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REVIEW

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 (30–80 Hz) 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 insights into the etiology of SCZ.

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Key words: EEG, schizophrenia, gamma.

Contents

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 electroencephalographic (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 and how it pertains to the detection of schizophrenia (SCZ) 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 SCZ.

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

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Abbreviations: ASD, autism spectrum disorders; DBS, deep- brain stimulation; DMN, default mode network; EEG, electroencephalographic; LFPs, local field potentials; MAM, methylazoxymethanol; NR1, NMDA-R subunit 1; NVHL, neonatal ventral hippocampus lesions; PV, parvalbumin; SCZ, Schizophrenia; SN, salient network.

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(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 SCZ, 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 suggests that the core physiological abnormality in SCZ 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 SCZ. 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 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 (LFPs) 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 LFPs (e.g. long-term potentiation), whole-cell 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 SCZ with relation to resting gamma activity

Gamma activity has been studied in preclinical animal models to use SCZ-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 SCZ 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) (Fig. 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) (Fig. 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 SCZ subjects have increased neuregulin-1- mediated activation of ErbB4, resulting in increased suppression of NMDA-R-mediated glutamate transmission. Additionally, developmental loss