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Cellular and Circuit Models of Increased Resting State Network Gamma Activity in Schizophrenia

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Abstract

Schizophrenia (SCZ) is a disorder characterized by positive symptoms (hallucinations, delusions), negative symptoms (blunted affect, alogia, reduced sociability, and anhedonia), as well as persistent cognitive deficits (memory, concentration, and learning). While the biology underlying subjective experiences is difficult to study, abnormalities in electroencephalographic (EEG) measures offer a means to dissect potential circuit and cellular changes in brain function. EEG is indispensable for studying cerebral information processing due to the introduction of techniques for the decomposition of event-related activity into its frequency components. Specifically, brain activity in the gamma frequency range (30–80Hz) is thought to underlie cognitive function and may be used as an endophenotype to aid in diagnosis and treatment of SCZ. In this review we address evidence indicating that there is increased resting state gamma power in SCZ. We address how modeling this aspect of the illness in animals may help treatment development as well as providing insight into the etiology of SCZ.

Keywords

EEG; schizophrenia; gamma

Introduction

Gamma oscillations are correlated with cognitive processes such as perception, attention, memory, and consciousness (Engel et al., 1997; Howard et al., 2003; Gregoriou et al., 2009; Herrmann et al., 2010; Panagiotaropoulos et al., 2012). In disease states these fast frequency brain oscillations are often perturbed when compared to control subjects (Uhlhaas and Singer, 2013). Furthermore, different aspects of gamma oscillatory activity are thought to be pertinent to abnormal brain activity and perhaps the pathophysiology of various disorders. Resting activity, event related/evoked activity, and task-related/induced activity are all aspects of EEG data that have been compared between controls and disease populations. This review will focus on the specific role of increased resting state gamma band activity

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and how it pertains to the detection of schizophrenia in humans. Specifically, we will present and discuss data suggesting that this measure may represent the primary underlying cause of a variety of behavioral abnormalities in schizophrenia.

Resting State Brain Activity

Resting state brain activity is defined as activity in the brain when a subject is awake but not performing a specific cognitive task or responding to sensory stimuli. This activity can be has been recorded using a multitude of techniques in humans and animal models. Brain oscillations at certain frequencies can be investigated using a variety of techniques. These different frequencies of activity are thought to underlie the coordinated firing of different brain regions that are associated with cognition. Hans Berger first described a dominant oscillation of ~10 Hz, which he termed alpha (Berger, 1929; Buzsáki and Draguhn, 2004; Buzsáki, 2006). Berger and others coined terms still used today to designate brain activity within specific frequency bands: delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (>30 Hz). Distinct frequency bands have been associated with unique cognitive processes and behavioral states (Basar et al., 2001). Specifically, there is a positive association between EEG gamma power and working memory load during an N-back task. Further, this association is altered in schizophrenia, such that the slope of the correlation is decreased in affected individuals. These data suggest that the cellular and regional mediators of gamma activity are engaged during cognitive tasks (Howard et al., 2003). This review is going to focus on gamma band activity because it has been seen to be perturbed in the pathophysiology of many psychiatric disorders (Herrmann et al., 2010; Gandal et al., 2012b; Port et al., 2014). Furthermore, gamma band activity underlies cognitive processes and is found in virtually all mammalian brain structures, at both cortical and subcortical locations (Buzsáki and Wang, 2012). Specific structures (e.g., thalamus, hippocampus, and cortex) contribute prominently to scalp recorded activity (Basar and Bullock, 1992).

Animal Models of a Noisy Brain

Defining Baseline Gamma in Animal Models

The constellation of data from the authors' previous studies suggest that the core physiological abnormality in schizophrenia is characterized by an increase in electrical noise in the brain. Furthermore, we have suggested that the source of this noise emanates from changes in inherent membrane properties in pyramidal cells as well as interneurons. The overarching hypothesis forwarded by the authors group suggests that cellular activity which is unrelated to either exogenous or endogenous signals creates the basis for deficits across the spectrum of disturbed capabilities and symptoms in the disease. The model systems and methods described below will be discussed in relation to how they inform the “noisy brain” hypothesis. Specifically, we will address the extent to which the data are either consistent with the idea that increased resting state activity contributes to the underlying pathology of deficits in schizophrenia. We will include *in vivo* as well as *in vitro* methods that assess the extent to which a manipulation in animals leads to increased excitability. *In vivo* methods will focus on the use of EEG, which provides the one of the most directly translatable measures between pre-clinical and clinical populations. Of note, there is often confusion regarding the terminology when recording *in vivo*, particularly when distinguishing local

field potentials (LFP) and EEG. The former refers to the use of high impedance electrodes that are sensitive to only the local area (e.g. 100s of microns) in which the electrode tip is placed. Alternatively, EEG refers to the use of low impedance electrodes that are sensitive to electrical activity, (i.e. vectors, generated throughout the brain) from a particular perspective. One also needs to be aware of how electrode configuration impacts the area from which electrical activity is sampled. Placing the positive and negative tips in close apposition yields a configuration which is relatively insensitive to distant electrical sources as the vector would be similar at both points. This would therefore favor accentuating local activity (Frankel et al., 2005). Alternatively, placing the electrodes at distant points from each other in the brain allows for differential activity from every vector, thus providing for sampling a wider spatial representation (Gandal et al., 2012c; Tatard-Leitman et al., 2015). Among these options, the low impedance electrodes placed far apart most accurately models the human EEG, and will therefore be the main focus of our discussion of *in vivo* studies. *In vitro* approaches include slice recordings of both local field potentials (e.g. long term potentiation), whole cells intracellular recording (patch studies) as well as special techniques that assess circuit dynamics in real time such as voltage sensitive dye (VSDi) (Carlson et al., 2011). For *in vitro* studies, we will review and discuss the extent to which changes in local circuits and cells are consistent with theories of how they may relate to the observed *in vivo* phenomena in humans.

Animal Models of Schizophrenia with Relation to Resting Gamma Activity

Gamma activity has been studied in preclinical animal models to use schizophrenia-like electrophysiological phenotypes to help expedite drug discovery. Considerable evidence has been reported to support the “noisy brain” hypothesis as a relevant feature of abnormal behavior and deficit states. Many groups have modeled schizophrenia endophenotypes in mouse and rat models by modifying the amount of functional NMDA-R in the brain by genetic perturbation of gene expression and/or environmental/developmental manipulations. Many of these models include changing the expression of the NMDA-R subunit 1 (NR1), as this subunit is required to form functional receptors alone, or in combination with NMDA-R2 subunits, of which there are several further subtypes (i.e. NR2 A–D). For example, mice with a global reduction in the amount of NR1 protein, called NR1 hypomorphic mice, display increased LFP/EEG baseline gamma power (Gandal et al., 2012c) (Figure 1). Subsequently, mouse models that selectively knock out NR1 in different neuronal cell types have also been investigated. Mice with a selective pyramidal cell knock out of NR1 have increased gamma baseline power as measured by EEG (Tatard-Leitman et al., 2015) (Figure 2). Similarly, mice with a selective knock out of NR1 in a subset of interneurons that express the calcium binding protein parvalbumin (PV) also have a significant increase in baseline EEG gamma power (Carlén et al., 2012; Billingslea et al., 2014). Additionally, animals with a developmental knock out of NR1 in a subset of interneurons (40–50% of cortical interneurons) exhibit a high spontaneous LFP activity in the primary auditory cortex (Nakao and Nakazawa, 2014). Interestingly, genetic manipulations of genes in signaling pathways that modify NMDA-R activity also support the role of these receptors in mediating increased resting state activity. For example, previous studies indicate that neuregulin-1 activity at ErbB4 reduces ion currents through NMDA-Rs. Importantly, post mortem studies demonstrate that schizophrenia subjects have increased neuregulin-1 mediated activation of

ErbB4, resulting in increased suppression of NMDA-R mediated glutamate transmission. Additionally, developmental loss of ErbB4 from fast-spiking basket and chandelier interneurons causes an increase in LFP gamma power in awake freely moving mice (del Pino et al., 2013). Dysbindin (*DTNBP1*) is another example of a gene that has received a great deal of attention due to its genetic association with schizophrenia. Dysbindin knockout mice (*Dys1^{-/-}*) show an increase in “late gamma” which the authors suggest is the manifestation of an inability to inhibit gamma activity (Carlson et al., 2011; Gandal et al., 2012b). As an alternative to genetic approaches, schizophrenia has also been modeled developmentally by administration of a mitotoxin methylazoxymethanol (MAM) on gestational day 17 (GD17) to rats. This model is thought to recapitulate a disruption of developmental process and leads to schizophrenia-like phenotypes in rodent offspring, which include altered neuronal processing (Lavin et al., 2005; Goto and Grace, 2006; Lodge and Grace, 2007). The MAM gestational model of schizophrenia also shows an increase in baseline gamma activity in the prefrontal cortex in awake animals (Kocsis et al., 2013). However another group found that there was no increase in gamma activity at rest (Phillips et al., 2012) and yet another (Lodge et al., 2009) found that there was no difference between groups for gamma power before auditory evoked responses (note: in some studies pre-stimulus baseline is used as a surrogate for resting state). Lastly, groups have used another developmental model of schizophrenia where injections of ibotenic acid are made bilaterally in the ventral hippocampus to create lesions on post natal day 6–7 (Vohs et al., 2009). Although the authors did not test for differences in spontaneous gamma activity, they note in the discussion that NVHL rats take significantly longer to return to pre-stimulus levels of neuronal activity, suggestive of baseline elevations. All of these findings are consistent with pharmacological studies using NMDA-R antagonists as both ketamine and MK-801, NMDA-R antagonists, cause an increase in background EEG gamma activity (Ehrlichman et al., 2009; Lazarewicz et al., 2010; Saunders et al., 2012) (Figure 3).

***In vitro* Examination of Animal Models of Increase Resting Gamma**

A variety of studies have focused on proteins that modify glutamate signal transduction through NMDA-Rs. Hippocampal pyramidal cells from NR1 hypomorphic mice (Gandal et al., 2012a) have an increase in inherent membrane excitability as indicated by both a reduction in the amount of current needed to elicit an action potential (lower rheobase value) and increased current to firing frequency relationship. This is similar to the pattern of changes found among mice with a pyramidal cell-selective ablation of NR1. Pyramidal neurons in these mice show an increase in current-frequency, spontaneous EPSC frequency and a decrease in resting membrane potential (Tatard-Leitman et al., 2015). Alternatively, mice with a selective reduction of NR1 limited to PV containing interneurons do not display increased pyramidal cell excitability *in vitro* (Korotkova et al., 2010; Billingslea et al., 2014).

Consistent with *in vivo* studies noted above, *ErbB4* conditional knockout mice also have increased membrane excitability (lower rheobase value) value than their wild type controls, which was observed in interneurons but not pyramidal cells (del Pino et al., 2013). However, pyramidal cells in these animals have an increase in spontaneous EPSCs consistent with the pattern of changes in pyramidal cell-selective reduction in NR1 expression. Importantly,

these data suggest that altering the modulation of NMDA-R function either by increased ErbB4 activity, as in schizophrenia, or decreased ErbB4/Neurotrophin-1 expression, as in animal models, yield similar outcomes with respect to baseline gamma power.

Although some animal models discussed above have not been extensively evaluated using *in vitro* electrophysiological methods, perturbation of genes associated with functional interneurons and/or cell numbers have been used as a surrogate for abnormal brain circuitry. MAM treated rats have a decrease in expression of PV and GAD₆₇ and a decrease in the number of PV interneurons in the frontal cortex (Lodge and Grace, 2009; Gill and Grace, 2014). GAD₆₇ or glutamic acid decarboxylase 67 is an enzyme that is crucial to the synthesis of GABA. The NVHL animals also have a decrease in the mRNA levels of GAD₆₇ in the medial prefrontal cortex (Lipska, 2004; Francois et al., 2009). Similarly, reductions in PV immunoreactive cells are also seen in dysbindin knockout mice (Carlson et al., 2011).

Relating Behavior to EEG/LFP Validation of Models

Models that recreate increased background activity can also be assessed with regard to the extent to which they result in a broader behavioral phenotype similar to schizophrenia (Papaleo et al., 2012). Therefore, in the subsequent section we will discuss the extent to which each model systems meet this criterion.

Cognitive deficits are at the core of schizophrenia, including difficulties in problem solving, social cognition, and working memory (Powell, 2010). Therefore, rodent models have focused on tasks associated with learning and memory, working memory, and cognitive flexibility. Animals with global reduction of NR1 or in which NR1 is selectively knocked out in pyramidal cells have deficits in spatial working memory using the T-maze performance task (Gandal et al., 2012a; Tatard-Leitman et al., 2015). ErbB4 conditional mutants also have a decrease in correct alternation using this task, suggesting a similar cognitive defect (del Pino et al., 2013). Baclofen, a GABA_B receptor agonist, rescued the T-maze phenotype in NR1 hypomorphs, coincident with its ability to restore normal background EEG gamma power, and reduce the abnormal inherent membrane properties in pyramidal cells. The role of NMDA-R in interneurons in mediating cognitive performance has been less consistent. For example, developmental knockdown of NR1 in a broad range of interneurons causes a decrease in short term memory (Belforte et al., 2010). However, animals with a selective knock out of NR1 in PV interneurons have reduced working memory in some studies (Korotkova et al., 2010) but significantly improved T-maze performance in others (Billingslea et al., 2014). Thus the role of impaired interneuron function in mediating functional deficits that are associated with increased resting gamma power remains unclear. Similar to data in the PV-selective NR1 knockout mice, studies in dysbindin knockout mice are also mixed.

Some studies indicate that these mice have increased T-maze performance while other find the converse (Hattori et al., 2008; Takao et al., 2008; Karlsgodt et al., 2011; Papaleo et al., 2012). Alternatively, dysbindin knockout mice display impaired spatial reference memory and novel object recognition performance (Karlsgodt et al., 2011; Papaleo et al., 2012). Freely moving rats treated prenatally with MAM have a diminished gamma band response during task performance and display working memory deficits (Flagstad et al., 2005; Le Pen

et al., 2006; Moore et al., 2006). Similarly, rats with neonatal ventral hippocampus lesions (NVHL) exhibit working memory deficits (McDannald et al., 2011; Lee et al., 2012).

Hyperactivity is also used as a behavioral surrogate to model the psychotic symptoms of schizophrenia in animals (Lipska and Weinberger, 2000). Although increased locomotor activity has relatively poor face and construct validity for psychosis, it does have good predictive validity with regard to pharmacological agents. Specifically, agents that make rodent increase their locomotor activity tend to have psychotomimetic properties in humans (Swerdlow et al., 2000; Jones et al., 2011). Among genetic models with increased baseline gamma activity, increased locomotor activity has been noted in NR1 hypomorphs (Gandal et al., 2012c), pyramidal cell selective NR1 knockout mice (Tatard-Leitman et al., 2015), mice with developmental knock out of NR1 in a subset of interneurons (Belforte et al., 2010) Erbb4 conditional knockout mice (del Pino et al., 2013) and dysbindin knockout mice (Karlsborg et al., 2011; Papaleo et al., 2012). Similarly, developmental lesion models including both MAM-treated and NVHL rats exhibit hyperactivity (Lipska et al., 1993; Lipska and Weinberger, 2000). Thus, there is a large degree of overlap among manipulations that cause animal behaviors that are predictive of psychosis, and which coincidentally cause an increase in background gamma activity.

Changes in social drive and social withdrawal are also symptoms of schizophrenia that can be modeled in animals (Miller et al., 2002). Preference for social interactions is typically tested with a three-chambered social choice test. In this test, a test mouse's propensity to choose a social interaction with another mouse as compared to an inanimate object is quantified. As with cognitive deficits and locomotion, there is a high degree of overlap between increased baseline gamma activity and reduced social interactions. For example, there is a reduction in social behavior in mice with knockout of 1) dysbindin, 2) Erbb4, 3) PV-selective NR1, 4) general interneuron NR1, 5) pyramidal cell-selective NR1 and 6) NR1 hypomorphs (Hattori et al., 2008; Belforte et al., 2010; Korotkova et al., 2010; Gandal et al., 2012c; Billingslea et al., 2014; Tatard-Leitman et al., 2015). Similarly, rats treated prenatally with MAM (Flagstad et al., 2004; Le Pen et al., 2006) and NVHL rats also have social deficits, suggesting that both genetic and developmental lesion models that cause increased baseline gamma power also cause social impairments (Sams-Dodd et al., 1997; O'Donnell, 2011). A summary of changes in gamma band EEG as well as corresponding behavioral changes is noted in Table 1.

Findings in Disease

Resting State Network and Gamma Oscillations in Schizophrenia

Baseline oscillatory activity can be investigated in two different contexts. First, in "default-mode" or "resting-state" paradigms, EEG/MEG is acquired while the subject lies still without engaging in a task. Second, during tasks with a repetitive time-locked event, "pre-stimulus" baseline oscillatory activity can be extracted to examine the receptiveness of neural networks to the next stimulus. In resting-state paradigms, several studies reported elevated high-frequency EEG activity in schizophrenia (Davis, 1942; Finley, 1944; Kennard and Schwartzman, 1957; Rodin et al., 1968; Itil et al., 1972, 1974; Giannitrapani and Kayton, 1974; Fenton et al., 1980; Winterer et al., 2004), although they tended to investigate

activity below 40 Hz. For example, in a large (n=100/group) clinical study, schizophrenia patients demonstrated increased 24–33 Hz activity (Itil et al., 1972) which was stable over three months (Itil et al., 1974). However, three did report elevations in high beta (20–30 Hz) power, interpreted as reflecting “cortical noise” (Kissler et al., 2000; Krishnan et al., 2005; Brockhaus-Dumke et al., 2008), although another did not (Miyauchi et al., 1990). A larger EEG study observed increased 20–50 Hz power in schizophrenia subjects and their relatives (Venables et al., 2009) and another group found broad band increases of baseline activity at all frequencies (Winterer et al., 2004). Although a similar MEG study employing source-space projections found opposite results (Rutter et al., 2009). These mixed results may reflect differences in sample size, imaging modality (EEG/MEG), or recording site (scalp vs. source-space projections). Several groups have examined “pre-stimulus” baseline gamma activity in schizophrenia. The issue of baseline gamma differences is important, given that most studies examining group differences in post-stimulus activity employ some form of baseline correction (Urbach and Kutas, 2006). Two very large studies reported elevated pre-stimulus gamma power in schizophrenia patients during auditory paradigms (Winterer et al., 2004; Hong et al., 2008), in accordance with our previous data (Turetsky and Siegel, 2007) (Figure 4). Two smaller studies found no group differences in pre-stimulus gamma band responses, but did report elevated baseline beta power in schizophrenia (Brockhaus-Dumke et al., 2008).

The default mode network (DMN) is functional brain activity across different regions at rest, when a person is being introspective or not interacting with the world (Damoiseaux, 2006; Buckner et al., 2008). It is thought that the DMN is an interconnected series of brain regions which are active at rest but which deactivate during performance of a wide range of cognitive tasks. The medial frontal cortex is one of the principal constituents of this network, along with the posterior cingulate cortex/precuneus, parts of the parietal and temporal lobe cortex and the hippocampus (Whitfield-Gabrieli and Ford, 2012). The salient network (SN) is the anterior insular salient network which contains the frontoinsula operculum and dorsal anterior cingulate cortex (Manoliu et al., 2014). The network responds to behaviorally salient events and seems to interact with the DMN. Several studies have evaluated the role of resting state activity and connectivity in the performance deficits demonstrated among people with schizophrenia. For example, data suggest that there is a failure of deactivation of the DMN during the working memory task in schizophrenia relative to healthy controls (Landin-Romero et al., 2014). Similar deficits were noted in schizophrenia during an auditory oddball task, which requires that subjects respond to a target stimulus which is presented among a background of non-target and distractor stimuli (Garrity et al., 2007). Furthermore, some investigators have attempted to relate the increase in resting state connectivity and/or failure to deactivate the DMN to the presence of delusions in schizophrenia patients. Studies using fMRI suggest that there is an increase in connectivity between the frontal cortex and the DMN early in the course of schizophrenia (Damoiseaux, 2006; Ongür et al., 2010; Karbasforoushan and Woodward, 2012; Orliac et al., 2013; Tu et al., 2013; Manoliu et al., 2014). Data indicate that there is an increase in connectivity between the frontal cortex and default motor network among early onset patients with schizophrenia (Tang et al., 2013). Additional studies suggest that there are also differences in the connectivity among five neural networks in schizophrenia including the

DMN, frontoparietal (FP), cingulo-opercular (CO), cerebellar (CER), and the salient network (SN) (Mamah et al., 2013). Consistent with these studies, combining DTI (diffusion tensor imaging), which is a measure of structural connectivity, and fMRI also indicates that there is a perturbation in functional connectivity in schizophrenia (Skudlarski et al., 2010). This is consistent with resting state fMRI studies that show patients with schizophrenia have a significantly lower global connectivity compared with healthy controls (Argyelan et al., 2014). Thus, combining different imaging techniques supports the hypothesis that there are differences in long range functional connectivity in schizophrenia (Spellman and Gordon, 2014).

Power and Coherence of Brain Activity

Power and coherence in various frequency ranges are thought to reflect the cross-sectional mental state of an individual, as evidenced by the level of symptoms at a given time. For example, There is a significant correlation between measures of EEG activity and the degree of hallucinations and delusions among people with schizophrenia (Herrmann and Demiralp, 2005). Some studies suggest that measures of EEG may also reflect traits of individuals with schizophrenia. A study in drug naive patients with schizophrenia during sleep found a decrease in the coherence of activity between the right central and right frontal areas in both beta and gamma frequencies (Yeragani et al., 2006). The investigators examined the coherence between the right central and the right frontal areas of the EEG during sleep states. Coherence involves the relationship of activity in two areas of the EEG in a specific frequency (Yeragani et al., 2006). Similarly, Andreou et al. examined resting-state EEG analysis during different microstates of brain activity in 3 different populations of people: high-risk individuals, clinical stable first episode patients with schizophrenia, and healthy controls. EEG microstates are periods of coordinated brain activity that are postulated to represent interactions between neural networks and local states (Andreou et al., 2014a). Their duration is about 100ms, which is considered to be congruent with the timeframe in which spontaneous thought takes place. These microstates capture the moment to moment interactions among brain networks within certain activity frequencies. They found that abnormalities in these microstates can lead to psychosis associated with schizophrenia. In a follow up study (Andreou et al., 2014b) the group found increased resting state gamma band connectivity with in networks associated with the pathology of schizophrenia.

Inherent Noise and Relationship to Symptoms in Schizophrenia

We propose that this increased autonomous gamma power throughout the brain leads to the misinterpretation of relationships among random events. Previously, some investigators have also suggested that gamma activity is used for feature binding – i.e. the mechanism of relating multimodal sensory stimuli and the context in which they occur into a coherent story with meaning (Engel et al., 1997; Lee et al., 2003). These misinterpretations of relatedness may then be the basis for referential delusions. Studies suggest that there is a link between deficits in the salient network and default motor network in schizophrenia, especially as these relate to resting state EEG studies. EEG studies indicate that schizophrenia patients showed an increase in functional connectivity in the DMN at low frequencies (0.06Hz) that is correlated with psychotic symptoms (Rotarska-Jagiela et al., 2010; Rolland et al., 2014). Aberrant salience, or lack of being able to identify relevant

features during cognitive tasks, has been linked to the presence of positive symptoms in schizophrenia (White et al., 2010; Manoliu et al., 2014). Specifically, connectivity scores during a cognitive task indicate that there is a decrease in activity of the right anterior insula, which is part of the SN, among patients with hallucinations. Other studies have linked alterations in resting state gamma band connectivity and the core symptoms of schizophrenia with EEG (Andreou et al., 2014b; Sun et al., 2014). Studies have found that there is an increase resting gamma activity in schizophrenia using MEG (Kim et al., 2014). Yet others find a decrease in gamma power in schizophrenia patients and their siblings as measured with MEG source localization analysis (Rutter et al., 2009).

Similar to their role in abnormal beliefs, we propose that increased gamma power at rest may contribute to hallucinations. Hallucinations are activation of sensory networks in the absence of external stimuli. Since there is an increase in activity throughout the brain this would also include sensory pathways (Uhlhaas and Singer, 2010; Northoff and Qin, 2011). Therefore, increased activity could be the basis for the active organization and formation of sensory experiences based on internally generated noise. Northoff has hypothesized that an increase in the resting state of the brain might contribute to auditory hallucinations (Northoff et al., 2010; Northoff, 2014). This group has seen an increase in resting activity in the auditory cortex preceding and during auditory hallucinations.

Summary and Conclusions

The increase in baseline resting gamma brain activity may underlie many of the symptoms of schizophrenia. For example, in humans one group has postulated that the increase in resting state gamma activity is a predictor for auditory verbal hallucinations (Northoff, 2014). Although such a link to subjective experiences may limit the capacity to model the relevant aspects of schizophrenia in rodents, it may also explain why mice with increased EEG resting gamma power are unable to respond to auditory stimuli in the same fashion as wild type animals. Interestingly, alterations in gamma power have been identified among other disorders that share some, but not all features of schizophrenia. Specifically, people with autism spectrum disorders (ASD) also display increased background gamma power, but do not experience hallucinations and delusions (Wang et al., 2013; van Diessen et al., 2014). We propose that the developmental timing during which increased background activity emerges determines the types of subjective and functional abnormalities that result. Specifically, the post-adolescent emergence of increased background gamma power may lead to interference with previously developed sensory (hallucinations) and higher order logical processing (e.g. delusions). However, if this increased gamma power is present from birth, as in ASD, we propose that sensory and higher order cognitive systems are able to incorporate the “noise” during development, and therefore do not introduce abnormal sensory or logical interference. As such, increased gamma band noise at rest, may not only underlie some of the common features among schizophrenia and ASD, like impaired social function and expression of language, but may also help explain some of the unique features to each disorder, based on the temporal nature of its development.

In addition to informing the pathophysiology of schizophrenia, the ability to model basic alterations in EEG power spectra at rest will facilitate the discovery of new therapeutic

approaches. Specifically, future research to find compounds that decrease baseline gamma power is likely to be among the most powerful tools in treating the basic underlying pathophysiology of schizophrenia. Furthermore, therapeutic agents that increase gamma signal-to-noise ratio by reducing background, pre-stimulus “noise” may improve perceptual abnormalities in schizophrenia. Likewise, compounds that reduce baseline and elevate evoked or induced gamma power during cognitive paradigms may help alleviate these deficits in schizophrenia.

In addition to pharmacological treatments noted above, neuromodulatory approaches may also hold promise for addressing fundamental abnormalities in brain rhythms that we believe are the root cause of symptoms and functional deficits in schizophrenia. For example, deep brain stimulation (DBS) might be able to ameliorate the reduction in cross frequency coupling and coordination between different brain regions. Previous studies in our group investigated a mouse model of DBS in auditory cortex of mice and found that the technique can modify slow wave activity (De Rojas et al., 2013). Similarly, DBS can reverse hippocampal information processing deficits among in animals with a variety of developmental manipulations thought to model schizophrenia (Ewing and Grace, 2013; Klein et al., 2013; Perez et al., 2013). In humans, transcranial direct current stimulation has been used to induce changes in brain activity, suggesting that non-pharmacological approaches may also have promise in treating the abnormal underlying brain rhythms in the disorder (Zaehle et al., 2010, 2011a, 2011b; Keeser et al., 2011; Jacobson et al., 2012).

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Gamma frequency activity contributes to cognitive function.

Abnormalities in gamma activity is an endophenotype of schizophrenia.

We address evidence that resting state gamma power is elevated in schizophrenia.

Modeling increased gamma in animals provides insight into the etiology of schizophrenia.

Models of perturbed gamma activity may aid in the creation of potential therapeutics.

Figure 1. NMDA-R disruption causes gamma band deficits that predict deficits in behavior
A. Baseline, pre-stimulus power is plotted as a function of frequency. **B.** NR1 hypomorph mice demonstrated significantly elevated baseline local field potential (LFP) power, most significantly at gamma frequencies. **C.** and **D.** Gamma power abnormalities predict deficits in social interactions and spatial memory. Figures (Adapted from Gandal et al. 2012)

Figure 2. Selective knock out of NMDA-R in pyramidal neurons perturbs baseline gamma power and behaviors

A. Baseline Gamma power is increased in the CamK2aCre-NR1-KO. **B.** These mice show deficits in working memory and **C.** social interactions. (Adapted from Tetard-Leitman VM et al. 2015)

Figure 3. Ketamine and MK-801 have a dose dependent effect on gamma activity

A. Total high-frequency power 0–60 ms post-stimulus was dose- dependently reduced following both ketamine and MK-801. **B.** Both agents dose-dependently increased high-frequency baseline power (adapted from Saunders JA et al 2012).

Figure 4. Patients with Schizophrenia have an increase in baseline gamma frequency baseline activity

Patients are shown in blue and controls in red. Schizophrenia patients have broad band increased resting state gamma band power above 40Hz as indicated by the black bar - ** - $p < 0.01$. Subjects were accrued and EEG recording was performed as previously described in (Turetsky et al., 2009) $n = 20$ control subjects and 20 schizophrenia subjects. Baseline EEG was analyzed using EEG toolbox (Delorme and Makeig, 2004).

Table 1
Summary of findings for baseline gamma power and behavioral changes across preclinical models

Animal Model	Baseline EEG Activity	Cognitive	Social	Anxiety	Locomotor Activity	References
NR1 Hypomorph	↑	↓	↓	↓	↑	Gandal MJ (2012); Halene TB (2009)
CamKII α NR1 Deletion	↑	↓	↓	↓	↑	Tetard-Leitman V (2015)
PV NR1 Deletion	↑	↑	↓	↔	↔	Billingslea E (2014); Carlén M (2012)
Interneuron NR1 Deletion	↑	↓	↑	↑	↑	Belforte J (2010); Nakazawa K (2012)
Dysbindin Knockout Animals	Not Assessed	↓	↓	↑	↓	Carlson GC (2011); Hattori S (2008); Papaleo F (2012)
Disruption of Neureglin1 Signaling	↑	↓	↓	↓	↑	Del Pino (2013); Ehrlichman R (2009)
Ketamine/MK-801 Administration	↑	↓	↓	↔	↑	Saunders J (2012); Amann LC (2009) Ehrlichman R (2009)
Neonatal Ventral Hippocampal Lesion	Not Assessed	↓	↓	↑	↑	Lee H (2012); Lipska B (2004)
MAM treated	↑↓	↓	↓	↔	↑	Flagstad P (2004); Le Pen G (2006); Lodge DJ (2009)