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Gamma synchrony: towards a translational biomarker for the treatment resistant symptoms of schizophrenia

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Abstract

The lack of efficacy for antipsychotics with respect to negative symptoms and cognitive deficits is a significant obstacle for the treatment of schizophrenia. Developing new drugs to target these symptoms requires appropriate neural biomarkers that can be investigated in model organisms, be used to track treatment response, and provide insight into pathophysiological disease mechanisms. A growing body of evidence indicates that neural oscillations in the gamma frequency range (30–80 Hz) are disturbed in schizophrenia. Gamma synchrony has been shown to mediate a host of sensory and cognitive functions, including perceptual encoding, selective attention, salience, and working memory – neurocognitive processes that are dysfunctional in schizophrenia and largely refractory to treatment. This review summarizes the current state of clinical literature with respect to gamma band responses (GBRs) in schizophrenia, focusing on resting and auditory paradigms. Next, preclinical studies of schizophrenia that have investigated gamma band activity are reviewed to gain insight into neural mechanisms associated with these deficits. We conclude that abnormalities in gamma synchrony are ubiquitous in schizophrenia and likely reflect an elevation in baseline cortical gamma synchrony ('noise') coupled with reduced stimulus-evoked GBRs ('signal'). Such a model likely reflects hippocampal and cortical dysfunction, as well as reduced glutamatergic signaling with downstream GABAergic deficits, but is probably less influenced by dopaminergic abnormalities implicated in schizophrenia. Finally, we propose that analogous signal-to-noise deficits in the flow of cortical information in preclinical models are useful targets for the development of new drugs that target the treatment-resistant symptoms of schizophrenia.

Keywords

schizophrenia; gamma oscillations; electrophysiology; endophenotype; animal models; GABA

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1.1 Introduction

Schizophrenia is a debilitating neuropsychiatric illness with a prevalence of 1–2%. Core impairments include positive symptoms (hallucinations, delusions), negative symptoms (flat affect, impoverished speech, social deficits, anhedonia, avolition), and cognitive deficits (attention, working memory, executive function). Additionally, there are significant abnormalities in sensory and perceptual processing. Numerous antipsychotic medications are available and are characterized by a strong correlation between dose and dopamine D2 receptor affinity. This led to the "dopamine hypothesis," which attributes disease pathogenesis to excess mesolimbic dopamine signaling. Whereas these drugs are effective in treating positive symptoms, they have little efficacy for negative and cognitive symptoms. These "treatment-resistant symptoms" are frequently associated, suggesting a potential pathophysiological link, and the severity of these deficits are the best predictors of long-term outcome (Barr et al., 2010; Green, 1996; Harvey et al., 1998; Milev et al., 2005; Park et al., 1999; Siegel et al., 2006).

Developing new therapies to target treatment-resistant symptoms requires identification of neural endophenotypes associated with these deficits (Braff and Light, 2005). Emerging evidence from EEG/MEG studies indicates that abnormal gamma range (30–80 Hz) synchrony may be such a biomarker, reflecting core pathophysiological features of schizophrenia including cognitive and perceptual abnormalities. Gamma oscillatory activity is thought to be a fundamental mechanism that integrates neural networks within and across brain structures, facilitating coherent sensory registration. In schizophrenia, gamma abnormalities have been reported in a variety of contexts, including in sensory-driven, cognitive, and resting-state paradigms. As reviewed below, these deficits are present at first-episode psychosis (Symond et al., 2005), in unmedicated patients (Gallinat et al., 2004), and, to a lesser degree, in unaffected relatives (Leicht et al., 2010a), suggesting that abnormal gamma synchrony is a heritable feature of schizophrenia. Gamma-band responses (GBRs) have been associated with symptom scales and cognitive performance, indicating that these measures are likely related to disease pathophysiology. Finally, abnormal GBRs have been reported in preclinical disease models, providing potential targets for treatment development.

2.0 Gamma Oscillations: Neurophysiology, Cognitive Correlates

2.1 Overview

Information processing is achieved in part by the coordinated firing of distinct neural populations (Buzsáki, 2006). Such synchrony is thought to be an emergent property of neural networks, generated by the temporal coordination between synaptic transmission and firing of individual neuronal populations. Hans Berger first described a dominant oscillation of ~10 Hz, which he termed alpha (Berger, 1929). 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)

2.2 Function

Gamma oscillations have been shown to mediate cognitive and perceptual processes in mammalian brains (Herrmann et al., 2010). Gray and Singer demonstrated that gamma synchronization within cortical columns of the cat visual cortex act as a mechanism for perceptual 'feature binding' – the ability to integrate different sensory features of a stimulus into a single coherent neural representation (Gray et al., 1989). Similar processes have been demonstrated in humans, leading to a more general hypothesis that the early-evoked (e.g. phase-locked) cortical GBRs reflect initial stages of sensory perception (Joliot et al., 1994;

Singer, 1999). Relationships between gamma oscillations and other cognitive processes have been reported, including selective attention (Fries et al., 2001; Tiitinen et al., 1993), stimulus salience (Roye et al., 2010), associative and perceptual learning (Miltner et al., 1999), sensorimotor integration (Murthy and Fetz, 1992), and object representation (Tallon-Baudry and Bertrand, 1999). Such findings, observed across human and animal studies, demonstrate a phylogenetically conserved role for gamma synchrony in coordinating distinct aspects of sensory information among distributed brain regions.

In addition to basic sensory processes, gamma responses play a role in higher cognitive functions. Several studies demonstrated a role for gamma activity in the encoding, maintenance, and subsequent recall of information during short- and long-term memory tasks (Sederberg et al., 2007; Tallon-Baudry et al., 1998). Other groups have shown that gamma synchrony is associated with social cognition (Williams, Whitford, Nagy, et al., 2009) and language function (Benasich et al., 2008; Meyer et al., 2005). Finally, some have argued that gamma activity plays a role in subjective consciousness (Llinas et al., 1998; Singer, 1998).

Physiologically, gamma oscillations have been associated with thalamo-cortical arousal (Griskova et al., 2007) and have been shown to couple local neuronal assemblies to enable synchronization (Canolty et al., 2006; Fries et al., 2007). Such synchrony tends to occur over relatively short distances, such as within a single cortical column, whereas longer-range functional neural coupling occurs at lower (e.g., beta-range) frequencies (Kopell et al., 2000). Finally, gamma activity has been shown to be important for gating of synaptic plasticity with high temporal precision (Uhlhaas et al., 2008; Wespatat et al., 2004)

2.3 Generators and Modulators

Gamma oscillations are found in virtually all mammalian brain structures, at both cortical and subcortical locations. Specific structures (e.g., thalamus, hippocampus, and cortex) contribute prominently to scalp recorded activity (Basar and Bullock, 1992). Gamma oscillations time- and phase-locked to a stimulus (i.e., “evoked”, see below) have been observed in auditory, visual, and somatosensory paradigms, usually around 40 Hz and within the first 100 ms post-stimulus (Tallon-Baudry and Bertrand, 1999). This transient 40-Hz evoked response is thought to be generated either in underlying primary sensory cortices (Pantev et al., 1991; Tallon et al., 1995) or via thalamo-cortical loops (Ribary et al., 1991), or by both structures in concert (Mulert et al., 2010). Later gamma activity tends to be time- but not phase-locked (i.e., “induced”) and is much more variable, likely reflecting widespread top-down changes in cortical network connectivity (Tallon-Baudry and Bertrand, 1999)

At the local circuit level, gamma activity is generated through feedback inhibition on pyramidal neurons by synaptically and electrically connected networks of fast-spiking interneurons expressing the calcium binding protein parvalbumin (PV+) (Tamas et al., 2000). Recent optogenetic studies have shown that activation of PV+ interneurons is both necessary and sufficient to generate gamma oscillations in the mammalian cortex, which in turn regulates cortical information processing (Cardin et al., 2009; Sohal et al., 2009). These studies have demonstrated than an increase in the excitatory input to these fast-spiking interneuron via selective, optogenetic stimulation leads to an increase in gamma activity. Such an elevation in gamma synchrony was not observed when selectively driving pyramidal cell excitatory input (Cardin et al., 2009). While the precise network and synaptic mechanisms underlying these effects remain unclear (Tiesinga and Sejnowski, 2009), phasic inhibition mediated by fast-spiking interneurons appears to be to the driving force behind gamma oscillations (Bartos et al., 2007), as opposed to tonic GABA(A) agonist application. Gamma activity can be pharmacologically modulated by directly or indirectly altering the

kinetics of GABAergic signaling, as detailed in (Whittington et al., 2000). Further details regarding the generation of cortical rhythms are described in a recent review (Wang, 2010).

2.4 Recording Paradigms

Gamma activity is generally investigated in one of three paradigms: (1) at rest, (2) during "bottom-up" sensory stimulation, or (3) "top-down" cognitively driven tasks. Such oscillations can be detected at various levels within the brain, ranging from macroscopic scalp recordings using electroencephalography (EEG) and magnetoencephalography (MEG), to acute brain slice recordings, to the mescoscopic level with single/multiunit recordings, to the microscopic level with intracellular/synaptic resolution. [FIGURE 1]

2.5 Recording Measures

A variety of signal processing methods are used to investigate oscillatory activity. The main approach is to decompose a neural time series into amplitude and phase information at a given frequency. Applying time-frequency transforms, one can investigate changes in frequency-specific measures during a given task with millisecond precision.

2.5.1 Power Measures—Power reflects the amplitude of an oscillation.[1] For a stationary signal, in which the EEG/MEG does not change over time, the Fast-Fourier Transform (FFT) is used to spectrally decompose the time-invariant signal into component frequencies. The "power spectrum" yielded by FFT analysis is used for resting-state tasks.

The analysis of non-stationary neural activity requires signal-processing methods that compute changes in oscillatory activity at a particular frequency across time. See (Ho et al., 2008; Roach and Mathalon, 2008; van Vugt et al., 2007) for recent reviews. Compared to a baseline period, changes in oscillatory power elicited by a repeated stimulus have been termed "event-related oscillations", "event-related spectral perturbation" (ERSP), or "event-related synchronization/desynchronization".

Oscillatory responses can be categorized by their phase- and temporal-relationship to repeated trials of a sensory or cognitive event (Galambos, 1992; Tallon-Baudry et al., 1998). Oscillations directly in phase with a stimulus (i.e., phase- and time-locked) are called **evoked oscillations**. Oscillatory activity that is in-phase with a stimulus averages across trials to produce an evoked-response.[2] **Induced** oscillatory activity is modulated by a stimulus but is not strictly phase-locked to event onset (i.e., time- but not phase-locked). In the time domain, such oscillations tend to average out and thus require different single-trial signal processing methods for identification. Finally, **total power** refers to the sum of evoked and induced power and is typically represented as difference from or a percentage change from pre-stimulus **baseline power** at each frequency.[3]

2.5.2 Phase Measures—Time-frequency transforms also provide measures of the phase of oscillations, allowing for investigation of "phase-synchrony." Phase-synchrony is independent of oscillatory amplitude and is therefore thought to be a more direct measure of the synchronization of neural signals.[4] Phase-synchrony can be investigated in several

[1]Power typically has units of μV^2 or is converted into decibels (e.g., $10*\log[\mu V^2/Hz]$) to approximate a Gaussian distribution.
[2]It may be useful to investigate oscillations phase-locked with a reaction response, rather than a stimulus, as some studies suggested that decision making processes are correlated more strongly with reaction time than stimulus onset (Spencer, 2004).
[3]It should be noted that baseline subtraction, although an important aspect of signal normalization, is potentially problematic when groups differ in background activity (e.g., cortical noise), which seems to be the case in schizophrenia.
[4]This also reflects the fact that weak coupling between two neural signals first affects their phases, before modulating amplitudes Herrmann, C. S., Grigutsch, M., Busch, N. A., 2005. EEG oscillations and wavelet analysis. In: Handy, T. C., (Ed), Event-related potentials : a methods handbook. MIT Press, Cambridge, Mass., pp. xi, 404 p..

contexts, depending on recording methodologies. Unfortunately, a lack of standardization in the terms applied to phase measures as well as the fact that there are several ways to compute "phase synchrony" has caused confusion in the clinical literature and sometimes led to an inappropriate comparison across studies (Roach et al., 2008). See Figure 2 for a description of various methods for computing phase synchrony. Briefly, the **"phase locking factor (PLF)"** (i.e., intertrial coherence, ITC) describes the similarity in phase at a given point in time across trials at a single electrode site. The "**phase locking index (PLI)**" (also called "phase synchronicity") describes the precise phase-relationships across multiple electrodes at a given time with respect to a repeated external stimulus. Finally, "**phase coherence**" describes the similarity between two continuous signals irrespective of an external stimulus. These measures are all unitless, ranging from 0 to 1. [FIGURE 2]

3.0 Gamma Oscillations in Clinical Studies of Schizophrenia

This section reviews clinical evidence for gamma abnormalities in schizophrenia, focusing on the experimental paradigms that are most directly translatable to model organisms – resting, passive sensory, and a few cognitive paradigms.

3.1 Baseline Gamma Oscillations

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; Fenton et al., 1980; FINLEY, 1944; Giannitrapani and Kayton, 1974; Itil et al., 1972; Itil et al., 1974; Kennard and Schwartzman, 1957; Rodin et al., 1968), 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). Several smaller studies did not detect group differences in resting gamma activity. However, three did report elevations in high beta (20–30 Hz) power, interpreted as reflecting "cortical noise" (Brockhaus-Dumke et al., 2008; Kissler et al., 2000; Krishnan et al., 2005), 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), 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 (Hong et al., 2008; Winterer et al., 2004), in accordance with our preliminary data (Turetsky and Siegel, 2007). Two smaller studies found no group differences in prestimulus GBRs, but did report elevated baseline beta power in schizophrenia (Brockhaus-Dumke et al., 2008) or elevated gamma power with outliers included (Reinhart et al. personal communiction).

3.2 Stimulus Evoked

3.2.1 Auditory—Auditory abnormalities in schizophrenia have been observed when examining both basic (listening to tone) and higher-order auditory processes (performing a cognitive auditory task) (Turetsky et al., 2009).

Auditory Single Stimulus: Paradigms involving simple auditory stimuli have investigated early (<150 ms) phase-locked GBRs, thought to reflect perceptual encoding (Pantev et al., 1991). The largest studies have observed gamma deficits in schizophrenia (Basar-Eroglu et al., 2009; Hall et al., 2010; Hall et al., 2009; Hirano et al., 2008; Krishnan et al., 2009; Lee et al., 2001; Leicht et al., 2010a; Leicht et al., 2010b; Lenz et al., 2010; Roach and Mathalon, 2008; Teale et al., 2008), in accordance with our preliminary findings (Turetsky and Siegel, 2007). A recent study found similar deficits in first-degree unaffected relatives (Leicht et al., 2010a). Gamma abnormalities are generally detected across all recording sites, although deficits are most pronounced at electrodes Cz and Fz or bilateral auditory cortices in sensor space (Leicht et al., 2010b). A twin study estimated the heritability of early evoked-gamma power and phase-locking at $h^2 = 0.65$ and 0.63, respectively (Hall et al., 2009).

Not all studies using transient stimuli have observed group differences in early phase-locked gamma activity (Blumenfeld and Clementz, 2001; Brenner, Krishnan, et al., 2009; Brockhaus-Dumke et al., 2008; Gallinat et al., 2004; Spencer, Niznikiewicz, et al., 2008). Negative results may reflect smaller sample sizes (<20/group), where findings were consistent in direction but not significant (Brenner, Kieffaber, et al., 2009; Clementz et al., 1997; Gallinat et al., 2004). Some of these studies also failed to observe other replicated neurophysiological biomarkers of schizophrenia, such as reduced P50/N100 peak amplitudes (Brenner et al., 2003; Brockhaus-Dumke et al., 2008; Johannesen et al., 2008; Spencer, Niznikiewicz, et al., 2008). A lack of findings in these studies may also be due to suboptimal time-frequency transform methods (Roach and Mathalon, 2008), lack of baseline correction, differences in trial numbers, or problems associated with examining multidetermined neural activity using scalp electrodes (Edgar et al., 2003).

Fewer studies have investigated late (>200 ms) gamma activity following auditory stimulation in schizophrenia. In oddball paradigms, three groups reported reduced late gamma activity in schizophrenia (Gallinat et al., 2004; Gordon et al., 2001; Haig et al., 2000). A fourth study found elevated late gamma power in schizophrenia patients, but did not baseline correct post-stimulus gamma activity like the other studies, which was also elevated (Hong et al., 2008). Finally, several studies investigated gamma phase-synchronicity (GPS) in schizophrenia. Schizophrenia patients have repeatedly shown deficits in GPS, particularly at early time points (<150 ms) and in the left hemisphere (Lee et al., 2003; Slewa-Younan et al., 2004; Symond et al., 2005; Williams, Whitford, Gordon, et al., 2009). A recent study investigated non-baseline corrected absolute values of GPS and found elevations in first-episode patients (Flynn et al., 2008). The authors suggested that diminished task-related GBRs occurred in the context of elevated ongoing gamma activity, a finding that was mirrored in a visual backward masking study (Williams, Whitford, Nagy, et al., 2009).

Auditory Steady State: The auditory steady-state response (ASSR), elicited to amplitude modulated tones or repetitive click trains, has enabled investigation of bottom-up neural synchronization. In normal subjects, maximal responses occur to stimuli with repetition rates around 40 Hz (Galambos et al., 1981). Schizophrenia patients have shown consistent gamma ASSR deficits, as reviewed by (Brenner, Krishnan, et al., 2009). Several groups reported reduced 40+ Hz ASSR power and/or phase-locking in schizophrenia (Brenner et al., 2003;

Hamm et al., 2011; Krishnan et al., 2009; Kwon et al., 1999; Light et al., 2006; Maharajh et al.; Spencer et al., 2009; Spencer, Salisbury, et al., 2008; Teale et al., 2008; Vierling-Claassen et al., 2008), but not for 20 or 30 Hz click trains (Kwon et al., 1999).

3.2.2 Visual—See Brenner et al. (2009b) and Spencer et al. (2008) for reviews on visual GBRs in schizophrenia. Using visual Gestalt stimuli to assess perceptual 'feature binding', multiple studies reported reduced early gamma phase synchrony in schizophrenia (Spencer et al., 2003; Spencer et al., 2004; Uhlhaas et al., 2006). Three studies employing visual backward masking paradigms also found reduced baseline-corrected gamma responses in schizophrenia (Green et al., 2003; Williams, Whitford, Nagy, et al., 2009; Wynn et al., 2005). Finally, schizophrenia patients showed reduced responses to steady-state visual stimuli at gamma-frequencies (Brenner, Krishnan, et al., 2009; Krishnan et al., 2005), although contrary findings have been reported (Riecansky et al., 2010).

3.2.2 Other Stimuli—Clinical studies have investigated GBRs elicited by other types of sensory and motor events. For example, early evoked-gamma reductions in schizophrenia have been observed during proprioceptive stimulation (Arnfred et al., 2010) and transcranial magnetic stimulation (Ferrarelli et al., 2008). In a button press paradigm, schizophrenia patients had reduced GBRs directly preceding the motor response ("corollary discharge") (Ford et al., 2007). These findings suggest that aberrant stimulus-evoked GBRs are a generalized impairment in schizophrenia likely reflecting widespread deficits in cortical gamma synchronization.

3.3 Task Driven

For a review of cognitively-evoked GBRs in schizophrenia, see (Haenschel and Linden, 2010). During working memory paradigms, multiple studies found that individuals with schizophrenia fail to mount a robust gamma response as a function of tasks demands (Barr et al., 2010; Basar-Eroglu et al., 2007; Gonzalez-Hernandez et al., 2003; Haenschel et al., 2009). Several of these report elevated levels of baseline gamma activity in schizophrenia despite a lack of task-specific activation (Barr et al., 2010; Basar-Eroglu et al., 2007; Gonzalez-Hernandez et al., 2003). Multiple groups found reduced gamma power in schizophrenia during selective attention paradigms (Basar-Eroglu et al., 2009; Cho et al., 2006; Kissler et al., 2000; Minzenberg et al.). These findings suggest greater absolute magnitude of gamma activity in schizophrenia coupled with reduced task-specific activations relative to healthy controls, although at least one study has reported contrary results (Pachou et al., 2008).

3.4 Association with Symptoms

Several studies reported associations between gamma activity and symptoms, although identifying such relationships is often difficult.5 Using an auditory paradigm, Haig et al. (2000) found that reduced GBRs predicted higher PANSS scores, although others did not replicate this finding (Hall et al., 2009; Leicht et al., 2010b). Hamm et al. (2011) recently found a significant inverse correlation between the gamma ASSR response and negative symptoms. Associations have been reported between deficits in gamma-power, reaction time, and illness duration (Gallinat et al., 2004; Hall et al., 2010; Reinhart et al.). Additional studies demonstrate that gamma abnormalities are associated with 'treatment resistant' symptoms, including impaired working memory (Light et al., 2006; Winterer et al., 2004), perceptual abnormalities (Johannesen et al., 2008), disorganization (Gordon et al., 2001), and psychomotor poverty (Gordon et al., 2001; Lee et al., 2003). In cognitive and visual

[5]Behavioral measures are often highly variable and necessitate large sample sizes, while exploratory analyses require stringent correction for multiple comparisons

paradigms, reduced GBRs have been associated with severity of negative symptoms (Uhlhaas et al., 2006), deficits in social cognition (Williams, Whitford, Nagy, et al., 2009), and disorganization (Cho et al., 2006). Finally, a recent clinical trial demonstrated that pharmacologic enhancement of frontal gamma activity was associated with improved cognitive function in schizophrenia (Lewis et al., 2008).

Associations between gamma alterations and positive symptoms have also been reported, although they tend to be opposite in direction to what might be predicted. In particular, multiple studies found that patients with larger (i.e., more "normal") early auditory or visual GBRs have more severe positive symptoms (Hirano et al., 2008; Lee et al., 2003; Spencer et al., 2004; Spencer et al., 2009; Spencer, Niznikiewicz, et al., 2008; Uhlhaas et al., 2006). One study reported that gamma activity was significantly elevated during somatosensory hallucinations (Baldeweg et al., 1998).

3.6 Synopsis

Previous sections have demonstrated widespread gamma abnormalities in schizophrenia. Early, evoked abnormalities are most consistent for PLF measures, which are independent of (potentially opposing) power measures and avoid baseline correction issues (Hall et al., 2009; Spencer et al., 2003; Uhlhaas et al., 2006). It is unclear whether the same neural circuit abnormalities contribute to the gamma abnormalities observed across sensory-evoked, cognitive, and resting-state paradigms. Future studies are needed to compare these different gamma measures in the same cohort of subjects. Deficits in sensory-evoked GBRs have been associated with cognitive impairments, suggesting a connection (Light et al., 2006). Likewise, it has been suggested that higher-order cognitive deficits result from impairments in early sensory processing (Haenschel and Linden, 2010).

4.0 Gamma Oscillations in Preclinical Studies of Schizophrenia

As in humans, gamma activity has been associated with a wide range of cognitive and sensory processes across species. For example, cats (Gray et al., 1989; Lakatos et al., 2004), rats (Sukov and Barth, 2001) and mice (Ehrlichman et al., 2009; Lazarewicz et al., 2010; Nase et al., 2003) show a peak in phase-locked gamma activity (~40 Hz) within the first 100 ms of auditory or visual stimulation, following a time course similar to that observed in humans (Pantev et al., 1991; Shibata et al., 1999). Indeed, similar evoked GBRs have been observed in insects during sensory stimulation, suggesting that gamma synchrony is a phylogenetically conserved neural coding mechanism (MacLeod and Laurent, 1996). Similar to the human studies, gamma oscillations have been shown to mediate cognitive processes in mice including selective attention (Lakatos et al., 2004), memory (Dzirasa et al., 2009), sensory perception (Cardin et al., 2009), and cortical information processing (Sohal et al., 2009). This section reviews preclinical studies of schizophrenia that have investigated gamma synchrony.

4.1 Neurotransmitter Disruption

4.1.1 Glutamate – Acute Models—Considerable evidence implicates reduced NMDA-receptor mediated signalling as the core pathophysiologic deficit of schizophrenia (e.g., the "Glutamate Hypothesis") (Coyle, 2006; Goff and Coyle, 2001). Preclinical studies have increasingly employed pharmacologic NMDAR blockade as a disease model, as this model shows deficits consistent with schizophrenia (Olney et al., 1999). Several studies demonstrated that NMDAR antagonists (including ketamine, MK-801, and PCP) produce a dose-dependent increase in baseline gamma power using *in vivo* LFP and EEG recordings in awake rodents (Ehrlichman et al., 2009; Hakami et al., 2009; Lazarewicz et al., 2010; Leung, 1985; Ma and Leung, 2000, 2007; Pinault, 2008). Consistent with this finding,

ketamine increases baseline gamma power in healthy human subjects (Hong et al., 2010). LFP recordings in awake rodents demonstrate ketamine-induced baseline gamma elevations throughout the cortex as well as in subcortical structures including amygdala, hippocampus, and thalamus (Hakami et al., 2009; Hunt et al., 2009; Leung, 1985). Behaviorally, this increase in gamma power is associated with locomotor hyperactivity and deficits in prepulse inhibition (Hakami et al., 2009; Leung, 1985; Ma and Leung, 2000, 2007). Mechanistically, it has been proposed that the effect of NMDAR antagonists on gamma oscillations (and their psychomimetic properties) is due to reduced excitation of PV+ interneurons (Lisman et al., 2008), as discussed below.

Acute brain slice preparations have also been used to investigate gamma synchrony in pharmacologic models of schizophrenia. Such rhythms are typically measured in the hippocampus, and after being induced by bath application of carbachol (Fisahn et al 1998) or kainate (Hajos et al 2000), modulation of this rhythm by NMDAR antagonists is then investigated. Such paradigms have demonstrated strikingly divergent results from the *in vivo* studies described above. Whereas *in vivo* studies demonstrated consistent brain-region independent increases in gamma activity with ketamine, slice studies reported increased gamma power only in auditory cortex, with no change in prelimbic cortex, somatosensory association cortex, medial orbital cortex, insula, and perirhinal cortex. Multiple studies have reported reduced gamma activity in entorhinal cortex following ketamine with no change in the hippocampus (Cunningham et al., 2006; Roopun et al., 2008). Using tetanic stimulation instead of carbachol/kainate to generate oscillatory activity, ketamine has been shown to reduce hippocampal gamma responses (Doheny et al., 2000; Faulkner et al., 1998). Several factors could explain the large discrepancies between findings from *ex vivo* and *in vivo* studies. Brain slices typically sever thalamo-cortical connections, which are important generators of gamma synchrony (Ribary et al., 1991; Whittington et al., 2000). Likewise, *ex vivo* gamma oscillations induced by carbachol, kainate, and tetanic stimulation have very different characteristics from each other. In light of this, it is unclear which, if any of the *ex vivo* measures, bears direct physiological relevance to those recorded in clinical paradigms at scalp electrodes (Wojtowicz et al., 2009).

4.1.1 Glutamate – Chronic Models—NMDAR antagonists produce acute receptor hypofunction and therefore fail to reflect chronic, developmental disruption in glutamatergic signalling that may underlie schizophrenia pathogenesis. In recent years, transgenic mice have been generated to model NMDAR disruption associated with schizophrenia.

The schizophrenia susceptibility genes neuregulin-1 (NRG1) and its receptor ErbB4 are highly expressed in interneurons where they negatively regulate NMDAR signalling (Banerjee et al., 2010; Hahn et al., 2006). In acute WT hippocampal rodent slices, bath application of Nrg-1 selectively increased the power of kainate- but not carbachol-induced gamma oscillations (Fisahn et al., 2009). The effect of Nrg-1 bath application on gamma was absent in ErbB4−/− mice, which showed a 60% reduction in kainate-indued gamma power as well as a reduction PV+ immunoreactivity (Fisahn et al., 2009).

To model the effects of constitutively reduced NMDAR signalling, Mohn et al. generated a line of NMDA-NR1^{neo}−/− mice which express 5–10% of the obligatory NMDAR1 subunit (Mohn et al., 1999). These mice show electrophysiological, behavioral, and molecular deficits consistent with schizophrenia (Dzirasa et al., 2009; Halene et al., 2009; Mohn et al., 1999). Similar to acute administration of NMDAR antagonists, NR1−/−mice show a marked increase in baseline gamma power (Dzirasa et al., 2009, supplement) as well as a reduction in stimulus-evoked gamma band responses (unpublished observation), mirroring findings in schizophrenia. During a working memory task, NR1−/− demonstrate reduced gamma-theta cross frequency phase-coupling between hippocampus and prefrontal cortex, consistent with

deficits in long range neuronal synchronization observed in schizophrenia (Dzirasa et al., 2009; Meyer-Lindenberg et al., 2005).

4.1.2 Dopamine—Dopaminergic agents like amphetamine are known to induce a schizophrenia-like psychosis, but fail to reproduce negative symptoms or cognitive deficits to the same degree as observed in the disease. In rodent cortex and hippocampus, activation of dopaminergic neurotransmission with acute *d*-amphetamine, apomorphine, or methamphetamine had no significant effect on baseline gamma activity (Ehrlichman et al., 2009; Ma and Leung, 2000; Pinault, 2008) or auditory evoked gamma power (Ehrlichman et al., 2009). Likewise, dopamine-transporter knockout (DAT1-ko) mice showed no difference in cortical gamma power (Dzirasa et al., 2009, supplement). Surprisingly, DAT1-ko mice did show extremely elevated hippocampal-PFC gamma phase coherence compared with WT controls (Dzirasa et al., 2009). In hippocampal slices, dopamine reduces pharmacologically induced gamma oscillations but augments stimulus-evoked gamma synchrony (Weiss et al., 2003; Wojtowicz et al., 2009), again in contrast to results from *in vivo* recordings.

Several clinical studies investigated the effect of polymorphisms in the dopamine system on gamma-band activity. Schizophrenia-associated polymorphisms in catechol-O-methyltransferase (COMT), which regulates dopamine degradation, have no effect on resting or auditory evoked gamma activity (Demiralp et al., 2007; Venables et al., 2009). Conversely, mutations in dopamine receptor D4 (DRD4) and DAT1 observed in schizophrenia were associated with elevated evoked GBRs, opposite to the findings in schizophrenia (Demiralp et al., 2007; Venables et al., 2009). These results suggest that dopaminergic dysregulation in schizophrenia likely does not contribute to resting state or stimulus evoked gamma abnormalities. Given the relevance of dopamine to cognitive function, particularly in the prefrontal cortex, future studies should investigate the effect of schizophrenia-associated alterations in DA neurotransmission on cognitively-evoked gamma activity.

4.1.3 GABA—The GABAergic system, in particular parvalbumin-expressing basket and chandelier cells, is integrally involved in the generation of high-frequency oscillations in the mammalian brain (Cardin et al., 2009; Sohal et al., 2009). A wealth of evidence implicates disturbances in GABAergic circuitry in schizophrenia, notably a downregulation of PV and GAD_{67} (1 of 2 enzymes responsible for GABA synthesis), which likely contributes to core symptoms (Guidotti et al., 2005; Lewis et al., 2005).[6]

Several preclinical models of schizophrenia demonstrate similar disruptions in PV+ interneurons and/or GAD_{67}, including models of redox dysregulation (Steullet et al., 2010), prenatal exposure to methylazoxymethanol acetate (MAM) (Lodge et al., 2009), reelin haploinsufficiency (Ammassari-Teule et al., 2009), ketamine exposure (Behrens et al., 2007), altered NRG1/ErbB4 signaling (Neddens and Buonanno, 2010), polymorphisms in DISC1 (Ayhan et al., 2010), neonatal lesions of the ventral hippocampus (Francois et al., 2009), prenatal inflammatory exposure (Jenkins et al., 2009), isolation rearing (Harte et al., 2007), chronic methionine exposure (Tremolizzo et al., 2005), the amygdala activation model (Berretta et al., 2004), lysophosphatidic acid 1 (LPA1) receptor-deficient mice (Cunningham et al., 2006), and constitutive NMDAR1 downregulation (Sisti et al., 2008). Although many of these models do not involve a primary perturbation in the GABAergic system, the fact that they share similar downstream disruptions in this neurotransmitter system suggests that PV cell-dysfunction may be a final common pathway connecting multiple schizophrenia genetic and environmental risk factors.

[6]There is some controversy whether these cells are actually reduced in number or whether they simply have downregulated expression of the calcium-binding protein parvalbumin.

There has been a strong effort recently to connect putative pathogenic disease mechanisms (i.e., NMDA-hypofunction) to downstream GABAergic dysfunction (i.e., loss of PV and GAD_{67}) and associated electrophysiological and neurocognitive deficits (Behrens et al., 2007; Belforte et al., 2010; Gonzalez-Burgos et al., 2010; Lisman et al., 2008; Rotaru et al., 2011). There have been some reports that NMDA-receptors on PV interneurons are more sensitive to pharmacologic blockade than receptors expressed on excitatory pyramidal cells, particularly in the hippocampus and entorhinal cortex (Grunze et al., 1996; Jones and Buhl, 1993; Middleton et al., 2008). However, other studies have shown that the NMDAR contribution to excitatory signaling in PV+ cells is much less than that on principle cells, such as in the prefrontal cortex (Rotaru et al., 2011; Wang and Gao, 2009). As such, it is currently unclear whether the loss of PV and GAD_{67} expression is a direct, or indirect, effect of NMDAR antagonism.

Nevertheless, the increase in gamma power associated with NMDAR antagonists is likely associated with reduced GABA release onto pyramidal neurons, as a number of studies have demonstrated elevated pyramidal cell activity following NMDAR blockade (Belforte et al., 2010; Jackson et al., 2004; Santana et al., 2011). In accordance with this theory, administration of the $GABA_A$ agonist muscimol reversed the baseline gamma power elevation (Ma and Leung, 2000) and loss of GAD_{67}, PV expression (Behrens et al., 2007) induced by NMDAR antagonists in rodents. Computational models have suggested that an extended inhibitory postsynaptic current (IPCS) decay time constant could account for the observed decreased 40 Hz evoked gamma activity (Vierling-Claassen et al., 2008). The authors suggested that the alternations in the GABA transporter GAT1 and GAD_{67} in fast-spiking interneurons which synapse onto the axon initial segment of pyramidal cells observed in patients with Sz (Lewis et al., 2005) may account for extended IPSC decay times and thus decreased 40 Hz evoked activity in patients.

Two recent studies have directly investigated the effect of reduced NMDAR signaling in PV + interneurons by cell-type selective knockdown of NR1, the obligatory NMDAR subunit. Early postnatal NR1 deletion from cortico-limbic interneurons caused a loss of PV and GAD_{67} immunoreactivity coupled with behavioral deficits analogous to the treatment resistant symptoms of schizophrenia, including impaired social interactions, decreased reward seeking behavior (i.e., anhedonia), and reduced working memory (Belforte et al., 2010). Although gamma activity was not assessed, the authors reported elevated baseline firing rates in cortical pyramidal neurons as well as decreased cross-correlation with nearby neurons. In a second study, selective deletion of NR1 from PV+ interneurons significantly increased hippocampal gamma power while disrupting cross-frequency synchrony and caused deficits in spatial and working memory (Korotkova et al., 2010). These findings further strengthen the association between NMDAR signaling, fast-spiking neurons, neuronal synchrony, and cognitive function.

4.1.4 Other Neurotransmitter Systems—Disturbances in other neurotransmitter systems have been linked schizophrenia, including acetylcholine (ACh), serotonin, and cannabinoids. While beyond the scope of this review, schizophrenia-like gamma abnormalities have been demonstrated following blockade of muscarinic ACh receptors (Rodriguez et al., 2004) and blockade of **α**7-nicotinic ACh receptors (Song et al., 2005), which localize heavily on hippocampal GABAergic interneurons (Ji and Dani, 2000). In rats, gamma activity is modulated by cannabinoid agonists (Hajos et al., 2008) and serotonin, likely through $5\text{-}HT_{1A}$ and $5\text{-}HT_{2A}$ receptors (Puig et al., 2010; Wojtowicz et al., 2009).

4.2 Other Preclinical Disease Models

Gamma synchrony has been investigated in other models of schizophrenia that do not involve strict neurotransmitter system disruption. A recent study investigated *in vivo* synchrony between prefrontal cortex and hippocampus (PFC-HC) during a working memory task in *Df(16)A*$^{+/-}$ mice. These mice model the human 22q11.2 microdeletion, which is strongly linked with schizophrenia (Sigurdsson et al., 2010). While the study focused on theta activity, gamma phase synchrony was qualitatively reduced (Fig 2c, Fig 3a). The authors reported the gamma difference as non-significant after Bonferroni post-hoc correction for tests across all frequencies. In the prenatal MAM rat model of schizophrenia, Lodge et al. (2006) reported a reduction in *in vivo* PFC and HC gamma power during a reversal-learning paradigm, and this gamma reduction predicted worse task performance. Baseline gamma activity, however, was not altered with MAM exposure. LPA1-receptor deficient mice, another strain proposed as an animal model of schizophrenia, showed erratic *ex-vivo* kainate induced gamma oscillations in entrorhial cortex (Cunningham et al., 2006). Vohs et al. investigated auditory evoked gamma activity in the neonatal ventral hippocampal lesion (NVHL) rat model of schizophrenia using a paired click paradigm (Vohs et al., 2009). Although NVHL rats showed no difference in baseline-corrected total gamma power following either stimulus, these rats showed significantly reduced gamma PLF, highly consistent with clinical findings. 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. Finally, Steullet et al. investigated hippocampal gamma synchrony in GCLM−/− mice, which are susceptible to elevated redox dysregulation due to impaired glutathione synthesis (Steullet et al., 2010). Kainate-induced gamma oscillations were weaker in brain slices from transgenic mice in ventral, but not dorsal, hippocampus.

4.3 Translational Potential of Gamma Synchrony

Emerging evidence indicates that gamma oscillations are disrupted in preclinical models of schizophrenia, often similar in pattern to that observed in schizophrenia. Importantly, such aberrant neuronal synchrony arises from selective perturbation of neurotransmitter signaling and/or gene expression relevant to schizophrenia, providing key insights into the pathophysiological bases of disease-related neuronal deficits. Altered GBRs may reflect disruptions of a final common GABAergic pathway downstream of etiologically diverse pathogenic insults that have been linked to schizophrenia, a pathway which may provide targets for pathophysiologically based therapeutic strategies (Lewis and Gonzalez-Burgos, 2006; Whittington et al., 2000).

The overarching hypothesis of this review is that gamma abnormalities are a biomarker for the treatment resistant symptoms of schizophrenia and can be used as a rationale target for therapeutic development. Preliminary evidence from a recent clinical trial bolstered the validity of this approach (Lewis et al., 2008). The identification of similar gamma-band abnormalities in preclinical models of schizophrenia provides a promising opportunity for drug development. Therapeutics that substantially increase gamma signal-to-noise during sensory processing tasks (e.g., reduce elevated background, pre-stimulus gamma-band “noise” and increase stimulus-evoked GBRs) may improve perceptual abnormalities in schizophrenia. Likewise, compounds that elevate gamma power during cognitive paradigms may help alleviate these deficits in schizophrenia. Although beyond the scope of this review, it is hypothesized that compounds which positively modulate selective GABA-receptor subtypes (Guidotti et al., 2005; Lewis and Gonzalez-Burgos; Lewis et al., 2004) or cholinergic signaling (Gray and Roth, 2007) are promising candidates for restoring gamma abnormalities in schizophrenia and associated neuronal impairments.

4.4 Caveats and Future Studies

While the translational potential of gamma oscillations in preclinical studies of schizophrenia is strong, there are a number of important caveats to consider. As with any other preclinical study of a complex human disease, one must evaluate the validity of the animal model before extrapolating to the clinical population (Chadman et al., 2009).

Construct validity indicates that the etiologic cause of phenotypic deficits in the preclinical model has been established as a risk factor (genetic, environmental, etc.) in the clinical population. As such, knockout mouse models for schizophrenia risk genes generally demonstrate excellent construct validity. However, one must be careful that the genetic change is similar to that observed in the patient population. Likewise, several groups (including ours) have employed acute NMDAR-blockade as animal models of schizophrenia, despite the fact that these models fail to reflect the neurodevelopmental consequences associated with constitutive NMDAR dysfunction.

Face validity indicates that a mouse model recapitulates core phenotypic (and endophenotypic) deficits associated with the clinical disorder. Models of elevated dopaminergic signaling do not demonstrate gamma abnormalities, indicating a lack of face validity for certain aspects of schizophrenia. When assessing the face validity of a mouse model, it is important to consider that phenotypic/endophenotypic indices are measured as similarly as possible between humans and mice. Since the gamma abnormalities in schizophrenia have been detected using scalp EEG/MEG recordings, similar skull recordings or those using large macroelectrodes performed in rodents are the most directly comparable human EEG/MEG studies (Gandal et al., 2010; Gandal et al., 2008; Umbricht et al., 2004). More localized LFP or unit recordings, which are extremely important for mechanistic understanding of neural information processing, likely have less face validity for human findings, given that such paradigms are difficult to perform in a clinical setting. In addition, questions remain about the face validity for *ex vivo* brain slice paradigms, given that these recordings are nearly impossible to perform in humans and tend not to replicate findings from unanesthetized *in vivo* recordings.

Finally, predictive validity indicates that an intervention which is effective in the preclinical setting translates successfully to the clinical population (and vice versa). This stipulation further demonstrates the pitfalls of acute NMDAR-blockade models. For example, pre-administration of $GABA_A$ agonists and benzodiazepines ameliorate several neuronal deficits in acute NMDAR-blockade models (Behrens et al., 2007; Castner et al., 2010; Ma and Leung, 2007), despite the fact that these drugs do not improve, or sometimes even worsen, schizophrenia symptoms (Buchanan et al., 2010; Menzies et al., 2007).

5.0 Conclusion

5.1 Synthesis: A Model of Gamma-Band Activity

Based on a comprehensive review of the literature, we suggest that there is reduced gamma signal-to-noise during cortical information processing in schizophrenia, a hypothesis previously suggested (Flynn et al., 2008; Kissler et al., 2000; Krishnan et al., 2005; Tseng et al., 2008; Williams, Whitford, Nagy, et al., 2009; Winterer et al., 2004; Winterer et al., 2000). There is strong evidence that pre-stimulus baseline gamma activity is elevated and that task-driven ‘evoked’ gamma-band responses are reduced in schizophrenia. Baseline elevations are most evident with pre-stimulus measurements, suggesting an impairment in the ability to rapidly return to a resting state prior to the next stimulus. Indeed, previous studies have reported a relationship between pre-stimulus power and the amplitude of an ensuing evoked response (Basar et al., 1987). This pattern suggests that the ability to attribute salience to incoming sensory stimuli is impaired in schizophrenia, as is the ability

to appropriately engage frontal neuronal networks during complex cognitive tasks. Physiologically, such findings could be explained by a dysfunction in inhibitory interneuron networks, which maintain appropriate resting 'inhibitory tone' but are also necessary for task-specific up-regulation of gamma synchrony, as recently demonstrated (Sohal et al., 2009).

5.2 Specificity

Although this review has focused on gamma oscillatory responses, it is important to note that abnormalities in other frequency bands (especially theta), have been well documented in the disorder (Edgar et al., 2008; Lisman and Buzsaki, 2008; Uhlhaas et al., 2008; Uhlhaas and Singer, 2010). Given the interdependence of neuroonal oscillatory activity in different frequencies (e.g., gamma-theta cross frequency coupling), it may be difficult to parse out the selective contribution of deficits within a single frequency range without considering others bands (Canolty and Knight, 2010; Varela et al., 2001).

5.3 Gamma Synchrony as a Common Endophenotype

Gamma alterations are not specific to schizophrenia. For example, similar deficits in evoked GBRs have been reported in preclinical and clinical studies of autism (Gandal et al., 2010) as well as in other neuropsychiatric diseases (Herrmann and Demiralp, 2005). Interestingly, several of these neuropsychiatric diseases have significant pathophysiological overlap. For example, schizophrenia and autism share common epidemiological characteristics (highly heritable, neurodevelopmental origin, 1–2% population prevalence), common core phenotypic deficits (e.g., social withdrawal, language problems, cognitive deficits), common neurological comorbidities (e.g., epilepsy, ADHD, sleep disruption), common endophenotypes (e.g., attentional deficits, deficits in sensory processing and prepulse inhibition), common genetic insults (e.g., mutations in NRXN1, DISC1, 22q11.2), common environmental etiologies (e.g., prenatal infection, oxidative stress), common approved but deficient treatments (e.g., risperidone), and common molecular disruptions (e.g., GABAergic interneurons) (Ching et al., 2010; Eagleson et al., 2010; Kilpinen et al., 2008; Levy et al., 2009; Ousley et al., 2007; Qin et al., 2005; Siegel and Ralph, 2011). It is our hypothesis that similar abnormalities in gamma synchrony across disorders reflect common neuronal circuit insults leading to shared downstream phenotypic deficits. In light of this, we speculate that gamma synchrony is an endophenotype for a common constellation of neuronal deficits independent of diagnostic categorization. Targeting gamma-band deficits (and the circuit insults they index) with novel therapeutic approaches could thus have implications for a broad group of patients, similar to the approach recently proposed as the "future of psychiatric research" (Akil et al., 2010).

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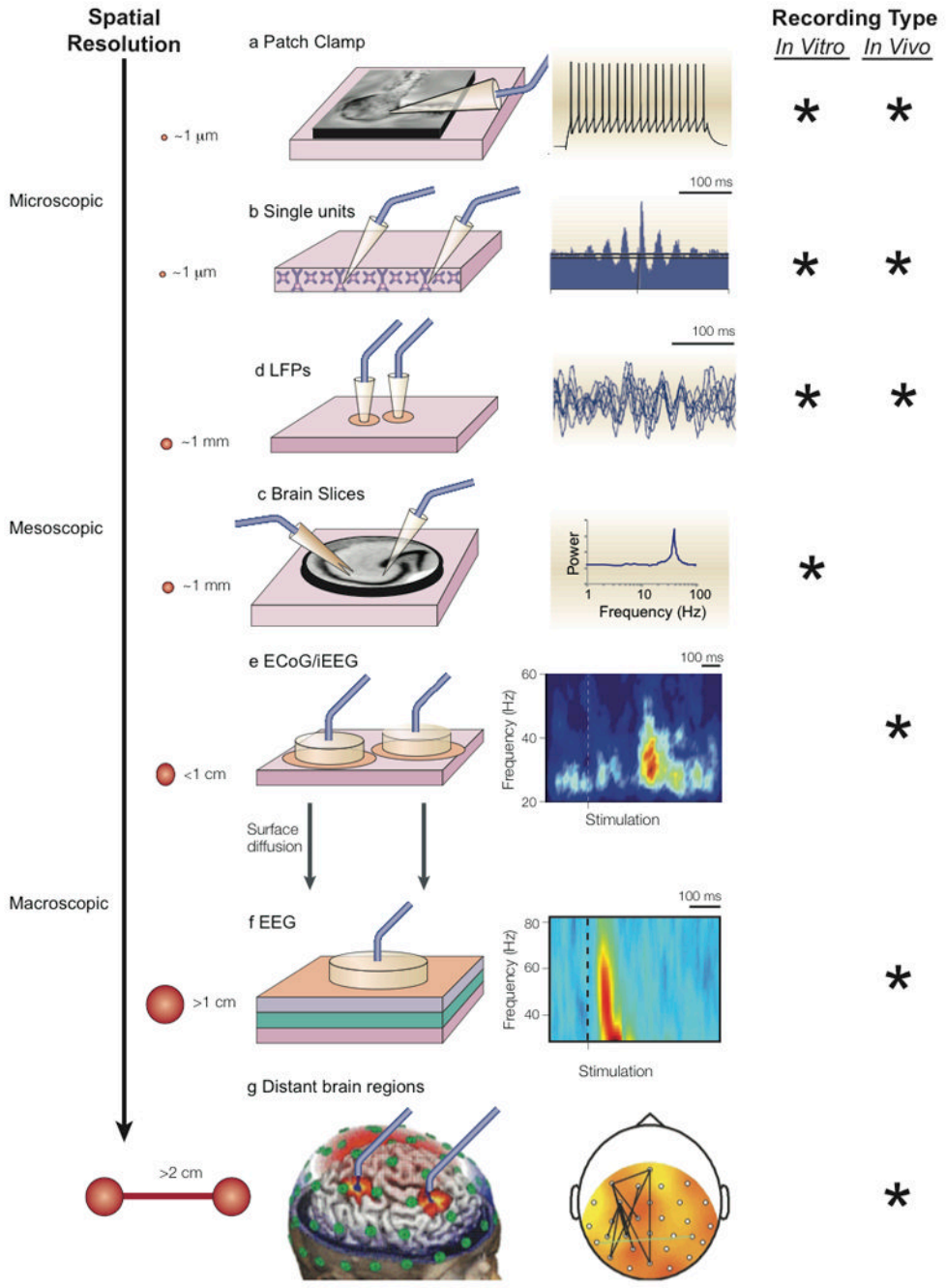

Figure 1.

Gamma oscillations can be detected at various levels of investigation. **A.)** At the microscopic level, patterns of oscillatory activity can be detected from intracellular current and membrane potential recordings using patch clamp **B.)** Inter-neural phase synchrony can be assessed using extracellular recordings from high impedance microelectrodes. When high-pass filtered (>500 Hz), single/multi-unit activity can be detected. **C.)** When low-pass filtered, such activity gives rise to the local field potential (1–500 Hz), reflecting the summation of synaptic potentials oriented in parallel. **D.)** In preclinical studies, neuronal synchrony can be investigated in acute, *ex vivo* brain slices kept alive for several hours by artificial cerebrospinal fluid. Intracellular and extracellular signals can be recorded from

these slices, as well as population averages of synchronously activated neurons using voltage sensitive dye imaging (Carlson and Coulter, 2008). Depending on the brain region and slice preparation, gamma oscillations can be spontaneously recorded (e.g., in auditory cortex), can be pharmacologically induced such as with carbachol or kainate, or can be induced using tetanic stimuli (Whittington et al., 2000). **E.)** At an intermediate level, gamma oscillations can be recorded from a more spatially localized region of the brain using subdural electrocorticography ('ECoG') grids or intracortical electrodes. These approaches record the synchronous synaptic potentials of regional pyramidal cells oriented in parallel. **F.)** At the macroscopic level, electroencephalography (EEG) and magnetoencephalography (MEG) measure electromagnetic brain activity. Whereas the EEG signal results from the extracellular volume conducted currents triggered mainly by the spatial summation of underlying cortical postsynaptic potentials, MEG is thought to arise from the intracellular branch of this process – from the currents flowing from the dendritic tree to the soma (Lewine and Orrison, 1995). Although gamma activity can be examined at the sensor (e.g., scalp) level, many studies also use source localization methods to examine gamma activity in source (i.e., brain) rather than sensor space. **G.)** Finally, gamma synchrony can be assessed between distant brain regions or scalp electrodes using phase-coupling methods. Figure adapted with permission from (Varela et al., 2001)

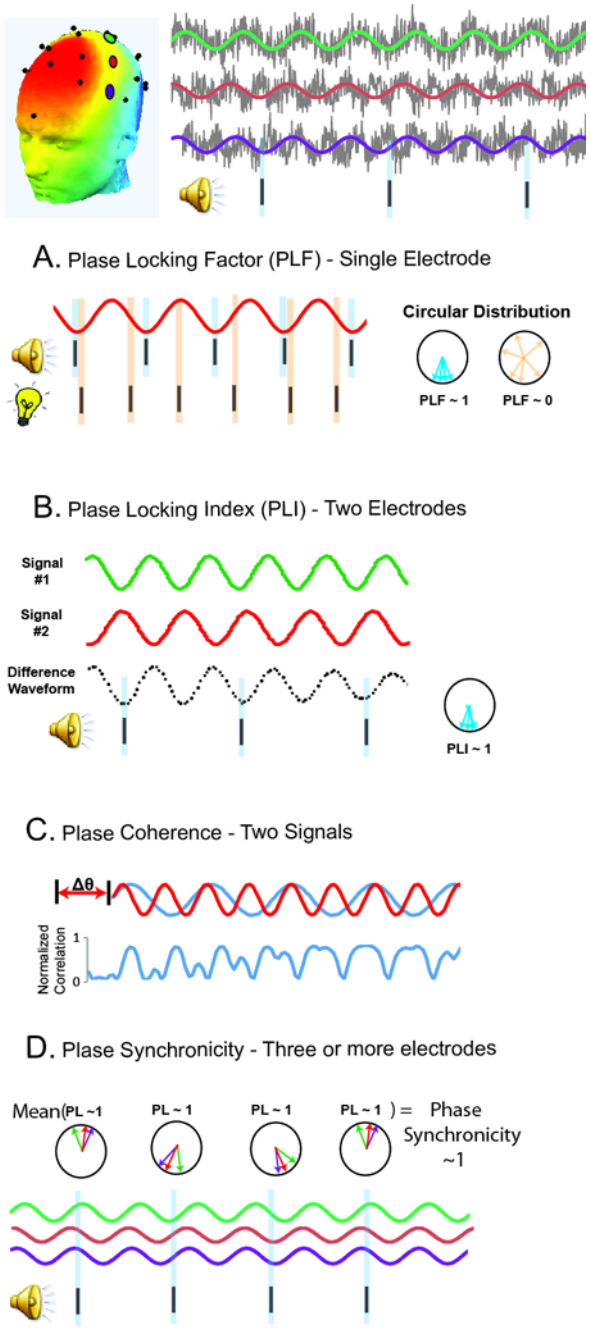

Figure 2.

Gamma “phase synchrony” can be measured using several different methods. A.) Phase-dependence between a series of repeated events (e.g., onset of an external stimulus) and a continuous time series (e.g., EEG/MEG) is referred to as the “phase-locking factor (PLF)”. If the phase measures across trials tend to align in the same direction at a given point in time, the PLF will approach 1, indicating a strong phase relationship between the signals. When measuring the phase-relationship between repeated sensory stimuli and EEG/MEG activity at a single electrode or source site, this measure has been termed “intertrial phase coherence (ITPC)” or “intertrial coherence (ITC)” (Light et al., 2006). We, and others, prefer to call this PLF, since the term “coherence” implies multiple neuronal signals are

being compared, whereas the PLF only depends on a single electrode site (Roach and Mathalon, 2008). An important feature of PLF is that this measure does not depend on the actual value of the phase-angles themselves; rather, PLF is simply a measure of the consistency of the phase-angles across trials. As such, PLF and evoked power are related measures (whereas event-related PLF and total power are independent). B.) Whereas PLF assesses phase synchrony at a single site, functional connectivity between brain regions with respect to a repeated stimulus is frequently assessed via the "phase-locking index (PLI)". Synchrony between two areas is computed by assessing the consistency across trials in the difference in the phase values in those areas. Like PLF, the PLI is a normalized measure, and varies between 0 (independent signals) and 1 (fixed phase-lag between the two signals). C.) The term "phase synchronicity" has been used to refer to the precise phase-relationships across 3 or more EEG/MEG electrodes at a given time with respect to an external stimulus. PLF and PLI are very different measures of neuronal synchrony. PLF assesses the temporal consistency of oscillatory phase across trials at a single site, while PLI provides a spatial measure of synchrony. Finally, both measures are highly sensitive to trial numbers, which may be problematic if experimental groups differ in number of artifact free trials or a paradigm with few trials is employed. D.) The phase-dependence between two continuous time series (e.g., two EEG electrodes) irrespective to a repeated discrete event is called "phase-coherence," or "phase coupling." Such measures require calculating Pearson correlation coefficients between the two frequency-filtered time series, after unit normalization to yield a measure of pure phase synchrony (independent of amplitude). To account for possible conduction delays between two electrodes/regions, phase-coherence is usually computed after discrete phase shifts and then corrected for multiple comparisons (Dzirasa et al., 2009; Varela et al., 2001). Finally, phase coherence can be assessed between two sites at different frequencies, for example, "cross frequency phase-coupling (CFPC)" between theta and gamma oscillations (Sigurdsson et al., 2010). A recent review describes such calculation of such measures and their functional role in cortical information processing (Canolty and Knight, 2010).

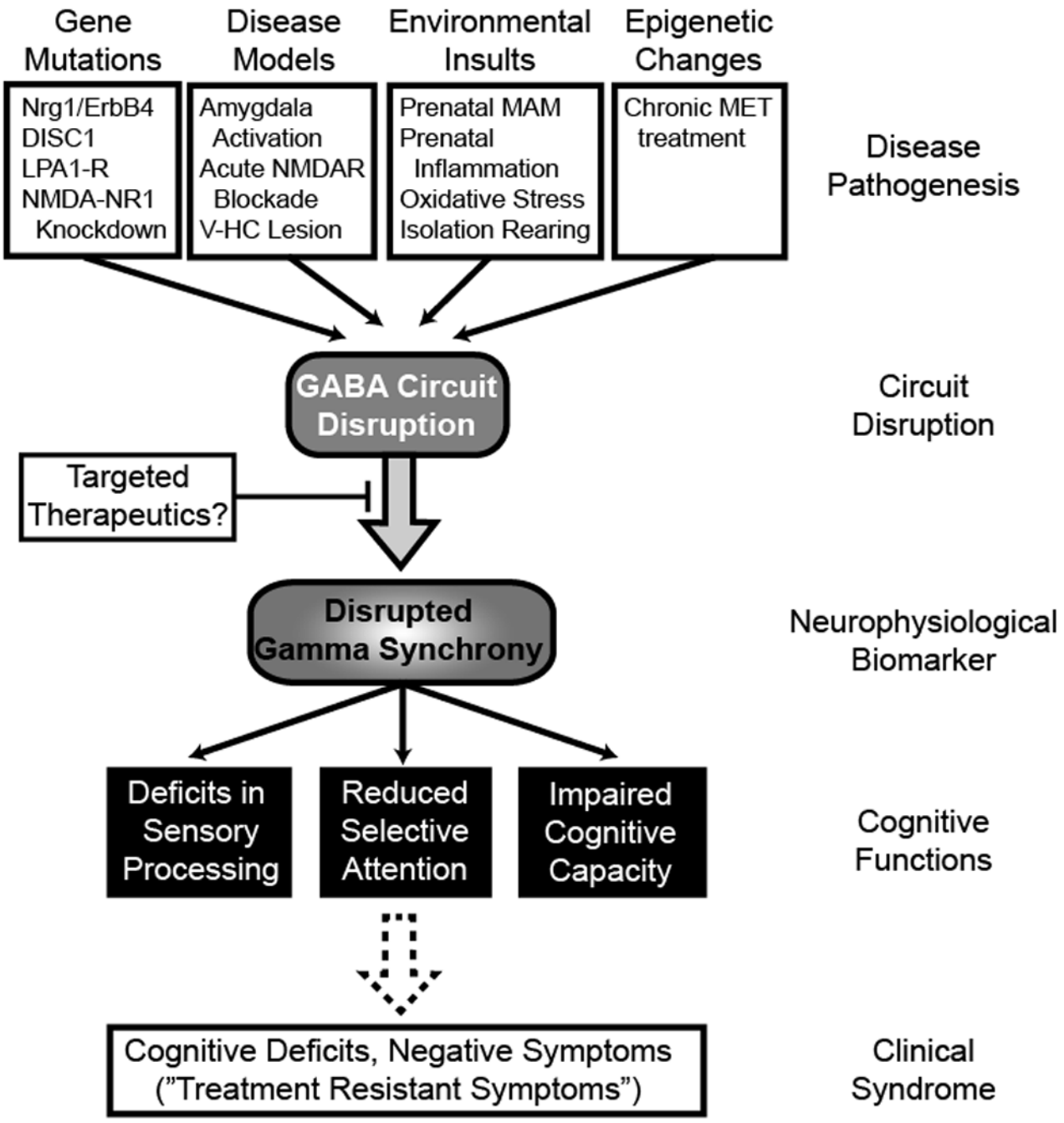

Figure 3.

Gamma oscillatory abnormalities represent an intermediate phenotype in schizophrenia that likely reflect pathophysiological deficits and contribute to core symptoms. Despite distinct pathogenic insults, several schizophrenia models converge on GABAergic circuit deficits, particular the disruption of fast-spiking parvalbumin-expressing interneurons. Dysfunctional fast-spiking interneuron activity appears to be a final common pathway in schizophrenia that could explain gamma abnormalities. This loss-of-inhibition phenotype could account for both elevated baseline and reduced stimulus-evoked endophenotypes. A lack of precise PV+ cell firing during task or stimulus-specific activation would prevent robust high-frequency synchronization of cortical pyramidal neurons, thereby leading to a reduced evoked gamma

response (i.e., decreased PLF). Likewise, appropriate inhibitory tone mediated in part by PV + cells would be required to restore neuronal oscillatory activity to an appropriate pre-stimulus resting state. Reduced activity of a subpopulation of interneurons could delay the ability of a circuit to return to this resting state, leading to the elevation in baseline gamma activity observed in clinical and preclinical settings.

Table 1

Several studies have investigated the early, evoked auditory gamma-band response (e.g., evoked-power or phase-locking factor) to simple tones or clicks in schizophrenia, which is associated with perceptual encoding of sensory information (Pantev et al., 1991). Of the published studies, 10/16 found significantly reduced early, evoked GBRs in schizophrenia, while 13/16 studies found qualitative and/or quantitative reductions in these measures. Study characteristics are detailed above, using the following abbreviations: interstimulus interval (ISI, seconds), baseline correction (B.C.), non-significant (N.S.), qualitative but non-significant reduction in the schizophrenia group (“(↓)”), continuous performance task (CPT), regional field activity (REFA), primary auditory cortex (A1), right hemisphere (RH), left hemisphere (LH), dorsal anterior cingulate cortex (dACC) and low-resolution brain electromagnetic tomography (LORETA). References: (1) Clementz et al., 1997; (2) Leicht et al., 2010a; (3) Hall et al., 2009; (4) Galliant et al., 2004; (5) Roach and Mathalon, 2008; (6) Spencer et al., 2008a; (7) Hall et al., 2010; (8) Lenz et al., 2010; (9) Hirano et al., 2010; (10) Blumenfeld et al., 2001; (11) Basar-Eroglu et al., 2009; (12) Brenner et al., 2009a; (13) Krishnan et al., 2009; (14) Brockhaus-Dumke et al., 2007; (15) Teale et al., 2008; (16) Leicht et al., 2010b.

Modality, # sensors	Paradigm (Stimulus)			Subject Type		Gamma Measure (Method)			SC2 Effect (*P*)	Sites Looked	Ref
	Duration	ISI (sec)	Trials	# SCZ	# CTL	Freq (Hz)	Time (ms)	B.C.		Site with Effect	
MEG, 148	Paired click (white noise)			Chronic, Meds		Power, Evoked Buttorworth, REFA)			(↓) N.S.	All	1
	0.1 ms	8–10s	200	10	10	24–48	Max				
EEG, 27	Pure tone (800, 1300 Hz)			Chronic, Meds		Power, Evoked (Wavelet)			↓ <0.02	Cz, Fz; Loreta	2
						32–48	20–80	Yes		Cz, Fz; A1, dACC	
						PLF (Wavelet)			↓ 0.004	Cz, Fz; Loreta	
	250 ms	2.5–7.5	30	90	90	32–48	20–80	Yes		Cz, Fz; A1, dACC	
EEG, 16	Oddball (1kHz, non-target)			Chronic, Meds		Power, Evoked (Wavelet)			↓ 0.001	Cz, Fz	3
						35–46	20–80	Yes		Cz, Fz	
						PLF (Wavelet)			↓ 0.001	Cz, Fz	
	20 ms	1.8–2.2	400	30	147	35–46	20–80	Yes		Cz, Fz	
EEG, 32	Oddball (1 kHz target)			Chronic, Unmeditated		Power, Evoked (Wavelet)			N.S.	All	4
						40 Hz	20–100	yes			
						Power, Evoked (Wavelet)			↓ 0.02	All	
	1 ms	1.5–4.6	55	15	15	40HZ	220–350	yes		RH, Anteror	
EEG, 26	Oddball (500 Hz non-target)			Chronic, Meds		Power, Evoked (Wavelet)			↓ 0.031	All	5
	50 ms	1.25	210	21	22	35–50	20–60	?		All	

Modality, # sensors	Paradigm (Stimulus)			Subject Type		Gamma Measure (Method)			SC2 Effect (*P*)	Sites Looked	Ref
	Duration	ISI (sec)	Trials	# SCZ	# CTL	Freq (Hz)	Time (ms)	B.C.		Site with Effect	
EEG, 60	Oddball (1kHz. non-target)			Chronic, Meds		PLF (Wavelet)			(↓) N.S.	Fronto-Contral electrode sites	6
						34–54	30–74	Yes			
						Power, Evoked (Wavelet)			(↓) N.S.	Fronto-Control electrode sites	
	70 ms	1.2	180	23	21	34–54	30–74	Yes			
EEG, 60	Paired click			Chronic, Meds		Power, Evoked (Wavelet)			↓ 0.001	All	7
	5 ms	10	160	51	34	35–48	−100—400	Yes		Widely distributed	
EEG, 20	Oddball (1 kHz non-target)			Chronic, Meds		Power, Evoked (Wavelet)			↓ 0.01	Fronto-Central	8
	500 ms	1.8–2.2	480			30–80	50–150	Yes		Fronto-Central	
	Oddball (2 kHz target)					Power, Evoked (Wavelet)			↓ 0.03	Fronto-Central	
	500 ms	1.8–2.2	480	18	19	30–80	50–150	Yes		Fronto-Contral	
MEG, 37	Puro tone (2 kHz)			Chronic Mode		Power, Evoked (Wavelet)			↓ 0.03	Temporal channels (10)	9
	200 ms	1–2	220	20	23	20–45	0–50	Yes		LH	
MEG, 148	Paired click			Chronic, Meds		Power, Evoked (FFT)			N.S	Spatial decomposition of channels	10
	0.04	9	120	20	20	20–50	0–200	No			
EEG, 4	Auditory CPT (−1440 Hz)			Chronic, Meds		Power, Evoked (FFT)			↓ 0.01	Fz, Cz, Pz, Oz	11
	300	1	28	10	10	28–48	0–200	No		Vertex	
EEG, 29	Oddball (paired click non-target)			Chronic, Meds		Power, Evoked (Wavelet)			(↓) N.S.	Cz	12
	3	7-11	130	21	22	30–50	32–74	No			
EEG, 29	Pure tone (1000 Hz)			Chronic, Meds		PLF (FIR, Hilbert)			N.S.	Cz	13
	1000	0.9	90	21	21	40	0–300 ms	No			
EEG, 32	Paired click			Chronic, Meds		PLF (Wavelet)			N.S	Cz	14
	1	10	96	32	32	33–60 Hz	25–125	Yes			
MEG, 248	Pure tone (1000 Hz)			Chronic, Meds		PLF (Wavelet)			↓ <0.06	LH, RH sources	15
	500	3.5	200	14	13	40	20–100	No		LH > RH	

Modality, # sensors	Paradigm (Stimulus)			Subject Type		Gamma Measure (Method)			SC2 Effect (*P*)	Sites Looked	Ref
	Duration	ISI (sec)	Trials	# SCZ	# CTL	Freq (Hz)	Time (ms)	B.C.		Site with Effect	
EEG, 27	Pure tone (800, 1300 Hz)			Chronic, Meds		Power, Evoked (Wavelet)					16
						32–48	20–80		↓ 0.004	Cz	
						PLF (Wavelet)					
	250	2.5–7.5	60	17	17	32–48	20–80		↓ 0 002	Cz	
										Cz	