Abnormal Gamma Oscillations in N-Methyl-D-Asparate Receptor Hypofunction Models of Schizophrenia

Supplemental Information

Baseline vs. Resting State

Baseline refers to the period buffering trials of stimulus presentation or cognitive tasks, while *resting state* refers to trials without any cognitive or stimulus-processing task; both involve periods without stimulus presentation or cognitive tasks. Although the terms *baseline* and *resting-state* are used distinctly in human studies, they are used interchangeably in the animal models (e.g. (1, 2)).

Evoked vs. Induced Power

The evoked component is estimated from the signal averaged across trials, whereas the induced component is calculated as the average of power estimated in individual trials after subtracting the evoked component (Figure S1).

Animal Models of NMDA Hypofunction

The pharmacological approach studies acute and long-term effects following repetitive treatment with NMDAR antagonists such as ketamine, MK-801 and PCP, in adults as well as perinatally (3-6). The genetic approach involves developing models with genetic knockout of specific NMDAR subunits in INs of the cortex (2, 7-9). Animal models for NMDAR hypofunction show several behavioral manifestations such as hyperlocomotion, deficits in habituation, working memory and associative learning resembling those observed in SZ patients (reviewed in (3)). In addition, they also demonstrate key changes in the GABAergic inhibitory system as shown in the prefrontal cortex in postmortem SZ samples (10-14).

Challenges to Comparison of EEGs in Humans and LFPs in Animal Models

Although EEG and LFP signals reflect summed electrical activity, the differences in neuronal populations sizes involved in each and the electrical consequences of direct/indirect contact with cortical tissue need to be kept in mind while assessing the different types of data. A future direction to bridge this gap could involve recording with surface electrodes in the animal models (15, 16), as has been in done in some studies in mouse models of SZ (17). It also remains to be investigated how similar or dissimilar the surface electrode recordings in mouse models could

be to human EEGs, since the two differ in the organization and topography of the cortex as well as the sheer size of the tissue.

Challenges to Computational Modeling of Altered Network Dynamics in Animal Models

Pharmacological Models: Several challenges exist to synthesizing appropriate computational models to capture the crucial aspects of pharmacological alterations. Identifying the precise mechanisms of GBO modulation in these models is not straightforward since the pharmacological agents target NMDARs in all cell-types to varying degree: for example, the relative sensitivity of the GABAergic neurons has been shown to be higher than that of non-GABAergic neurons to NMDAR antagonists (18). In addition, the specificity of antagonists to NMDARs is variable and can have differential extent and patterns of antagonism to more than one neurotransmitter system.

Genetic Models: There is a large variety of GABAergic INs in both the neocortex and hippocampus (19, 20) that are connected to each other and the primary excitatory cells in complex ways (21-23) (Figure 4). Hence, identifying the mechanisms of altered GBO in animal model where NMDARs are affected across subtypes of GABAergic neurons (e.g. (8)) is a challenge. Further, given their crucial role in synaptic plasticity, ablation of NMDARs at different time points during development is expected to alter the developmental path of the cortical circuit in the genetic models in different ways. This further challenges the idea that common mechanisms underlie similar GBO modulations seen in the genetic and acute models.

Predictions for GBO Alteration in the Presence of "Dysfunction of Disinhibition"

GBO in an ISN-PING model would be predicted to weaken if NMDAR hypofunction in GABAergic neurons tilts the overall balance to dis-inhibition of the local excitatory activity (Figure 4D); this suggests a potential role for GABAergic neurons other than PV+ INs in altering GBO. It should be noted that if the disinhibition of cortical activity also results in increase in the activity of the PV+ INs during stimulus processing, several computational models predict a strengthening of GBO (Table 1). In a study involving a computational model of hippocampal CA3 theta-modulated GBO, with NO-PING and NO-ING mechanisms in different parts of the theta cycle, explored the effect of two inhibitory neuronal populations (24). The study concluded the GBO were altered mainly by NMDAR alteration in inhibitory neurons with SOM+ OLM interneuron type connectivity to the pyramidal neurons and not in inhibitory neurons with PV+ basket cell type connectivity to the pyramidal neurons.

Other Modulators of Inhibition in the Cortex

The prefrontal cortex is heavily invested with neuromodulatory projections, which also control the level of excitability and state of cortical networks. These inputs directly influence the excitability of neurons by modulating their intrinsic properties (25), which can also affect the amplitude and frequency of GBO. Studies in area V1 and V2 of the macaque show distinct patterns of expression of cholinergic receptors between pyramidal neurons and INs (26); in mice, SOM+ and PV+ INs show differential expression of the Lynx family of nicotinic receptor modulators (27). Studies have shown a modulatory effect of cholinergic input on GBO in the local circuit in visual and prefrontal cortices as well as the hippocampus (28-30). Recent data suggests that activity in mouse visual cortex is affected by the behavioral state of the animal; the study demonstrates that locomotion increases both sensory response and GBO in visual area V1 (31). A follow-up study has identified VIP+ neurons as the IN population responding to the locomotion state in V1 superficial layers; the sensory response is shown to depend on cholinergic activation of the VIP+ cells (23). Taken together, these studies suggest further investigation into a role for differential targeting of INs by the neuromodulatory system in the modulation of GBO in the brain.

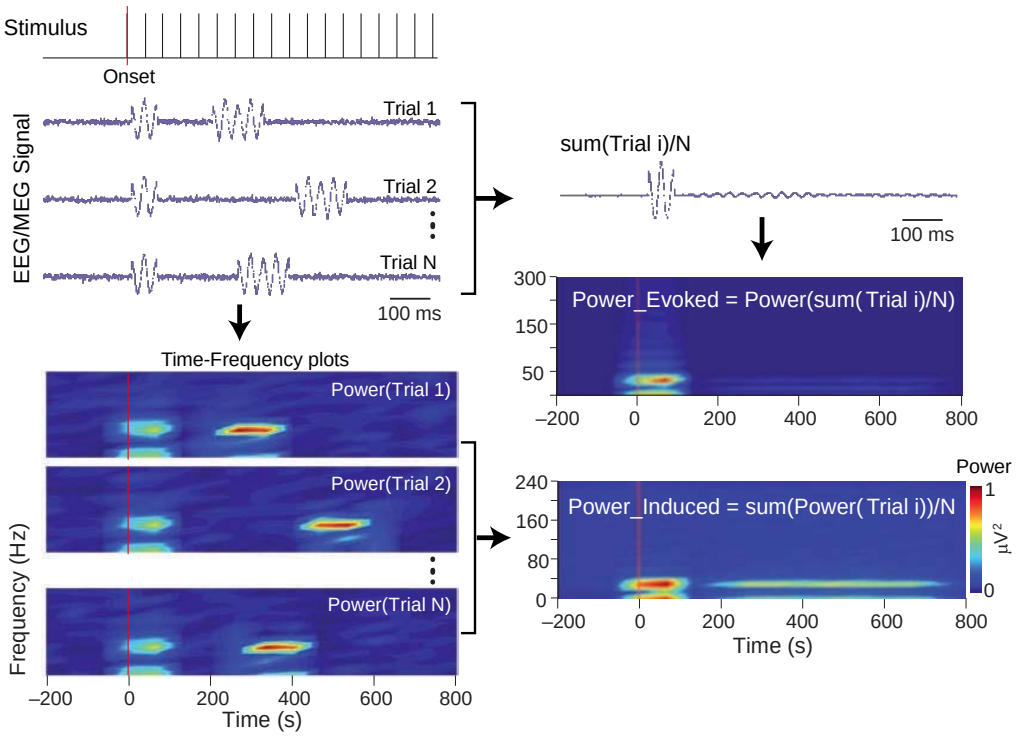

Figure S1. Estimation of evoked and induced power in EEG/MEG signals. EEG/MEG signals recorded in response to periodic sensory stimulation at 20 Hz. The signals show an oscillatory component that is time-locked to the stimulus and another one that emerges at varying times in each trial. The time-frequency plots reveal the time and frequency at which narrowband power increases in the EEG/MEG signal. (Adapted from (2)).

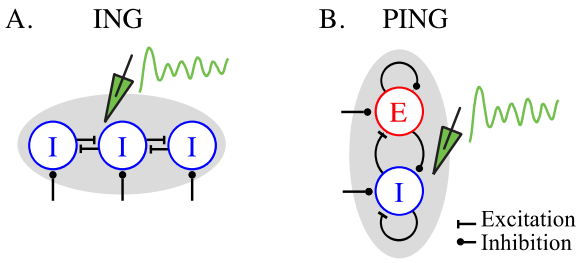

Figure S2. Two types of network arrangements for generating GBO. E: Excitatory neuronal population; I: Inhibitory neuronal population.

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