanism by which these interneurons monitor pyramidal cell activity and try to stabilize it homeostatically. Thus, if NMDAR-mediated transmission is reduced, interneurons falsely sense less pyramidal cell activity and therefore reduce inhibition [10]. It would follow that GAD-67 would also be reduced if there were less pyramidal cell activity as a consequence of reduced excitatory input. This possibility is important to consider because in SZ there is reduced layer 3 spine density of PFC excitatory cells, a reduction that could be a consequence of the SZ risk genes, including DISC1 [11,12].

NMDAR antagonist also has acute effects by blocking the NMDAR-mediated EPSP that occurs in some interneurons and that results in reduced inhibition of pyramidal cells [*13]. Disinhibition of pyramidal cells due to a reduction of the firing of interneurons is seen *in vivo* [14] and can be counteracted by mGluR2/3 or mGluR5 agonists [15,16].

New optogenetic methods have made it possible to increase activity in excitatory cells by illumination of channel rhodopsin (related methods can fire parvalbumin-containing interneurons). An increase in the excitation/inhibition balance in mPFC produced a deficit in social interactions, as occurs in SZ [17]. Such methods open the door to critically testing the causation of deficits but will have to be combined with models that relate cellular function to behavioral function. Toward this goal, a computational model shows how recurrent excitation and inhibition can produce the persistent firing that underlies working memory function and how the effects of dopamine on synaptic and intrinsic conductances make this possible [18].

Gamma oscillations

A second line of work focuses on how an abnormal balance of excitation and inhibition might give rise to the abnormal gamma frequency oscillations observed in SZ. Oscillations in the gamma frequency range can be understood in terms of negative feedback in the local circuit [19–21]. Pyramidal cells having excitatory drive will fire and then excite interneurons. The fast-spiking interneurons that contain parvalbumin (basket and chandelier cells) produce perisomatic inhibition of pyramidal cells, which stops their firing (Fig.1). Once this inhibition decays, firing is reinitiated, thus starting the next oscillatory cycle. The high degree of convergence/divergence of the synaptic connections results in oscillatory synchrony among the cells involved. There are at least two known functions of gamma oscillations: 1) they allow only the most excitable cells to fire, thereby selecting the cells that form an ensemble [22]; and 2) they synchronize the cells of an ensemble, allowing the ensemble to be recognized by downstream networks using coincidence detection [23]. Multi-part messages can be coded by different ensembles firing in different gamma subcycles of slower theta oscillations [24]. Given the importance of gamma in neural coding, it would not be surprising that abnormalities in gamma would lead to confused messages. It has therefore been tempting to argue that disorganized thought in SZ might occur because of gamma abnormalities.

Gamma EEG oscillations in humans can be stimulated by a task, induced by a stimulus, or evoked by repetitive inputs. In almost all cases, the amplitude of gamma is reduced in SZ [**25]. This has prompted efforts to understand the mechanism of this abnormality. Computational modeling is an important tool for this effort because gamma, as observed in the field potential, depends in complex ways on both the number of pyramidal cells that fire and on their synchronization. The gamma evoked by 40 Hz clicks is reduced in SZ, and this,

as well as simultaneous changes in the 20 Hz response, can be accounted for by a model in which inhibition is slowed in SZ [26].

In another study [27], inhibition was attenuated by genetic deletion of AMPARs that mediate input to fast-spiking interneurons. This was found to reduce gamma in the field potential. Both experiments and computational modeling indicated that the reduced gamma was due to desynchronization of pyramidal cells (even though they fired more). This study thus supports the idea that the reduced gamma in SZ could be due to reduced excitation of interneurons.

Given the ability of NMDARs to induce many of the symptoms of SZ, it has been of interest to determine whether gamma oscillations are affected by block of these channels. Here the results have been somewhat confusing. NMDAR antagonist in slices increases gamma in some brain regions, but decreases it in others [28]. Experiments done *in vivo* show an increase in gamma power in response to NMDAR antagonist [29]. Several studies have knocked out NMDARs from fast-spiking interneurons [30–32], producing an enhancement of baseline gamma oscillations and deficits in various behavioral paradigms. The increase in gamma is consistent with most pharmacological studies, but is difficult to reconcile with the decrease in gamma found in SZ.

Part of the difficulty in understanding changes in gamma amplitude is the multitude of factors that can affect it. In elucidating the mechanisms that produce changes in gamma in SZ, it will be important to differentiate the local mechanisms (e.g., changes in the efficacy of feedback inhibition) from external task-dependent effectors (e.g., neuromodulatory inputs that depend on motivation and behavioral state). One method that may minimize the influence of task-dependent effectors is the use of a pulse of transcranial magnetic stimulation in the absence of a task. With this method, gamma frequency oscillations are induced and their power is found to be reduced in SZ [33]. There are many methods for inducing gamma in the slice, but gamma induced by a pulse-like tetanus [34] may be particularly useful because it allows comparison to the human results using a pulse of transcranial magnetic stimulation.

Is the deficit in SZ global or due to specific brain circuits?

Is SZ a general disease of the brain, or is there some specific circuit involved? Cognitive testing has shown that there are very few spared functions in SZ. Consistent with this, examination of arrays of genes related to inhibition (GAD-67 being only one) show abnormal expression not just in PFC, but in all regions examined, including visual cortex [35]. Such changes in visual cortex may well account for deficits in early visual function in SZ [36]. Thus, one view is that global abnormalities in cellular function change the balance of excitation and inhibition (and gamma). These diffuse changes might then account for the large number of functional deficits in SZ. On the other hand, the highly unusual positive symptoms of the disease suggest that some very specific brain processes are affected. The following sections deal with specific brain circuits that might account for such symptoms.

Hippocampus-dependent upregulation of the dopamine system

The hippocampus has been implicated in schizophrenia because there are changes in its functional activation and because there are memory deficits associated with the disease [37,38]. However, changes in hippocampus may have their largest effect not by changing hippocampal memory function, but by affecting down-stream targets of the hippocampus. Experiments show that direct excitation of the hippocampal region can, through a polysynaptic pathway, excite dopamine cells of the VTA [39,40] (Fig.1). This pathway is part of a learning circuit [41] by which a novelty signal computed in the hippocampus leads

to excitation of the VTA. This, in turn, leads to release of dopamine in the hippocampus that is vital for stable LTP and memory [42].

The link between the hippocampus and the dopamine system may be very important in SZ. Damage to the neonatal ventral hippocampus produces symptoms of SZ in adult animals [43]. Physiological analysis shows that the hippocampus is hyperactive, probably because of loss of interneuron function [44]. This hyperactivity leads to elevation in the firing of dopamine neurons in the VTA. Importantly, procedures that normalize hippocampal activity normalize the firing of dopamine cells and behavior [45].

Remarkably, the effects of neonatal hippocampal lesion can lead, in completely other regions, to some of the cardinal symptoms of SZ: a reduction of GAD-67 in the PFC and a reduction of gamma oscillations [44]. This spread to other regions may be mediated by hippocampal-induced abnormalities in the dopamine system. Notably, dopaminergic modulation of PFC interneurons develops abnormally, leading to PFC disinhibition [46].

Delta/theta oscillations originating from the thalamus via an NR2C-dependent mechanism

As noted above, there are EEG abnormalities in the gamma frequency band in SZ, but abnormalities have also been found in low-frequency (theta (4–8Hz) and delta (1–4Hz) ranges. Indeed, two recent meta-analyses conclude that enhanced low-frequency oscillations in the delta/theta frequency band of the EEG or MEG is a highly replicable finding in SZ [3,47]. The abnormality is seen in non-medicated patients and is not seen in unaffected relatives, making it a good marker for the disease.

Delta oscillations are normally present during slow-wave sleep, so their presence in the awake state in SZ suggests that part of the brain may be in an inactive sleep-like state [48]. MEG localizes these slow oscillations to the medial ventral PFC [49] (Fig.2A). Remarkably, the same region is one of the few locations where NMDAR antagonist lowers metabolism [50] (Fig.2B). This correspondence makes sense given studies of slow wave sleep showing that delta oscillations lower metabolism, probably because cell firing and gamma oscillations occur during only a small fraction of the delta cycle [51]. Indeed in this way, the presence of delta might account for the lowered average gamma power in SZ.

NMDAR antagonist can induce many of the symptoms of SZ, and recent work shows that this is also true for delta oscillations [52]. Insight has been gained into the mechanism by which NMDAR antagonist induces delta: antagonist acts on NR2C receptors in the nucleus reticularis of the thalamus (Fig.1), a region that contains PV-containing GABAergic cells and that is implicated in the control of thalamic relay cells and their interactions with cortex [53], in the sensitivity to NMDAR antagonist, and in SZ [54–58]. NR2C lacks Mg^{2+} block and can thus be partially activated at resting potential by ambient glutamate. Blocking these channels therefore produces hyperpolarization, and this removes inactivation from T-type Ca channels, leading them to produce bursting at delta frequency. This bursting can spread to thalamic relay nuclei and from there to hippocampus and parts of cortex.

All regions of cortex have thalamic innervations, but SZ is unlikely to result from a uniform deficit in neuronal function. It is therefore of interest that c-fos studies show that thalamic midline nuclei are particularly activated by NMDAR antagonist (Fig.3A). Among these is the nucleus reuniens [59], which receives input from the mPFC and sends output to the entorhinal cortex and CA1 region of the hippocampus [60]. The delta oscillations in the reuniens leads to excitation of the CA1 region [61]. Such excitatory input might explain the selective activation of CA1 in SZ [62].

As noted earlier, activity in the hippocampus can produce dopamine release. Among the regions of dopamine release is the nucleus reticularis of the thalamus, where dopamine produces hyperpolarization that promotes delta [62]. Thus, the thalamo-hippocampal-VTA loop has the potential for positive feedback (the thalamus excites the hippocampus, which stimulates the VTA, which promotes the bursting in the thalamus). One proposal is that genetic risk factors or prenatal insults move this loop closer to the threshold for positive feedback [63]. Conditions that stimulate strong dopamine release, such as stress, might push the loop above the threshold for positive feedback, thereby accounting for the sudden transition to the psychotic state. This, in turn, could activate the multiple targets of the dopamine system, including the PFC (Fig.1) and striatum. Schizophrenia generally does not occur until adolescence. Interestingly, positive feedback depends on NR2C in the thalamus, the expression of which does not occur until adolescence in the rat [64]. It would be important to determine the temporal expression of NR2C in humans.

Deficits in corollary discharge might underlie first-rank symptoms

The “first-rank symptoms” of schizophrenia are delusions, hallucinations, and the feeling that one is not controlling one’s own actions. It is this cluster of symptoms that seems most difficult to explain, but one class of models has led to progress [65,66]. The idea is that self-initiated action (e.g., speech) is identified as self by a comparison of the resulting sensation to the prediction of that sensation. The prediction arrives from motor-planning regions and is called corollary discharge. If the comparison produces a “match,” it provides the feeling that the speech was self-generated; if the comparison produces a “mismatch,” as would occur if the speech was due to someone else, there is the appropriate feeling of otherness. It is posited that this system fails in SZ by producing a mismatch signal to self-generated speech, leading the affected person to feel inappropriately that the speech was generated by “other.” In the absence of seeing someone else, it would be logical to conclude that the speech was “implanted by the FBI.”

In support of this class of model, theta frequency synchronization between frontal areas of motor control and temporal areas of sensory processing is poor when recorded speech is heard, but high during self-generated speech, perhaps reflecting the synchronizing ability of corollary discharge. If corollary discharge is defective in SZ, synchronization should be poor in both conditions. Experiments have shown this to be case [67]. The pathways that carry corollary discharge are generally not known, but in the one case that has been extensively studied, the corollary discharge about eye movements is sent from the superior colliculus to frontal eye fields via a thalamic pathway [68]. Thus, the corollary discharge for speech might also involve thalamic nuclei and possibly the nucleus reuniens (Fig.1). The delta state of sleep is known to interfere with normal information transmission by the thalamus. Thus, delta in SZ might interfere with corollary discharge. If this could be confirmed, it would provide a mechanistic understanding of some of the first-rank symptoms.

Conclusions

This brief review has highlighted areas of recent progress in understanding how specific circuit deficits might underlie SZ. Several important topics, including sensory gating and latent inhibition, could not be dealt with because of space limitations. A large number of susceptibility genes for SZ have been identified and can be found at: <http://www.szgene.org/>. Many of these are involved in glutamatergic transmission [10], while others (notably the ErbB4, a binding partner of the SZ risk gene, neuregulin) have a special role in interneurons [69–71]. Recent work extends the study of neuregulin-1 by showing that it affects the hippocampal-striatal pathway [72]. In terms of the certainty of linkage to SZ, neuregulin ranks 26th. The highest ranking gene (3d), and the only of the top

3 with known neuronal function, is the calmodulin binding protein, neurogranin. As noted earlier, midline thalamic nuclei are preferentially activated by NMDAR antagonist (Fig.3A). These same nuclei have local interneurons that are preferentially activated by neuroleptics [73] (Fig.3B). It was thus of interest to ask whether neurogranin is especially concentrated in midline nuclei. Fig.3C shows that this is the case. There are thus three quite independent lines of evidence pointing to the importance of midline thalamic nuclei in SZ.

The understanding of how brain circuits interact to perform function is an important goal for SZ research. The fact that no single gene strongly affects schizophrenia and that many genes have small effects makes it unlikely that a unique molecular process is involved. Similarly, it seems unlikely that any single brain region is involved; indeed, the abnormalities in GABA-related proteins are widespread. But still, the very unique and unusual properties of SZ suggest that something very specific must be involved. One resolution is that the changes in interneuron GAD-67 and the resulting changes in local circuitry lead to altered gamma. These local circuit changes are, however, quite general, leading to widespread modest cognitive deficits, many of which precede the psychotic break. These problems may arise from multiple genetic or developmental risk factors. At the same time, the reduced inhibition leads to enhanced brain activity that biases a specific brain circuit toward a sudden transition to abnormal function during the psychotic break. The thalamic-hippocampal-VTA loop discussed above is such a possibility. The specific large-scale loop would be commonly affected by a variety of risk factors. The identification of such a malfunctioning loop offers hope for therapeutic intervention; rather than having to treat the myriad gene abnormalities and perinatal insults that are risk factors for the disease (with different combinations in each individual), agents that normalize the function of the large-scale loop would have more general efficacy.

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Highlights

- Analysis of postmortem tissue shows a reduction in the GABA synthesizing enzyme, GAD-67, in schizophrenia. Experiments in which this reduction is mimicked show a reduction in functional inhibition.
- Gamma oscillations during a task are reduced in schizophrenia, perhaps because of reduction in feedback inhibition onto pyramidal cells. Procedures that reduce gamma lead to memory and cognitive deficits.
- Delta oscillations in parts of the thalamo-cortical system are enhanced in the awake state in schizophrenia, a symptom that has been mimicked by application of NMDAR antagonist to the thalamus. The sleep-like delta oscillations in specifically affected thalamic nuclei may interfere with normal function. Three lines of evidence point to a particular role of the midline thalamic nuclei.
- The best explanation for psychosis is the interference with corollary discharge, a process that for speech involves theta frequency synchronization between frontal and temporal cortex. This synchronization is abnormal in schizophrenia, perhaps because of thalamic delta oscillations.

Neonatal damage to hippocampus produces hyperactivity and hyperdopaminergic state

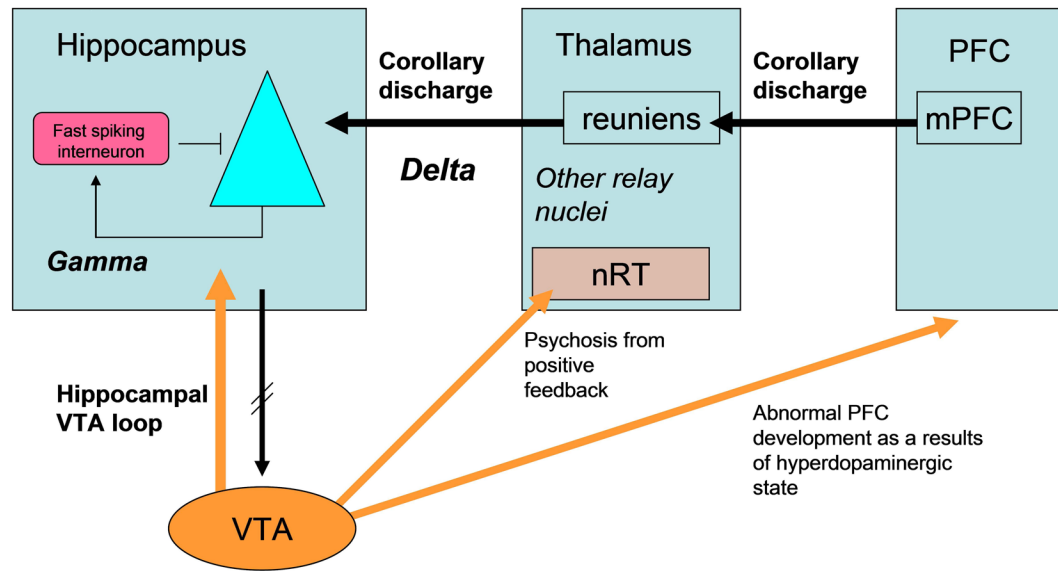


Fig. 1. Interactions between brain regions proposed to produce symptoms of SZ.

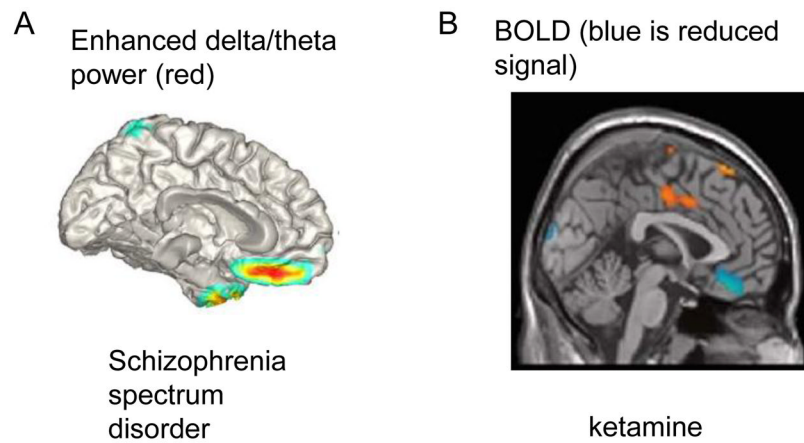


Fig. 2. Evidence for medial ventral prefrontal cortex involvement in SZ and response to NMDAR antagonist. **A.** Regions of enhanced delta/theta power in the resting awake state in schizophrenia spectrum disorders, as measured by MEG. (Reproduced with permission from authors as originally published in [**49]). **B.** Regions of decreased BOLD signal (blue) in response to ketamine. (Reproduced with permission from [**50]).

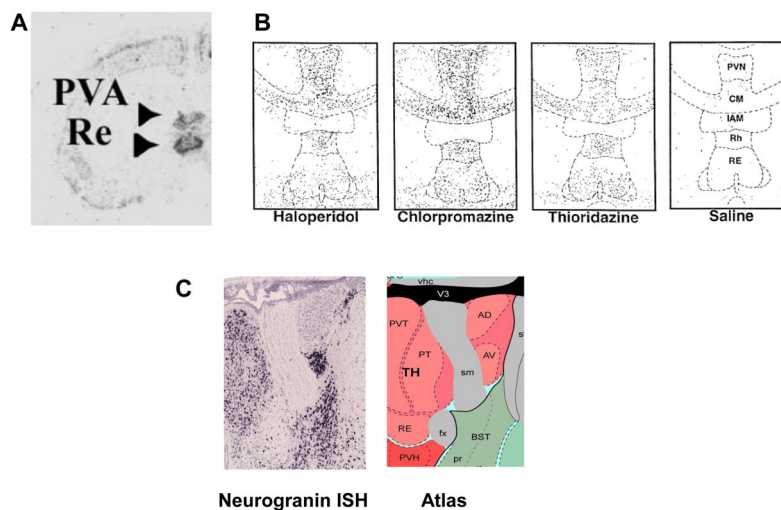


Fig. 3.

Evidence of special involvement of midline thalamic nuclei in SZ-related assays. **A.** c-fos activation in response to systemic NMDAR antagonist (Reproduced with permission from [59]). **B.** c-fos activation in response to neuroleptics used to treat SZ. Response is in local interneurons. (Reproduced with permission from [*74]). **C.** The midline group of the dorsal thalamus is labeled in this neurogranin RNA *in situ* hybridization image (left) from the Allen Brain Atlas. In the atlas key (right), thalamic nuclei are pink. The midline group consists of the paraventricular (PVT (PVN in B)) nucleus, the parataenial nucleus, and nucleus of reuniens (RE). Also shown in these images are the anteromedial (AM) and anteroventral (AV) thalamic nuclei. Note that A,B,C are at different magnification and at different sections through the thalamus.