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# Abnormal gamma oscillations in NMDAR hypofunction models of schizophrenia

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## Abstract

NMDA receptor (NMDAR) hypofunction in Parvalbumin-expressing (PV+) inhibitory neurons (IN) may contribute to symptoms in patients with schizophrenia (SZ). This hypothesis was inspired by studies in humans involving NMDAR antagonists that trigger SZ symptoms. Animal models of SZ using neuropharmacology and genetic knockouts have successfully replicated some of the key observations in human subjects involving alteration of gamma band oscillations (GBO) observed in EEG and MEG signals. However, it remains to be seen if NMDAR hypofunction in PV+ neurons is fundamental to the phenotype observed in these models. In this review, we discuss some of the key computational models of GBO and their predictions in the context of NMDAR hypofunction in INs. While PV+ INs have been the main focus of SZ studies in animal models, we also discuss the implications of NMDAR hypofunction in other types of INs using computational models for GBO modulation in the visual cortex.

### Keywords

schizophrenia; gamma oscillations; NMDA hypofunction; parvalbumin; inhibition; computational models

## Introduction

Schizophrenia (SZ) is a mental disorder that afflicts about 1% of the population and is manifested as mild or debilitating episodes of hallucinations and delusions, and cognitive deficits. Sensory-triggered hallucinations, disordered thoughts and delusions are termed *positive symptoms* and respond better to medication. Social withdrawal, lack of motivation and flat expressions form the *negative symptoms* and respond poorly to medication. Alterations in fundamental brain processes of perception as well as executive function are

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thought to underlie these outcomes in SZ patients (1, 2). Unlike conditions such as Alzheimer's (3), the disease does not involve major neuronal degeneration, although subtle deficits in certain neuronal populations have been described [(4-6), but see (7)]. Prior to clinical assessment, Schizophrenia thus remains a difficult to detect and poorly understood brain disorder.

Diagnostically, several functional and behavioral measures using electro-encephalograms (EEG), magneto-encephalograms (MEG) and functional magnetic resonance imaging (fMRI) are being developed to identify the SZ population from control. For example, sustained oscillations in these signals, that reflect coordinated activity of neural populations, are identified as an increase in power in a narrow band of frequency and are compared between control and SZ patients in terms of both their strength/amplitude/power and frequency. The narrowband power is compared in various behavioral states: *stimulus*- or *task-driven* state when the subject is actively processing a stimulus and/or performing a cognitive task, and *baseline* or *resting* at other times (Supplement 1). Since resting state in rodents is ill defined, we refer to both as *baseline* in the review of animal models. The *stimulus/task-driven* power is compared both in terms of its *evoked* component as well as *induced* (2) (Figure S1 and text in Supplement 1). This review focuses mainly on observations of induced narrowband power in the Gamma range (30-80 Hz), commonly referred to as Gamma Band Oscillations (GBO); GBO are of interest because they have been implicated in synchronization of neural ensembles during working memory, feature binding, dynamic routing of information and attention (8, 9). The review first summarizes the observations on GBO abnormalities in patients and the related data in a class of animal models of SZ. It then discusses several computational models of induced GBO for mechanistic insights. Finally, the review discusses the implications of recent findings about the microstructure of the local cortical inhibitory circuits for the computational models and ultimately the animal models of the disease.

## Abnormal GBO in schizophrenia patients

Abnormalities in the strength of GBO power in EEG and MEG have been consistently observed in studies with SZ patients (2, 10). GBO power has been reported to be both higher and lower compared with control subjects depending on the task and brain state.

### Task dependence

GBO are reduced in SZ patients during sensory processing and working memory [(2, 11-14); but see (15, 16)]. In addition, the severity of the *positive* or *negative* symptoms co-varies with alteration of GBO power: a pattern of enhanced GBO emerges in patients with more severe *positive* symptoms (11, 15, 17, 18), but a clear pattern does not emerge in cases where GBO is reduced in SZ patients (15, 16). The differences that are reported are significant for groups but have low predictive power on individuals.

### Brain-state dependence

GBO modification in SZ patients depends on the brain state during which activity is monitored. GBO are weakened during sensory processing across multiple modalities (12,

15, 18, 19). For the same group of patients, GBO activity was higher than control subjects before presentation of sensory stimulation (20) (Figure 1A), or *baseline*, but lower during sensory processing, or *stimulus-driven state* (17) (Figure 1B). It should be noted that the increase of *baseline* GBO was significant only at 40 Hz, the frequency of the steady-state stimulation. In addition, the increase was not significant across all electrodes (Figure 1A). However, others studies have reported a decrease in *baseline* GBO (21). Reconciling GBO changes across studies will require separating the effect in stimulus-locked, or *evoked*, EEG signal vs. *induced* part of the signal (22). Each component reflects different aspects of information processing in the cortex: Evoked GBO reflects bottom-up sensory transmission, whereas induced GBO represent the emergent dynamics within cortical networks.

## Animal models of SZ

The development of animal models has been confined to measurable symptoms of the disease such as altered sensory processing, locomotion and social behavior. These models have explored several hypotheses about deficits in specific neurotransmission systems that could form the basis of the modified neural processing in SZ patients. Dopamine system has been implicated because antipsychotic drugs target mainly dopamine D2 receptors (23, 24). However, results suggested that glutamate might also be involved (25); low doses of ketamine or phencyclidine, antagonists for glutamate receptor N-methyl-D-aspartate (NMDA), produce a syndrome similar to a psychotic episode in healthy humans (26-34). The main mechanism behind the psychotic effects of these antagonists is thought to be the disinhibition of excitatory circuits in brain (35-37). Postmortem studies in the prefrontal cortex in SZ patients, on the other hand, have shown deficits in the neurotransmitter gamma-amino butyric acid (GABA) that is released by a majority of inhibitory interneurons (IN) in the brain (1, 38-42).

These findings have inspired the hypothesis that disruption of NMDAR neurotransmission in INs leads to abnormalities in the GABA neurotransmission machinery in SZ. Indeed, postmortem evidence in the anterior cingulate cortex suggests that the density of GABAergic INs that express the NMDAR NR2A subunit is decreased in SZ patients in general (43); in particular, the glutamatergic innervation of subsets of GABAergic cells might be differentially altered (44). This has been recently explored in both *pharmacological* and *genetic* animal studies (Supplement 1). In addition to behavioral performance, changes in GBO have been observed during *baseline* and tasks in both surface EEG recordings as well as local field potentials (LFP), a surface-localized “depth” EEG using penetration micro-electrodes.

## Abnormal GBOs in animal models of NMDAR hypofunction

Abnormal GBO are observed in pharmacological as well as genetic NMDAR hypofunction models of SZ (45, 46), which are summarized in the following text.

### Pharmacological models

*In* vitro, acute treatment with ketamine, a nonspecific NMDAR antagonist, decreases the strength of kainate-induced GBO in medial entorhinal cortex (47). However, the same

treatment increases the kainate-induced GBO in the primary auditory cortex (48). *In vivo,* chronic treatment with NMDAR antagonists reduces the strength of hippocampal GBO activity (49). However, acute systemic treatment with NMDAR antagonists causes a significant increase in GBO power in the hippocampus and frontal cortex both before and during stimulus processing (49-52). Increase in baseline GBO power *in vivo* in response to acute treatment with several NMDAR antagonists has been seen in multiple studies in rodents (53-60). Pharmacological models thus demonstrate a mixed dependence of GBO on brain state as well as frequency and duration of drug treatment; the latter requires careful further investigation since differences in this factor can translate to immediate (GABAergic disinhibition) vs. long-term (compensatory homeostatic mechanisms) modification of the cortical network with unique downstream effects on GBO.

## Genetic models

In addition to several SZ-like symptoms, genetic models show abnormalities in GBO power in a brain-state dependent manner (Figure 2). In models involving genetic ablation of NMDARs in PV+ INs, increased GBO power is observed in the *baseline* LFPs recorded from awake behaving mice, in both the neocortex (61) and the hippocampus (62). The increase in power is broadband, but is shown to be statistically significant in the gamma range of frequencies. In the same model, “stimulus-processing state” GBO induced by optogenetic stimulation have reduced power as compared to control (61). In other models involving hypofunction of NMDARs in GABAergic INs that is not restricted to the PV+, and occurs earlier in development, the *baseline* LFPs also show a broadband increase in power (63). At the same time, the *stimulus-processing state* GBO show a decrease in response to auditory stimulation. In general, the genetic models show a consistent dependence of GBO on brain states. One proposed hypothesis for the reduced GBO during sensory processing in both humans and rodent models is that the increased GBO power during *baseline* period causes a ceiling effect, preventing further GBO recruitment during cognitive tasks (20, 64). However, in the genetic model of NMDAR hypofunction in GABAergic INs not restricted to PV+ (63), the baseline GBO power in the period between repeated presentations of auditory stimuli does not shown any change from control animals; the ceiling effect does not thus explain the entire dataset and requires further investigation in terms of differences in the brain state between the two protocols; a separate definition of *baseline* vs. *resting state* in the animal models would be a step in the direction of reconciliation of the data. Caution also needs to be exercised while comparing human and animal studies; GBOs in most animal models are analyzed in LFPs while human studies involve EEG or MEG (Supplement 1).

Several hypotheses have been proposed regarding the mechanisms underlying the GBO alterations in both the SZ patients and animal models (2, 10). GABAergic INs are crucial to the generation of oscillations in the cortical population activity and PV+ INs are considered a major contributor to the generation of GBO (65-68). However, unraveling the mechanism of GBO modification in SZ, even for the animal models, is challenging due to at least two key reasons: imprecise understanding of the action of NMDAR antagonists in the pharmacological model and the effects of homeostatic mechanisms during development in the genetic models (Supplement 1). Given these complex issues, computational modeling of

GBO is an invaluable tool to explore the various hypotheses regarding the changes in networks that not only modify the GBO, but also ultimately lead to SZ symptoms. GBO computational models have been broadly categorized as those involving IN-IN interactions also termed as ING (*Interneuron Network Gamma*), or those involving PN-IN interactions, termed as PING (*Pyramidal-Interneuron Network Gamma*) (Figure S2). They can be further categorized based on the underlying mechanisms and their unique predictions (Table 1). While these models have been previously reviewed in great detail (66), we discuss some of the most relevant ones in the context of the data considered in this review.

## Computational models of GBO modulation

### Modeling the increase in baseline GBO

*Baseline* activity in animal models of NMDAR hypofunction shows a moderate to robust increase in GBO power. Since this is also observed in the genetic knockout model of NMDARs in the PV+ INs, altered PV+ inhibition in the cortical network could have a key role in this effect. This hypothesis was explored in a computational model (61) that is based on the GBO mechanism of synchronization of neural oscillators, which we term here as NO-ING or NO-PING (Neural Oscillator based ING or PING) (Table 1)(69-73). The modified cortical circuit in the NMDAR receptor knockout mice was captured as decreased excitability of fast spiking INs in the computational model (61) (Figure 3A). In the presence of noisy background activity, this modification to the model resulted in reduced spontaneous activity in the PV+ INs during minimal (baseline period) excitation, resulting in increased synchronous activity of excitatory population. Since reduced excitability of the model INs required more synchronized excitation to activate them, it resulted in more synchronous inhibition at gamma frequency and hence an enhancement of GBO (Figure 3B). Other models exhibited stronger GBO with weakened E-to-I connections as a result of NMDAR hypofunction in an E-I network (74, 75).

However, these computational models conflict with the observation that, in at least one animal model of NMDAR hypofunction, disinhibition of cortical excitatory neurons is accompanied by reduced neuronal synchrony (76). It should however be noted that in this animal model the hypofunction was not limited to PV+ neurons in the cortex. In addition, as was pointed out earlier, the alterations in NMDAR function in the different animal models occur at different points during development; it is thus not clear how comparable the different animal models are in terms of the GBO observations. A recent *in vivo* study has revealed that cortical disinhibition achieved by MK-801, an NMDAR antagonist, causes an increase in GBO power but a reduced synchronization in the firing of action potentials in the mPFC of free-moving rats (60). While INs have been shown to be more sensitive to NMDAR antagonists (77), a broad range of cortical INs are expected to be affected in these experiments (60), similar to the genetic knockout model of Belforte et al. (76). This suggests the possibility that the increase in *baseline* GBO power in the animal models of cortical NMDAR hypofunction could also reflect a robust increase in synaptic inputs due to disinhibition, and not a true increase in synchronization of neural activity, as seen in the computational models (61, 70, 71, 73). Finally, a key issue with the models of GBO that are based on synchronization of neuronal oscillators is that they show a narrow distribution of

inter-spike interval (ISI), whereas, experimental data from cortex and the hippocampus suggests a broad distribution of spike ISIs during GBO (78-80).

We recently explored the modulation of GBO power and frequency in a special case of Wilson-Cowan (81) oscillation model based on an Inhibition-Stabilized PING model (ISN-PING) with superlinear inhibition (82, 83). The strong inhibition in this model stabilizes the positive feedback in the population of pyramidal cells. This model replicated a range of observations on GBO modulation in the primate visual cortex (82). The model predicted rate-level oscillations, rather than spike to spike, with a broad distribution of ISI. In this regime, the power of GBO in the model is proportional to the ratio of stimulation to the local excitatory and inhibitory neurons, other factors remaining relatively unchanged; if this ratio increases, power in GBO increase (82, 83). The model predicts an increase in the GBO strength if the key effect of NMDAR hypofunction is captured as reduction in the excitability of INs (83). However, the model predicts a decrease in the GBO strength if the key effect of NMDAR hypofunction is captured as a selective decrease in the strength of excitatory connections to the INs (83).

Finally, it is not known how the cortical circuit re-organizes through compensatory mechanisms in the genetic knockout models. This makes it difficult to accurately model the effects of genetic knockout of NMDARs in PV+ neurons in this as well as other computational models, especially since the alteration occurs at different developmental time points in different animal models. A clean way to test the computational models would be acute suppression of NMDARs selectively in PV+ neurons (thus allowing the circuits to develop normally), which could be a possibility in future.

### Modeling the decrease in GBO during stimulus processing

As discussed above, several studies in SZ patients and rodent model of NMDAR hypofunction demonstrate a reduction in GBO strength during sensory stimulus processing (Figures 1 & 2). An underlying cause is thought to be the reduced excitability of PV+ INs, which are crucial to GBO generation. Most computational models show sensitivity of GBO strength to the excitability of INs (Table 1), and predict weaker gamma in response to reduced excitability, such as through NMDAR hypofunction in the INs. Here we discuss the specific predictions of different computational models and how they might be tested in future.

Computational models based on synchronization of integrate-and-fire type neurons, which we group and term here as NO-ING or NO-PING (70, 72, 84-88) (Table 1) predict unsustainable GBO when the drive to inhibitory neurons through NMDAR hypofunction is sufficiently reduced. Other models of PING-type GBO exhibit similarly synchronous firing with Hodgkin-Huxley type spiking mechanism in INs (74, 88, 89). One such model predicts stronger GBO with reduced feedback excitation to INs from the local E neurons (74), while another predicts weaker GBO with reduced feedforward excitation to INs (88). Since reduced excitability of INs affects both feedforward and feedback coupling to PV+, it remains to be seen how these effects interact in a computational model of NMDAR hypofunction. One prediction is that GBO could either decrease or increase when the local network is strongly driven by the stimulus, depending on the balance of feedforward vs.

feedback excitation to INs. Computational modeling, anatomical evidence, *in vitro* experiments as well as those using knockout mice shows that gap junctions between GABAergic INs can facilitate GBO, specifically the ING type (90-92). While gap junctions are an important mechanism for synchronizing neuronal activity, the evidence for their disruption in GABAergic neurons in SZ is not clear. We have thus limited this review to examining the connection between oscillatory disruption observed in SZ patients and disruption in chemical synaptic function.

Oscillations in networks can also arise from a mechanism that does not rely on synchronization of individual neural oscillators. In such models, the oscillations are not spike-to-spike, but are observable in the firing rates (93, 94). The mechanism relies on communication delays such as axonal conduction delays and synaptic transmission; the frequency of oscillations is sensitive to these delays. GBO strength in these models, which we term here as D-ING or D-PING (*Delay based ING or PING*), depends on the drive to the INs; they predict weakened oscillations with reduced drive. This would predict weakened GBO with NMDAR hypofunction in the INs. However, in computational models involving both AMPA and NMDA-mediated excitatory conductances, GBO has been shown to be sensitive to mostly AMPA (and not NMDA)-mediated excitation (93). The high sensitivity of GBO to AMPA receptor hypofunction is explained by the need of fast excitation to IN to sustain oscillations in the computational models of GBO; AMPA sensitivity of GBO has also been experimentally demonstrated in animal models with genetic modification of AMPA receptors in PV+ GABAergic neurons (95).

The ISN-PING model captures a range of observations on GBO modulation in the primate visual cortex (82, 83). If a modification of relative stimulation to local E-I population results in an increase in the net firing rates in the network, it predicts a decrease in GBO power (Figure 4A). When NMDAR hypofunction is modeled as selective decrease in excitation to PV+ neurons that relieves the net inhibition in the local network, the model predicts a decrease in GBO power, as is also observed the genetic models (61) (Figure 4B). However, a recent study with selective NMDAR ablation in pyramidal neurons, in the cortex and hippocampus, also infers a reduction in GBO power (96). While the study reports an increase in the excitability of pyramidal neurons in the animal model, it is not clear if this translates to an increase in spiking response to stimulation. If it does, the computational model provides a mechanism for the observed decrease in GBO power.

Finally, computational models have several limitations in their ability to shed light on underlying mechanisms. They do not address the effects of the cellular/molecular consequences of chronic NMDAR antagonist treatment or ablation of NMDARs in early life, nor the extent to which NMDARs or other receptors are blocked in non-PV+ IN types. Acute NMDAR blockade in adulthood is probably the best understood case in terms of likely cellular changes, with the most potential for successful exploration (computational and otherwise) of modulation of GBO and other network behavior. In addition to more precise characterization of the effect of NMDA hypofunction, predicting the circuit-level disinhibitory effect will involve taking into consideration the additional complexities of connections between the different IN types found in the cortex and hippocampus; some of these have been recently revealed to provide disinhibition to the excitatory neurons. Future

efforts in computational modeling will necessitate the evaluation of these disinhibitory mechanisms.

## Mechanisms of cortical disinhibition

The reciprocal interaction between the pyramidal neurons and the PV+ INs is the core of the feedback circuit that generates GBOs using the PING mechanism. Inputs to this circuit include thalamo-cortical projections, lateral interactions from neighboring columns and feedback from other areas. Additional cortical circuits involving non-PV INs modulate the gain of the network and the overall level of activity level. For example, a series of studies using optogenetic techniques have uncovered a disinhibitory circuit involving somatostatin positive (SOM+) and vasoactive intestinal polypeptide immunopositive (VIP+) INs (97-99) (Figure 4C). In multiple cortical areas in the mouse, SOM+ INs target both pyramidal and PV+ INs, but silencing SOM+ INs increases the overall excitatory activity in the cortex (100). Integrating these details in different computational models will have unique predictions (Figure 4D; Supplement 1). The predictions related to disinhibition in the cortex due to NMDAR hypofunction in non-PV+ IN types have not been explicitly tested in animal models, but in the final section we briefly discuss the literature that supports a role for alterations in non-PV+ IN types in causing GBO alterations seen in SZ.

## NMDAR hypofunction in non-PV neurons: Postmortem studies

Several lines of experimental evidence suggest that hypofunction of NMDARs is more robust in INs than pyramidal neurons [(22, 77, 101), but see (102)]. Alteration in neurochemical markers of GABA transmission is most prominent in PV+ INs in response to NMDAR hypofunction in the adult cortex (103). However, postmortem studies show that not all classes of cortical INs are affected equally in SZ patients (39, 41, 42, 104). Significant expression deficits in mRNAs associated with GABAergic neurons, including mRNAs of the neuropeptides SOM, Y, and cholecystokinins have been detected in postmortem prefrontal cortical tissues of SZ subjects (39). In hippocampal tissue of SZ subjects, a reduction in the number of PV+ and SOM+ interneurons, and the level of PV+, SOM+ and glutamic acid decarboxylase mRNA expression has been reported (105) (Figure 5A). On the other hand, the levels of calretinin (an interneuron cell-type marker, like PV and SOM, of cortical GABAergic interneurons) are largely unaffected (6, 39, 106). The deficits also show specificity along the cortical laminae; in postmortem studies in prefrontal cortical tissue, SOM mRNA expression is significantly reduced in layers 2 to superficial layer 6 in SZ patients (41) (Figure 5B). Amalgamation of several postmortem studies suggest that SZ patients show alteration of SOM+ inhibitory neurotransmission to the apical dendrites of pyramidal neurons whose cell bodies are present in the deep layers of the DLPFC (107) (38).

## NMDAR hypofunction in non-PV neurons: Neuropharmacology & Computational models

In a recent EEG study in rats, several NMDAR antagonists show non-monotonic dose–response effects on cortical GBO power (108). A recent computational study demonstrates

that NMDAR manipulation in a single IN population can give rise to a non-monotonic U-shaped dependence of stimulus-induced GBO on NMDAR efficacy (109). On the other hand, at least two local IN populations with either “low” or “high” sensitivity to NMDAR antagonists are crucial to the conceptual model proposed for GBO modulation in response to NMDAR antagonists (108). While PV+ INs are implicated in the GBO generating population (67, 68), the involvement of subpopulations of PV+ INs with differential sensitivity to NMDAR antagonists, or even non-PV+ classes of INs is a possibility (110). In addition to deficits in the GABergic system itself, there are other modulators of inhibition that could play a role in the deficits observed in the disease and need further consideration (Supplement 1).

## Conclusions and Future directions

We have examined the empirical data and computational models that support the hypothesis that NMDAR hypofunction in inhibitory neurons, specifically the PV+ ones, may contribute to the observed GBO abnormalities and ultimately the symptoms in patients with SZ. However, possible contribution of other inhibitory systems cannot be ruled out. NMDAR hypofunction in non-PV+ cortical INs, such as SOM+ INs, that exert inhibitory control on cortical activity may also be involved; this finds support in postmortem studies. In addition, recent characterization of SOM+ INs in the rodent somatosensory cortex suggests that they provide differential inhibition to excitatory neurons as well as PV+ INs in a cortical layer specific manner (111). How the disregulation of this sub-system influences the dynamics of the mature cortical circuit both in terms of GBO and otherwise is an important question. In summary, studies focused on the developmental aspects of the complex inhibitory/disinhibtory systems will help elucidate how and when its dysfunction leads to the permanent alterations in cortical circuitry responsible for the observed changes in oscillatory activity in schizophrenia.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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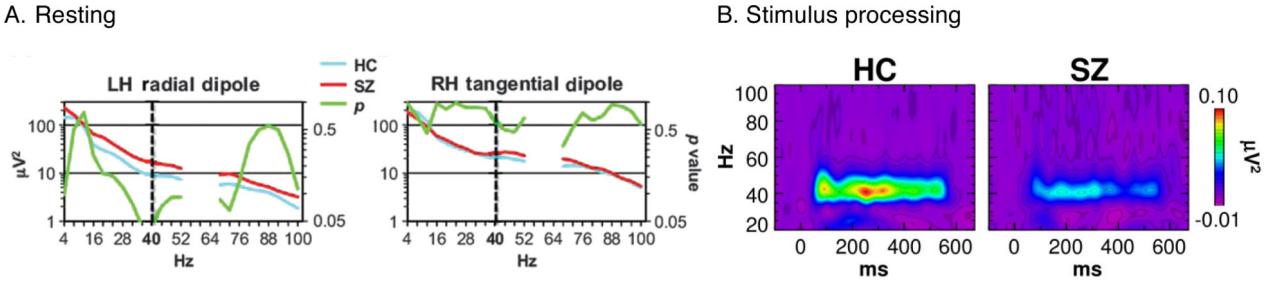


**Figure 1. Brain-state dependent modulation of GBO in SZ**

EEG signals recorded during resting state (A) and stimulus-processing (B) states in SZ patients and healthy controls (HC). Stimulus-processing state data were recorded during periodic auditory stimulation at 20 Hz. (A) Time-averaged power in different frequency bands in the EEG signal (blue and red). Also shown is the *p*-value (green). (B) Power in different frequency bands in the EEG signal as a function of time. (Adapted from (17, 20))

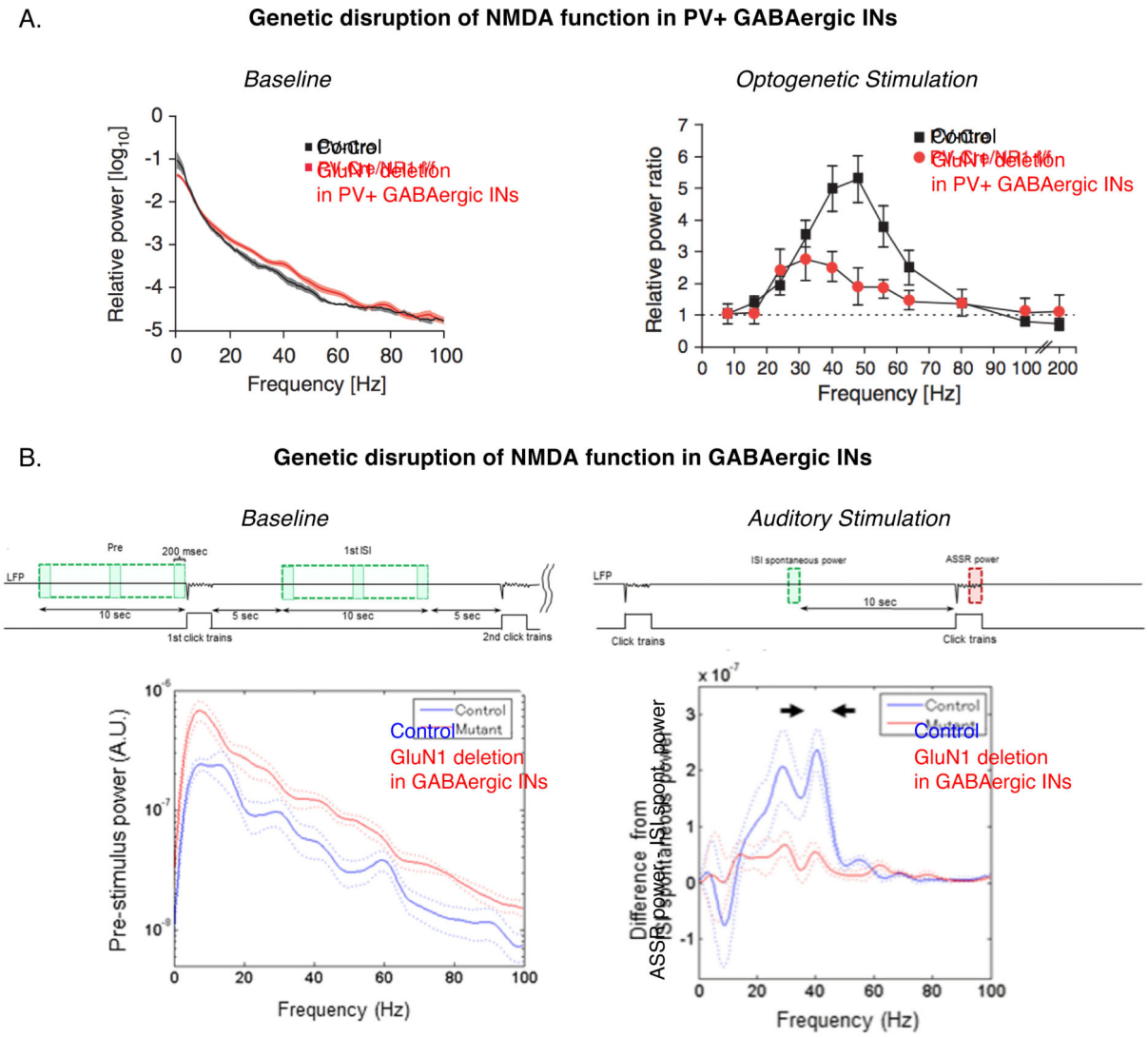


**Figure 2. GBO alteration in genetic NMDAR hypofunction models of SZ**

(A) Power in different frequency bands in the EEG signal recorded from anaesthetized control mice (black) and those with deletion of GluN1 subunit of NMDARs in PV+ GABAergic neurons (red). *Left*: Baseline, *Right*: Stimulus-processing state (Adapted from (61))

(B) Power difference in different frequency bands in the EEG signal recorded from control mice (blue) and those with deletion of GluN1 subunit of NMDARs targeting all GABAergic neurons (red). *Left*: Baseline, *Right*: Stimulus-processing state (Adapted from (63))

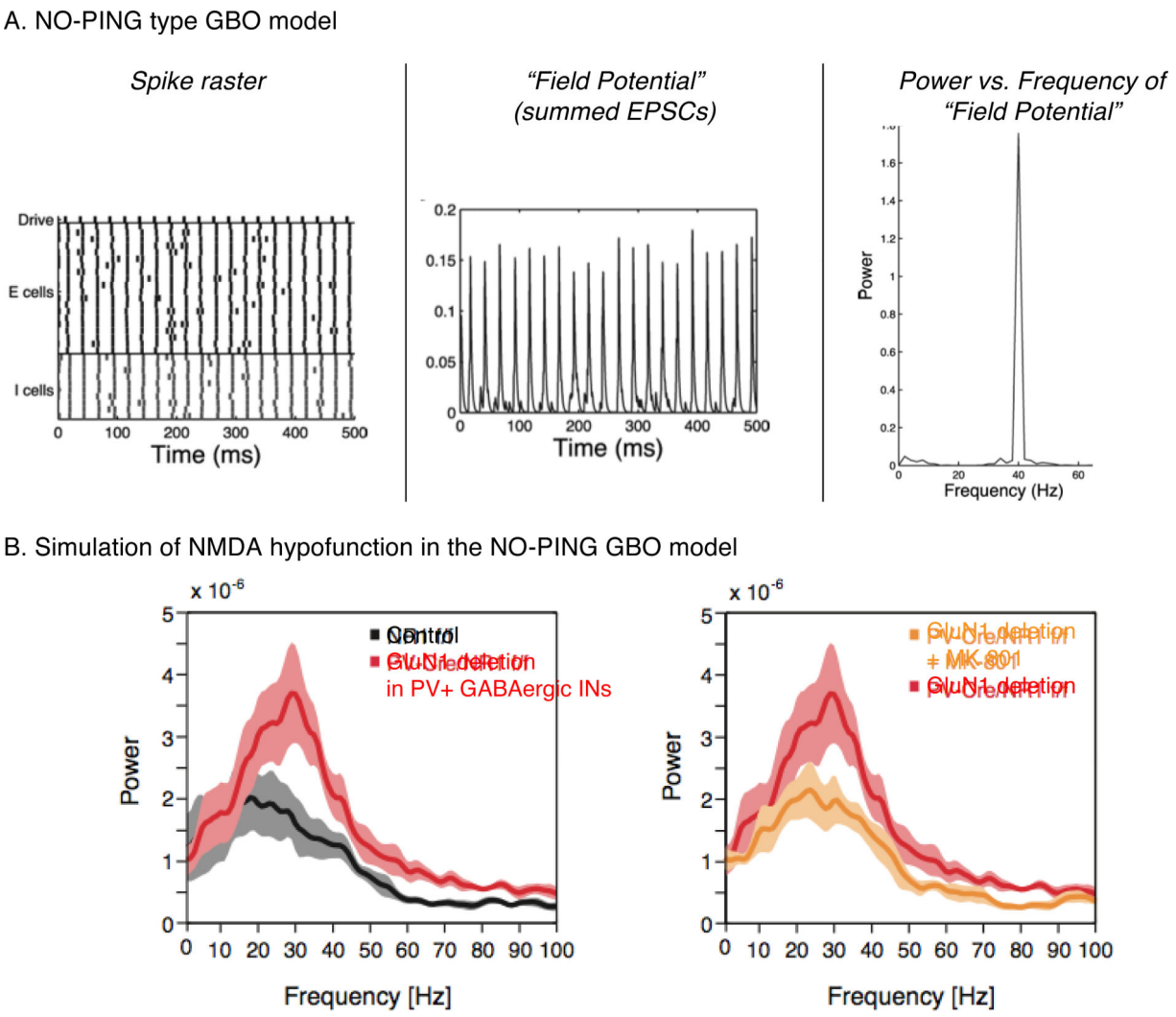


**Figure 3. Computational models of changes in baseline GBO**

(A) Spike rasters and "LFPs" in the Neural oscillator-Pyramidal-Inhibitory neuron network Gamma (NO-PING) model.

(B) Simualtion of NMDAR hypofunction in PV+ INs by reducing excitatbility of INs in the NO-PING model shown in (A).

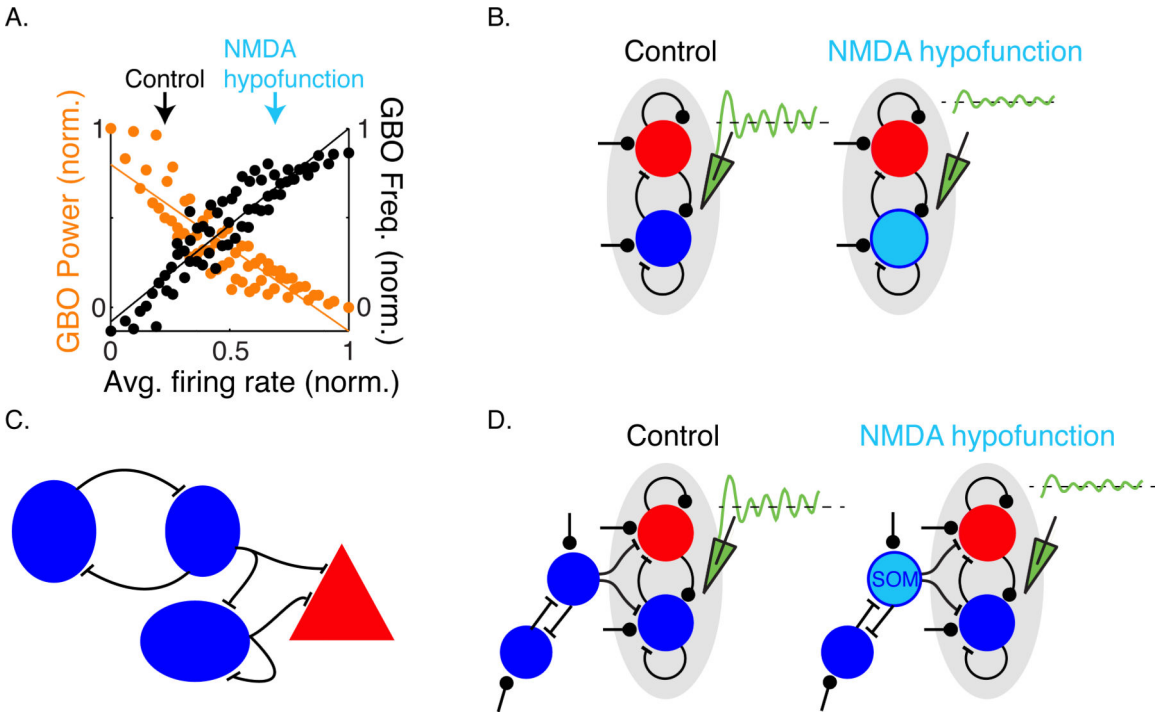


**Figure 4. Stimulus induced GBO due to NMDAR hypofunction in an ISN-PING model**

(A) Co-variation of average spiking activity and GBO power and frequency in an ISN-PING model (Adapted from (82)). The arrows indicate how GBO power changes in response to changes in the activity of PING network. The variation in activity level and GBO properties is plotted in response to changes in the excitatory drive to the PING network, such as in the case of NMDAR hypofunction.

(B) NMDAR hypofunction in PV+ INs modeled as reduced excitation predicts disinhibition and weaker GBO in the model.

(C) Local inhibition circuit in the cortex (97-99). PV+ INs inhibit each other as well as excitatory neurons. SOM+ INs inhibit both PV+ INs and excitatory neurons. VIP+ INs disinhibition excitatory neurons by inhibiting SOM+ INs.

(D) The ISN-PING model predicts reduced power of stimulus-induced GBO if NMDAR hypofunction in SOM+ INs relieves inhibition of both excitatory neurons and PV+ INs such that the average activity is increased in the network.

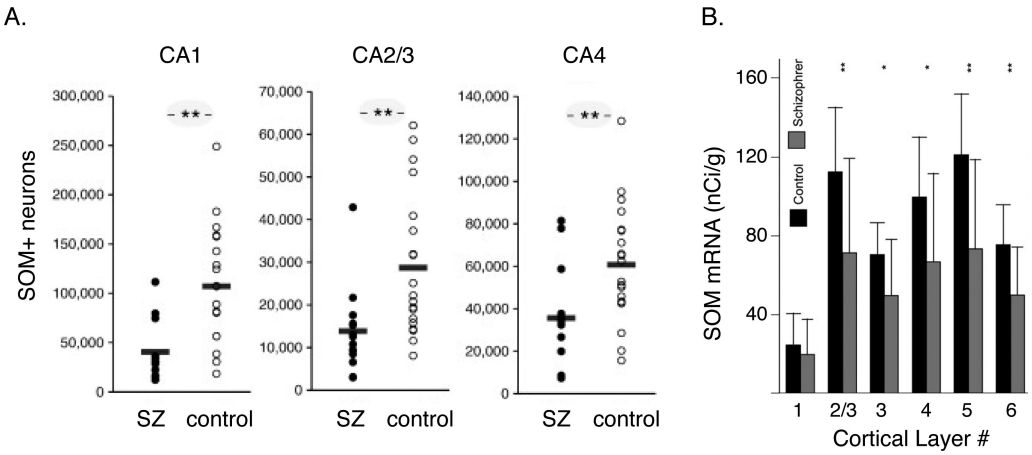


**Figure 5. Alteration of non-PV+ inhibition in schizophrenia**

(A) Immunohistochemical estimate of SOM+ neurons in the hippocampus in postmortem SZ subjects (closed circle) and control (open circles) (105).

(B) Laminar expression of the mRNAs for SOM in dorsolateral prefrontal cortex (DLPFC) in postmortem SZ subjects. Mean film optical density (OD) for mRNA expression in each cortical layer between comparison and schizophrenia groups (Adapted from (41)).

## Table 1

Computational models of GBO

| ***Model*** | **NO-ING*** | **NO-PING**** | **D-ING** | **D-PING** | **ISN-PING** | **SR-ING** | **SR-PING** |
|---|---|---|---|---|---|---|---|
| *GBO Mechanism* | Spike synchronization of neuronal oscillators (NO) in an I-I network. | Spike synchronization of neuronal oscillators (NO) in an E-I network. | Oscillation in firing rates induced by conduction delays (D) in an I-I network. | Oscillation in firing rates induced by conduction delays (D) in an E-I network. | Oscillation in firing rates induced by inhibition-stabilized network (ISN) connectivity regime in an E-I network. | Stochastic resonance (SR) - Noise induced sustenance of damped oscillations - in an I-I network. | Stochastic resonance (SR) in an E-I network. |
| | [e.g. (84-87)] | [e.g. (70, 72, 88)] | [e.g. (93, 94)] | [e.g. (93, 94)] | [e.g. (81-83)] | [e.g. (112)] | [e.g. (113-116)] |
| ***Firing pattern*** | **Regular** | **Regular** | **Irregular** | **Irregular** | **Irregular** | **Irregular** | **Irregular** |
| *GBO Frequency determinant* | **Decay time constants** of IPSCs. | **Decay time constants** of IPSCs. | **Delays** in synaptic transmission. | **Delays** in synaptic transmission, **Decay time constants** for IPSCs and EPSCs. | **Connection strength** of E-E, E-I, I-E and I-I, **Decay time constants** for IPSCs and EPSCs. | **Decay time constants** for IPSCs. | **Decay time constants** for IPSCs (113), **Connection strength** of E-E, E- I, I-E and I-I, **Decay time constants** for IPSCs and EPSCs (114-116) |
| *GBO Power determinant* | Excitation to INs | | Excitation to INs. | Excitation to INs and ENs. | Excitation to INs. | Noise level in network activity and/or input. | Noise level in network activity and/or input. |

*ING: Interneuron Network Gamma

**PING: Pyramidal-Interneuron Network Gamma