GAMMA OSCILLATION DEFICITS AND THE ONSET AND EARLY PROGRESSION OF SCHIZOPHRENIA

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Abstract

There has been a fascinating convergence of evidence in recent years implicating the disturbances of neural synchrony in the gamma frequency band (30–100 Hz) as a major pathophysiologic feature of schizophrenia. Evidence suggests that reduced glutamatergic neurotransmission via the N-methyl-D-aspartate (NMDA) receptors that are localized to inhibitory interneurons, perhaps especially the fast-spiking cells that contain the calcium-binding protein parvalbumin (PV), may contribute to gamma band synchrony deficits, which may underlie the failure of the brain to integrate information and hence the manifestations of many symptoms and deficits of schizophrenia. Furthermore, because gamma oscillations are thought to provide the temporal structure that is necessary for synaptic plasticity, gamma deficits may disturb the developmental synaptic reorganization process that is occurring during the period of late adolescence and early adulthood, which may contribute to the onset of schizophrenia and the functional deterioration that is characteristic of the early stage of the illness. Finally, reduced NMDA neurotransmssion on inhibitory interneurons, including the PV-containing cells, may inflict excitotoxic or oxidative injury to downstream pyramidal neurons, leading to further loss of synapses and dendritic branchings. Hence, a key element in the conceptualization of rational early intervention and prevention strategies for schizophrenia may involve correcting the abnormal NMDA neurotransmission on inhibitory interneurons, possibly that on the PV-containing neurons in particular, thus normalizing gamma deficits and attenuating downstream neuronal pathology.

Schizophrenia was classically described as a "splitting of the psychic functions" (Bleuler 1950/1911), in which various aspects of thought and personality were disintegrated. In modern accounts of this illness, it has been proposed that the disorder arises from a failure of the brain to integrate the activity of local and distributed neural circuits (Andreasen 2000; Benes 2000; Friston and Frith 1995). Orchestrated oscillations of neural circuits in the gamma frequency band (30–100 Hz) have been proposed to be the mechanism that supports the integration of brain activities (Engel and Singer 2001; Singer et al 1990; Tallon-Baudry 2004; Uhlhaas and Singer 2006). As a result, there has been increasing interest in recent years in trying to understand how gamma oscillations might play a role in the

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pathophysiology of schizophrenia. In fact, the role of gamma oscillations in higher brain functions in humans in both normal and disease states, including schizophrenia, has been a major area of research (Engel and Singer 2001; Herrmann and Demiralp 2005; Lee et al 2003a; Lewis et al 2005; Lewis and Moghaddam 2006; Tallon-Baudry 2004; Uhlhaas and Singer 2006). There have also been several excellent reviews that specifically address the roles of gamma deficits in the pathophysiology of schizophrenia (Gonzalez-Burgos and Lewis 2008; Roach and Mathalon 2008; Spencer 2008; Uhlhaas et al 2008). Here, our goal is to critically evaluate the literature in an attempt to integrate the clinical findings of gamma deficits and the well-established observations of inhibitory neuronal dysfunction in schizophrenia. We introduce the hypothesis that the onset and post-onset functional deterioration of schizophrenia may be a manifestation of progressive gamma deficits that result from disturbances of the peri-adolescent maturation of inhibitory neural circuits in the cerebral cortex (Woo and Crowell 2005).

Gamma Band and Higher Cortical Functions

Interest in gamma oscillations and brain functioning can be dated back to the late 80's when the Eckhorn and Singer groups demonstrated in a series of experiments, first in cats and then in monkeys, that synchronized oscillations of neuronal activity in the gamma frequency band appeared to mediate the integration or binding of visual features that give rise to coherent visual perception (Eckhorn et al 1988; Engel et al 2001; Engel et al 1991; Gray et al 1992; Gray et al 1989; Gray and Singer 1989; Singer et al 1990). The presumed role of gamma in the synchronization of neural circuits for the representation and integration of information is not limited to the sensory/perceptual domain, but it may also mediate a range of other cognitive operations (Salinas and Sejnowski 2001). For example, gamma oscillations may help to mediate selective attention (Fries et al 2001; Salinas and Sejnowski 2001; Tallon-Baudry 2004; Tiitinen et al 1993), working memory (De Pascalis and Ray 1998; Howard et al 2003; Tallon-Baudry et al 1998), long-term memory (Fell et al 2001) and motor control (Schoffelen et al 2005).

In humans, gamma activity is commonly measured by the electroencephalogram (EEG) during the performance of various tasks. "Evoked" gamma oscillations are phase-locked to a stimulus and therefore show inter-trial phase locking whereas "induced" gamma oscillations are not strictly phase-locked to a stimulus (Tallon-Baudry and Bertrand 1999) (see Fig. 1). Although the precise functional significance of the two forms of gamma activities remains unclear, it has been suggested that early sensory-evoked gamma may reflect sensory or perceptual processing, whereas induced gamma may reflect higher-level cognitive processes (for review see (Engel et al 1992; Pulvermuller et al 1999; Tallon-Baudry and Bertrand 1999)). In addition, in the auditory modality, the repeated presentation of a simple stimulus (such as a click) or the modulation of a sine-wave tone at the frequency of 40 Hz generates a resonant response, the 40 Hz auditory steady-state response (ASSR) (Galambos et al 1981).

Gamma Band Abnormalities and the Clinical Manifestations of Schizophrenia

Recent evidence suggests that the underlying neural mechanism(s) that generates and/or supports gamma oscillations, including evoked, induced, and steady-state gamma, seems to be impaired in schizophrenia. To date, a number of studies have demonstrated abnormalities in the power and/or phase locking of gamma oscillations in this disorder, suggesting that the neural mechanisms that mediate gamma may be functionally deficient. The most widely studied and replicated effect is the reduction of the 40 Hz ASSR in patients with schizophrenia (Brenner et al 2003; Hong et al 2004a; Kwon et al 1999; Light et al 2006; Spencer et al 2008; Wilson et al 2007a), which is apparent in both the evoked power and

phase locking measures. Furthermore, schizophrenia patients demonstrate decreased phase locking of the early visual-evoked gamma oscillation (Spencer et al 2003; Spencer et al 2007), although the early auditory-evoked gamma oscillation does not appear to be affected (Gallinat et al 2004; Spencer et al 2007). Other gamma abnormalities have been reported in association with early auditory processing (Clementz et al 1997; Hong et al 2004b), auditory target detection (Gallinat et al 2004; Haig et al 2000; Symond et al 2005), visual perception (Spencer et al 2004; Wynn et al 2005), and somato-motor processing (Lee et al 2003b).

Given the hypothesis that working memory and prefrontal cortex dysfunction is a core deficit of schizophrenia (e.g. (Goldman-Rakic 1994; Lewis and Gonzalez-Burgos 2007; Park and Holzman 1992; Tan et al 2007)), it is notable that there is evidence that gamma oscillations associated with working memory may be impaired in patients with schizophrenia (Basar-Eroglu et al 2007; Cho et al 2006; Kissler et al 2000). For instance, Basar-Eroglu et al (Basar-Eroglu et al 2007) demonstrated that gamma power fails to increase as working memory load increases, as is seen in healthy control subjects (Gottesman and Gould 2003). Similarly, Cho et al. reported that during the performance of an executive control task containing a working memory component, schizophrenia patients failed to show an increase in gamma activity as cognitive control demands increased, and this deficit was associated with impaired performance of the task (Cho et al 2006).

It is well-established that many of the neurocognitive processes that may be supported by gamma, as described above, are deficient not only in subjects with schizophrenia, but also in their first-degree relatives and in patients with schizophrenia spectrum disorders, such as schizotypal personality disorder (Faraone et al 1999; Gur et al 2007; Seidman et al 2006; Voglmaier et al 1997). Interestingly, gamma band deficits may also occur in first-degree relatives of patients with schizophrenia (Hong et al 2004a). Furthermore, such deficits appear to already exist in first-episode schizophrenia patients (Gallinat et al 2004; Spencer et al 2008; Symond et al 2005). Together these observations raise an interesting possibility that gamma band abnormalities may represent a neurobiologic endophenotype (Gottesman and Gould 2003) and may predate the onset of illness. In this regard, it would be important in future studies to understand whether gamma deficits may occur in individuals at risk for schizophrenia, such as those who are in the prodromal phase of the illness, subjects with schizotypal personality disorder, or children of parents who have schizophrenia, and to possibly link gamma deficits to candidate genes of the illness.

Perhaps one of the most important questions that need to be addressed is whether gamma oscillation disturbances may exhibit any clinical correlates. Indeed, gamma abnormalities have been found to be associated with various symptom domains of schizophrenia, such as hallucinations, thought disorder, disorganization, and psychomotor poverty (Gallinat et al 2004; Lee et al 2003a; Lee et al 2003b; Spencer et al 2004). For example, Spencer et al have shown that in patients with schizophrenia, the strength of the phase locking of visual perception-related oscillation was positively correlated with some of the positive symptoms such as thought disorder, conceptual disorganization and visual hallucinations (Spencer et al 2004). In the domain of motor control, Ford et al. (Ford et al 2007) found that the degree of phase locking of an oscillatory correlate of a corollary discharge mechanism was reduced in schizophrenia patients, and this reduction was related to avolition/apathy symptoms. Also, Gallinat and colleagues have found that there is a positive correlation between the degree of reduction in late gamma in an auditory oddball task and both the positive symptom scale of the PANSS (Positive and Negative Symptom Scale) and the duration of illness (Gallinat et al 2004). Finally, the reduction in gamma power and synchrony deficits have also been shown to be positively correlated with the negative symptomatology of schizophrenia (Lee et al 2003b). In spite of these potentially informative observations, more studies are needed

before any conclusions can be drawn about how different kinds of gamma disturbances may be related to the assortment of clinical symptoms of schizophrenia.

Despite the recent excitement surrounding the possible link between the pathophysiology of schizophrenia and gamma band deficits, a number of caveats need to be carefully considered and many questions remain unanswered. First, the strength of the explanatory power of the concept of gamma activity in mediating a variety of brain functions may also represent a major weakness of this concept. For instance, the symptoms and deficits of many neuropsychiatric disorders have all been associated with gamma band abnormalities, such as Alzheimer's disease (Ribary et al 1991), autism (Welsh et al 2005; Wilson et al 2007b), Tourette's syndrome (Kalanithi et al 2005; Leckman et al 2006), bipolar disorder (Bhattacharya 2001; O'Donnell et al 2004), attention deficit and hyperactivity disorder (Yordanova et al 2001), or even traumatic brain injury (Slewa-Younan et al 2002). We certainly do not expect that all of these diseases and conditions share identical pathophysiologic mechanisms; thus, gamma band abnormalities may simply be a very sensitive readout or an epiphenomenon of pertubation of cerebral cortical network functions and lack diagnostic specificity. Nevertheless, in this case, gamma band disturbances may still be useful as a clinical outcome measure or as an index of treatment response (Lewis and Moghaddam 2006).

Second, the correlations between gamma abnormalities and behavioral deficits, such as symptoms and cognitive dysfunction, in patients on the whole have not been strong. If gamma synchrony is an essential mechanism for information processing, then it would be expected that gamma abnormalities and behavioral deficits would be linked. However, the evidence for such links may be relatively sparse at this point because many studies do not have a behavioral component (e.g., the ASSR studies), or because tasks were not designed to be sensitive to such relationships (e.g., gamma oscillations elicited in oddball tasks may reflect a variety of processes unrelated to simple target detection). We note that studies in which gamma oscillations do appear to reflect essential mechanisms for task performance in healthy individuals have reported associations between gamma abnormalities and behavioral deficits and/or symptoms in schizophrenia patients (e.g. (Cho et al 2006; Ford et al 2007; Spencer et al 2004)).

Third, the potential effects of antipsychotics on gamma band oscillations are not well understood. The limited data available so far seem to suggest that haloperidol may suppress auditory evoked gamma band activity (Ahveninen et al 2000), raising an important question as to whether previous findings of gamma band deficits in patients with schizophrenia may, at least in part, reflect antipsychotic effects. However, there have also been data suggesting that atypical agents, such as clozapine and olanzapine, may have the opposite effects (Hong et al 2004a; Sperling et al 1999). In addition, abnormal gamma activity has also been observed in unmedicated schizophrenia patients (Gallinat et al 2004), lending support to the notion that gamma abnormality may in fact be intrinsic to the disease process of the illness.

Finally, neurons or neuronal assemblies also oscillate in a variety of other frequency bands (Buzsaki 2006) and the possible pathophysiologic relationship between these oscillation patterns and schizophrenia is largely unexplored. For example, in addition to gamma band disturbances, there is evidence suggesting that synchronized oscillations in the beta frequency band (13–30 Hz), which are thought to link together spatially distributed information across distant regions of the cerebral cortex (Kopell et al 2000), may also be deficient in patients with schizophrenia (Hong et al 2004b; Uhlhaas et al 2006; Yeragani et al 2006). Evidence of oscillation abnormalities in lower frequencies has also been reported, such as the theta band (4–7 Hz) (Koenig et al 2001; Schmiedt et al 2005), and the alpha band (8–13 Hz) (Jin et al 1997).

Disturbances of Parvalbumin-Containing Inhibitory Neurons and Gamma Band Deficits in Schizophrenia

Notwithstanding the caveats raised above, perhaps one of the strongest pieces of evidence in support of the idea of gamma band disturbances playing a role in the pathophysiology of schizophrenia is the increasing understanding that inhibitory interneurons in the cerebral cortex seem to be functionally disturbed in this disorder (Benes and Berretta 2001; Costa et al 2004; Lewis et al 2005), as gamma oscillations are known to emerge from the intricate interplay between inhibitory interneurons and the pyramidal cells they target (e.g. (Whittington et al 2000)). Pyramidal cells drive oscillations among inhibitory interneurons, which in turn phasically modulate the firing rates of pyramidal cells, leading to a synchronized gamma-band oscillation in the whole network. The frequency of the oscillation is determined in part by the decay time constant of inhibitory synaptic conductances via the GABA (γ-aminobutyric acid)$_A$ receptor (Brunel and Wang 2001). It should be noted, however, that our current understanding of the neurobiologic mechanisms that mediate gamma oscillations derives virtually exclusively from in vitro experiments using brain slices or in vivo studies in animals. In these studies, gamma oscillations and synchrony are measured based on recordings from individual neurons or small groups of neurons. In humans, on the other hand, gamma oscillations, as measured by EEG, reflect the coordinated activities of neural assemblies that consist of very large numbers of neurons. Therefore, it is unclear whether or if so how mechanisms that support gamma at the level of single neurons as discovered in animals may be applicable to understanding the mechanisms that underlie gamma oscillations within and between very large groups of neurons in humans. Nevertheless, it does appear that the subset of inhibitory neurons that have been found to play a crucial role in sustaining gamma in animals have in fact been found to be altered in postmortem brains from subjects with schizophrenia.

Disturbances of PV-Containing Neurons in Schizophrenia

Multiple lines of evidence strongly suggest that inhibitory interneurons in the cerebral cortex are disturbed in schizophrenia (Benes 2000; Benes and Berretta 2001; Costa et al 2001; Keverne 1999; Lewis et al 2005). For example, the concentrations of GABA and the GABA transporter GAT-1 have been demonstrated to be reduced in the prefrontal cortex (PFC) (Ohnuma et al 1999). In addition, the density of neurons that express the mRNA for GAT-1 and those that express the mRNA for the 67kD isoform of the GABA synthesizing enzyme, glutamic acid decarboxylase (GAD$_{67}$), have also been found to be decreased in the cerebral cortex in schizophrenia (Akbarian et al 1995; Guidotti et al 2000; Hashimoto et al 2003; Volk et al 2001; Volk et al 2000; Woo et al 2004). In fact, the latter observation is the single most replicated finding in schizophrenia postmortem studies (Akbarian and Huang 2006). Because the amount of expression of GAT-1 or GAD$_{67}$ mRNA in individual neurons seems to be unaltered and cell loss is not believed to be occurring, at least not in large scale, in the PFC (Selemon and Goldman-Rakic 1999), it appears that the expression of these transcripts in a subset of GABA cells is decreased to a level that is experimentally undetectable. In what may be a compensatory mechanism, postsynaptic GABA$_A$ receptor binding has been found to be increased (Benes et al 1996; Benes et al 1992; Newell et al 2006). However, more recent data suggest that, at least at the transcript level, specific subunits of GABA$_A$ receptor may be differentially regulated, e.g. the alpha 1 subunit mRNA has been found to be down-regulated (Hashimoto et al 2007; Kim et al 2005) (but see (Ohnuma et al 1999)) whereas the alpha 2 transcript may be up-regulated (Kim et al 2005; Volk et al 2002).

GABA neurons are morphologically, connectionally, chemically, molecularly and biophysically heterogeneous (Gabbott and Bacon 1996; Kawaguchi and Kondo 2002; Kawaguchi and Kubota 1997; Markram et al 2004; Soltesz 2005; Wang et al 2004; Wang et

al 2002). Among them, the fast-spiking cells that contain the calcium-binding protein parvalbumin (PV) appear to play a particularly critical role in the generation of synchronized gamma activity (Bartos et al 2007; Cunningham et al 2006; Hajos et al 2004; Klausberger et al 2003; Soltesz and Deschenes 1993). Accumulating evidence suggests that the PV-containing neurons are among the GABA cells that are disturbed in schizophrenia (Lewis et al 2005), thus providing a basis for the pathophysiology of gamma band oscillation abnormalities.

PV-containing neurons consist of two subpopulations of cells, chandelier cells, which synapse onto the axon initial segment of pyramidal neurons (Howard et al 2005), and basket cells, which provide perisomatic inhibitory inputs to pyramidal cells (Freund 2003; Somogyi et al 1983). Lewis and colleagues have shown that the number of cells containing PV mRNA that express a detectable level of GAD_{67} mRNA is decreased by as much as 45% in the PFC in schizophrenia (Hashimoto et al 2003). Furthermore, in the same study, it was found that the expression of PV mRNA in individual neurons was significantly reduced whereas the expression of the mRNA for calretinin, a calcium-binding protein that is localized to a non-overlapping population of GABA cells, was unaffected (Hashimoto et al 2003). Moreover, the density of the axon terminals of chandelier neurons, which can be immunohistochemically visualized with an antibody against GAT-1 (DeFelipe and Gonzalez-Albo 1998; Inda et al 2006), has been found to be decreased by as much as 40% (Pierri et al 1999; Woo et al 1998). Consistent with this finding, $GABA_A$ receptor subunit α2-immunoreactive profiles, which represent the postsynaptic sites of chandelier terminals, and the expression of mRNA for this subunit in pyramidal cells appear to be upregulated in schizophrenia (Kim et al 2005; Volk et al 2002). Together with chandelier cells, the fast-spiking PV-containing basket cells are also crucial in mediating cortical oscillatory dynamics (Csicsvari et al 2003; Freund 2003; Klausberger et al 2003; Mann et al 2005; Tamas et al 2000). However, unlike that of chandelier neurons, axon terminals of basket cells cannot be reliably identified with light microscopy. Therefore, there is currently no definitive evidence directly implicating the involvement of basket cell terminals in the pathophysiology of schizophrenia. However, because basket cells represent the majority, perhaps as many as 80–90%, of all PV-containing neurons in the cortex (Kawaguchi 1995; Krimer et al 2005; Markram et al 2004; Zaitsev et al 2004), it seems almost certain that at least a subset of basket cells must also be involved in order to account of the magnitude of change observed by Hashimoto et al (Hashimoto et al 2003).

Altered Glutamatergic Modulation and Disturbances of PV-Containing GABA Neurons

It has long been known that treatment with N-methyl-D-aspartate (NMDA) receptor antagonists produces a syndrome that is highly reminiscent of the clinical picture of schizophrenia, including positive symptoms, negative symptoms and cognitive deficits (Javitt and Zukin 1991; Krystal et al 1994; Newcomer and Krystal 2001), and these data lead to the NMDA receptor hypofunction model of the disorder (Olney and Farber 1995; Olney et al 1999). The paradoxical excitotoxic effects observed by Olney and Farber with NMDA antagonists were explained, at least in part, by blockade of the NMDA receptors that are located on GABA neurons, which have been shown to be some 10-fold more sensitive to NMDA receptor antagonists than the NMDA receptor on pyramidal neurons (Greene et al 2000; Grunze et al 1996; Olney and Farber 1995). Interestingly, it has recently been demonstrated that, in both the anterior cingulate (Woo et al 2004) and prefrontal (Woo et al 2008) cortices, the density of GABA cells, identified with GAD_{67} labeling, that express the NMDA NR2A subunit is significantly decreased in schizophrenia. These findings are also consistent with the observation that the expression of the mRNA for the vesicular glutamate transporter vGluT1, which is a marker for cortically originated glutamatergic terminals (Fujiyama et al 2001; Kaneko and Fujiyama 2002), appears to be reduced in the PFC in

schizophrenia (Eastwood and Harrison 2005). Furthermore, in primary neuronal cultures, Kinney and colleagues have recently found that the amount of NR2A in PV-containing GABA cells seem to be 5-fold greater than that in pyramidal cells at both the transcript and protein levels (Kinney et al 2006). In addition, NR2A, but not NR2B selective antagonist appears to down-regulate GAD_{67} mRNA and PV expression in PV-containing GABA cells (Kinney et al 2006). Similar reductions of PV expression by NMDA antagonism have been reported in vivo in the prefrontal cortex (Braun et al 2007; Cochran et al 2003; Reynolds et al 2004) and hippocampus (Abdul-Monim et al 2007; Braun et al 2007; Keilhoff et al 2004; Rujescu et al 2006). Also, in a recent study, repeated administration of phencyclidine, an NMDA antagonist, has been shown to reduce the number of PV-expressing axo-axonic cartridges, which presumably represent the axon terminals formed by chandelier cells, in monkeys (Morrow et al 2007). Finally, in line with the idea that PV-containing neurons play an important role in gamma oscillations, NMDA receptor blockade has been found to robustly disrupt gamma rhythms in the entorhinal cortex (Cunningham et al 2006) and it is speculated that this disruption may be mediated by the NMDA receptor on the PV-containing neurons (Cunningham et al 2006). Taken together, reduced glutamatergic inputs onto PV-containing neurons via NMDA receptors, perhaps especially those that contain the NR2A subunit, may mediate, at least in part, the down-regulation of GAD_{67} and PV and the disruption of gamma band synchrony in schizophrenia. In fact, using double in situ hybridization, we have recently found that the density of PV-containing neurons that express NR2A mRNA seems to be decreased by as much as 50% in subjects with schizophrenia (Bitanihirwe et al 2007). As a result of reduced excitatory drive to PV-containing neurons, cells that are downstream to these neurons may become disinhibited and thus may be rendered more susceptible to excitotoxic or oxidative insults (Lisman et al 2008; Olney and Farber 1995). Short of leading to cell death, cellular injury may be manifested in the form of neuritic and synaptic atrophy (Bernstein and Lichtman 1999; Garden et al 2002; Gilman and Mattson 2002; Glantz et al 2006; Jarskog et al 2005; Mattson et al 1998).

PV Neuronal Disturbances, Gamma Band Synchrony Deficits and the Onset and Progression of Schizophrenia

Synaptic Connectivity Deficits of Schizophrenia

In the past few years, there has been increasing appreciation that deficits in glutamatergic synaptic connectivity may represent a core pathophysiologic feature of schizophrenia (Garey et al 1998; Glantz and Lewis 2000; Kalus et al 2000; McGlashan and Hoffman 2000; Mirnics et al 2001). Of interest, using unbiased counting methods, Selemon and Goldman-Rakic (Selemon and Goldman-Rakic 1999) found that in the PFC it was the volume of neuropil, which contains dendritic and axonal processes and synapses, among other elements, but not cell number that was decreased in schizophrenia. Furthermore, this hypothesis is also consistent with numerous imaging studies demonstrating reduced gray matter volume in patients with this illness (see review in (Shenton et al 2001)), although the possible effects of antipsychotic medications on brain volume remain unclear (Dorph-Petersen et al 2005; Lieberman et al 2005).

One of the strongest pieces of evidence for synaptic deficits in schizophrenia is the observations of reduced expression of synaptic vesicle proteins such as synaptophysin (Eastwood et al 1995; Glantz and Lewis 1997), SNAP-25 (Halim et al 2003; Honer et al 2002), Rab3 (Davidsson et al 1999), complexin (Sawada et al 2002), and VAMP (Halim et al 2003) in the cerebral cortex; the reduction in the expression of some of these proteins may reflect post-translational changes, because in situ hybridization studies have revealed that the mRNA transcripts for these proteins are not affected (Eastwood et al 2000; Glantz et al 2000; Karson et al 1999). In addition, microarray studies have shown that, in the PFC, the

expression of many genes encoding proteins that regulate synaptic structure and function are also down-regulated (Hakak et al 2001; Lehrmann et al 2003; Mirnics et al 2000; Pongrac et al 2002; Vawter et al 2001).

In the PFC, the density of spines on the proximal dendrites of layer 3 pyramidal cells, which furnish both feedforward and feedback (recurrent) glutamatergic projections (Pucak et al 1996), both locally and between spatially dispersed cortical regions, is decreased by about 20–50% (Garey et al 1998; Glantz and Lewis 2000). It is also noteworthy that Sweet et al. (Sweet et al 2003) found that pyramidal cell somal area was reduced in layer 3b in Brodmann's area 42 (auditory association cortex), and noted that this was most compatible with loss of dendritic volume, as that laboratory and others had found in the PFC (Black et al 2004; Kalus et al 2000; Pierri et al 2001). These findings also suggest that, in schizophrenia, both the local cortical excitatory circuitry and the long-range corticocortical connections are disturbed, providing the possible neuroanatomical basis for gamma band synchrony deficits.

Gamma Band Synchrony Deficits May Mediate the Onset and Progression of Schizophrenia by Disturbing Peri-Adolescent Synaptic Pruning

One conundrum in schizophrenia research has been whether the illness represents a purely neurodevelopmental disorder in the sense that deficits that are associated with the pathophysiology of the illness occur early in development or whether there is also a peri-onset process of progression that is neurobiologically distinct (Keshavan 1999; Lewis and Levitt 2002; Lieberman 1999; Weinberger 1987). We think this is an unnecessary dichotomy, that many of the processes that are important in development, such as synaptic and dendritic remodeling and pruning, are also important in the peri-onset changes.

The fast-spiking basket and chandelier cells that contain PV, which exert perisomatic and axo-axonic inhibition (and possibly excitation under some circumstances (Szabadics et al 2006)), respectively, on pyramidal neurons, are known to play a critical role in regulating synchronous neuronal discharges in multiple frequency bands (e.g. theta, gamma, ripple, etc) via both chemical and electrical synapses (Buzsaki et al 2004; Freund 2003; Klausberger et al 2003; Tamas et al 2000; Whittington and Traub 2003). The biophysical characteristics of these neurons that lead to their ability to synchronize neuronal outputs are beyond the scope of this review but have been discussed elsewhere (Buzsaki 2006; Buzsaki and Draguhn 2004; Pike et al 2000; Steriade et al 1998; Traub et al 1998; Whittington and Traub 2003). Here, it is postulated that PV neuronal disturbances may contribute to the onset and progression of schizophrenia via at least two mechanisms: (1) perturbing gamma oscillations and hence activity-dependent synaptic and dendritic remodeling and/or (2) promoting synaptic and dendritic atrophy via an excitotoxic mechanism.

PV-containing basket and chandelier neurons in the cerebral cortex are generated from the same progenitors in the medial ganglionic eminence during development (Wonders and Anderson 2006; Xu et al 2004). These neurons begin to express PV during embryonic stage, but subsequently PV expression dramatically declines until the postnatal period when its expression gradually increases and then stabilizes (Alcantara and Ferrer 1994; de Lecea et al 1995; Gao et al 2000; Patz et al 2004). The postnatal maturation of PV expression in the sensory cortices appears to temporally coincide with the period of experience-dependent refinement of neural circuits (Alcantara and Ferrer 1994; de Lecea et al 1995; Gao et al 2000; Patz et al 2004). The neurobiologic mechanisms that regulate the onset and termination of the synaptic refinement process are just beginning to be unraveled; it appears that the maturation of GABA neural circuits, particularly that of PV neurons, may play a crucial role (Hensch 2005; Jiang et al 2005). For example, Tropea et al have found that dark rearing, which is known to prolong the duration of critical period and the maturation of the

visual cortex, is associated with a significant down-regulation of the transcript for PV (Tropea et al 2006). Interestingly, it has been found that the effects of dark rearing can be rescued by overexpression of the neurotrophin brain-derived neurotrophic factor (BDNF) (Gianfranceschi et al 2003). Furthermore, in transgenic mice in which the BDNF is developmentally over-expressed, the maturation of PV neuronal circuits in the visual cortex is accelerated and, at the same time, the critical period for developmental synaptic plasticity is also precociously terminated (Hanover et al 1999; Huang et al 1999). The fact that PV-containing neurons appear to highly express trkB (Cellerino et al 1996; Gorba and Wahle 1999), the high affinity receptor tyrosine kinase for BDNF, is also consistent with the idea that BDNF/trkB signaling may be particularly important in mediating the maturation of these neurons and hence determining the time course of developmental synaptic plasticity.

The functional maturation of the PFC is quite protracted; the underlying process of refinement of glutamatergic synapses is not completed until late adolescence and early adulthood (Bourgeois et al 1994; Huttenlocher 1979; Woo et al 1997), which coincides with the period of time when schizophrenia symptomatology typically begins to emerge. Interestingly, it is also during this period of development when PV neuronal circuits appear to gradually achieve maturation, as reflected in their attaining the adult pattern of PV protein expression (Anderson et al 1995; Erickson and Lewis 2002). At the same time, as these neurons apparently are becoming functionally mature, gamma power also progressively increases (Poulsen et al 2007; Rojas et al 2006). Furthermore, available evidence indicates that BDNF and trkB also achieves the adult patterns of expression during the peri-adolescent period (Hayashi et al 2000; Ohira et al 1999; Webster et al 2002). Taken together, these observations raise a tantalizing possibility that in schizophrenia disturbed BDNF/trkB signaling during the peri-adolescent period may, at least in part, lead to disturbances in the maturation of PV-containing neurons. Consistent with this idea, postmortem studies have in fact shown that the expression of BDNF and trkB mRNAs in the PFC is decreased in schizophrenia (Hashimoto et al 2004; Weickert et al 2003). Finally, most, but not all (Shimizu et al 2003) studies have found that serum BDNF level appears to be reduced in patients with schizophrenia (Grillo et al 2007; Pirildar et al 2004; Tan et al 2005; Toyooka et al 2002), including first-episode patients (Buckley et al 2007).

Synaptic refinement is an activity-dependent process that is governed by the Hebbian principle of coincidence detection (Hebb 1949; Katz and Shatz 1996). In the simplest term, when the pre-and post-synaptic elements of a synapse are coincidentally (within a narrow time window) active, the synapse is strengthened; otherwise, the synapse is either not strengthened, weakened or eliminated. Interestingly, the duration of the time window that is required for activity-dependent strengthening of synapses via coincidence detection closely matches the time scale of gamma oscillations (Bi and Poo 1998; Buzsaki and Draguhn 2004; Engel et al 1992; Harris 2005; Harris et al 2003; Konig et al 1996; Magee and Johnston 1997) and some evidence actually points to a direct relationship (Wespatat et al 2004). In other words, gamma oscillations may provide a temporal structure for activity-dependent synaptic refinement to take place. Thus, functional disturbances of PV neurons, perhaps mediated by disturbances of BDNF/trkB signaling, may lead to aberrant pruning of synapses (Feinberg 1982; Keshavan et al 1994; McGlashan and Hoffman 2000) by disturbing gamma oscillations. Furthermore, BDNF/trkB signaling appears to play an important role in regulating the expression of NMDA receptor, perhaps especially the NR2A subunit (Caldeira et al 2007; Glazner and Mattson 2000; Margottil and Domenici 2003; Small et al 1998). Hence, disturbed BDNF/trkB signaling could potentially also explain the finding of reduced NR2A expression in PV-containing neurons (Bitanihirwe et al 2007). Reduced glutamatergic activity on PV neurons may inflict excitotoxic damage to pyramidal cells via disinhibition, which may then lead to additional loss of dendrites and synapses (Bernstein and Lichtman 1999; Garden et al 2002; Gilman and Mattson 2002; Glantz et al 2006;

Jarskog et al 2005; Mattson et al 1998). This idea appears to be supported by the results of a recent study in which Moghaddam and colleagues found that NMDA receptor blockade reduced inhibition furnished by GABA neurons but increased, at a delayed rate, the firing of pyramidal cells (Homayoun and Moghaddam 2007). Together, these mechanisms may play a role in triggering disease onset and leading to progressive functional deterioration during the early phase of the illness. The observations of progressive reduction in gray matter volume in both clinically high risk individuals (Job et al 2005; Job et al 2006; Pantelis et al 2003) and during the early post-onset course of the illness (Cahn et al 2002; DeLisi et al 1997; Ho et al 2003; Lieberman et al 2005; Salisbury et al 2007) are consistent with this idea. So far, the bulk of the evidence for gamma deficits in schizophrenia has come from studies in patients who are in the chronic phase of the illness. In future studies, it will be important to map the course of emergence and progression of gamma abnormalities in prodromal and first-episode schizophrenia patients to see if it correlates with the clinical course of disease onset and progression to chronicity and MRI gray matter measures. In addition, the pathophysiologic model proposed here can be tested in animals by experimentally perturbing the BDNF/trkB signaling cascade during adolescence to see if the neurobiologic and clinical phenotypes of schizophrenia, such as PV neuronal disturbances, glutamatergic synaptic deficits and gamma impairment can be reproduced in the experimental conditions.

Implications for Treatment, Early Intervention and Prevention

In recent years, there has been increasing momentum towards realizing the concept of early intervention and ultimately perhaps even prevention of the onset of schizophrenia. Despite the excitement and hope that have been generated, at present, it is unclear what specific early intervention and prevention strategies may be effective. The interesting convergence of recent preclinical and clinical findings implicates gamma oscillatory synchrony deficits mediated by disturbances of the PV-containing class of GABA cells as a key feature in the pathophysiology of schizophrenia. It is postulated that abnormal gamma synchrony may disturb the peri-adolescent synaptic and dendritic remodeling process, which may play a role in triggering the onset and functional deterioration of schizophrenia. An important goal in future studies would be to further define the cellular and molecular mechanisms that mediate gamma band synchrony (via animal studies) and how these mechanisms may be disturbed in schizophrenia (via postmortem human brain research), and then to translate this understanding into meaningful intervention strategies. As the tradition of the development of schizophrenia therapeutics has been one of serendipity, it is exciting that we can now begin to think about rational strategies that aim at correcting a possible pathophysiologic pathway that may mediate the onset of schizophrenia.

The idea that drugs or compounds that modulate glutamate neurotransmission via the NMDA receptor may be effective in the treatment of schizophrenia is based on strong theoretical rationale and has been advocated by many investigators (e.g. (Goff and Coyle 2001; Goff et al 2001; Javitt 2004; Krystal et al 2003; Moghaddam 2004; Tsai et al 2004)). However, direct stimulation of NMDA receptors may carry serious risks such as seizures or stroke. Thus, drugs that indirectly enhance NMDA neurotransmission, such as the metabotropic glutamate receptor agonists (Lewis and Moghaddam 2006; Moghaddam 2004), have been a focus of interest. In fact, the preliminary results of a phase II clinical trial testing the possible efficacy of a novel class II metabotropic receptor mGlu2/3 agonist appear to be very encouraging (Patil et al 2007). The data reviewed in this article extend the concept of glutamatergic enhancement to suggest that selective strengthening of the glutamatergic inputs to the NMDA receptors on PV-containing neurons may be particularly important. In fact, metabotropic glutamate receptors, such as the class I subunits mGluR1 and mGluR5, are expressed by PV-containing GABA neurons (Muly et al 2003), although

the expression of mGluR2/3, to our knowledge, has not been studied. Furthermore, stimulation of mGluR5 subunit powerfully elicits long-term potentiation at glutamatergic synapses on PV-containing neurons (Tennigkeit et al 2006). In addition, activation of mGluR1 and 5 receptors induces gamma and theta oscillations (Gillies et al 2002; Martin 2001; Whittington et al 1995). However, because mGluR1 and mGluR5 receptors are not selectively expressed on PV-containing GABA neurons, but are also localized to other neuronal types, including pyramidal cells (Muly et al 2003), it is potentially difficult to predict the functional outcomes of enhancement of these receptors. Given the reported efficacy of the mGluR2/3 agonist, it would be interesting to find out if this subunit may be selectively, or at least preferentially localized to PV-containing neurons. Before we can develop strategies that can enhance NMDA transmission on PV-containing neurons, it will be necessary to better define the pharmacologic and/or downstream signaling mechanisms that are specific for PV-containing neurons. However, it should be mentioned that in addition to the gamma rhythm, other rhythms, such as the higher beta band, are also known to be disrupted in schizophrenia. In contrast to gamma oscillation, the generation of beta band rhythm does not appear to require GABA inhibition but can be partly replicated by acute NMDA receptor blockade. Hence, dysfunction of NMDA receptors on neural elements other than PV-containing neurons must also contribute to disrupted brain dynamics in schizophrenia (Roopun et al 2008).

In a recently published proof-of-principle study, Lewis and colleagues observed that working memory deficits in schizophrenia patients appeared to respond to treatment with a partial agonist of the $GABA_A$ alpha 2 subunit, which is preferentially localized to synapses formed by chandelier neurons (Lewis et al 2008). In addition, they found that such treatment resulted in improvement in gamma band power in the PFC in these patients. It would be interesting to see if this compound might be efficacious in correcting or reversing the hypothesized deficits that occur during the peri-onset phase of schizophrenia.

So far, we have emphasized the role of PV-containing cells in the generation of gamma oscillations. However, in addition to these neurons, another class of basket cells that do not contain PV but contain the neuropeptide cholecystokinin (CCK) appears to play a crucial role not necessarily in the generation but in the fine-tuning of network oscillatory activities (Freund 2003; Freund and Katona 2007). In fact, gene expression studies have revealed that the expression of the mRNA for CCK may be decreased in the frontal (Hashimoto et al 2007; Virgo et al 1995) and temporal (Virgo et al 1995) cortices in subjects with schizophrenia. An interesting aspect of these cells is that their axon terminals selectively express the cannabinoid CB1 receptor (Katona et al 2001; Katona et al 1999). Thus, these presynaptic CB1 receptors may be a critical element in the modulation of gamma oscillation by controlling the release of GABA by CCK-containing cells (Beinfeld and Connolly 2001; Hajos et al 2000). In addition, the relative selectivity in the localization of the CB1 receptor, as has already been noted by other investigators (Lewis and Gonzalez-Burgos 2007), may further increase its attractiveness as a potential drug target in any attempt to modulate gamma band oscillation. In addition, the possible role of cannabis in contributing to the development of schizophrenia in vulnerable individuals (Broome et al 2005; Moore et al 2007; Semple et al 2005) might well be mediated by its effects on cortical oscillatory synchrony (Hajos et al 2007; Hajos et al 2000; Skosnik et al 2006). Finally, CCK-containing basket cells also appear to preferentially express the nicotinic α7 receptor subunit (Frazier et al 1998; Freedman et al 1993), raising the interesting possibility that the potential cognitive enhancing effects of nicotinic α7 receptor agonists (Martin et al 2004; Olincy et al 2006) may be mediated, at least in part, by modulating gamma band oscillations via regulating the activities of CCK-containing basket cells. In light of this, it has recently been demonstrated that nicotine seems to enhance gamma-band power in the context of auditory sensory gating (Crawford et al 2002). Together these findings may also provide a physiological basis for

the exceedingly high prevalence of cigarette smoking in patients with schizophrenia (Brown et al 1999; Dalack and Meador-Woodruff 1996).

In summary, there has been compelling evidence linking PV neuronal dysfunction to the pathophysiology of gamma deficits in schizophrenia. Furthermore, disturbances in the functional maturation of PV neurons during the peri-adolescent period may lead to gamma deficits and hence aberrant synaptic pruning, triggering the onset of schizophrenia. Thus, in future studies, it would be important to characterize the genetic and molecular cascades that mediate the functional disturbances of PV-containing neurons, as such knowledge will inspire the conceptualization and development of rational, neurobiology-based treatment, early intervention and prevention strategies.

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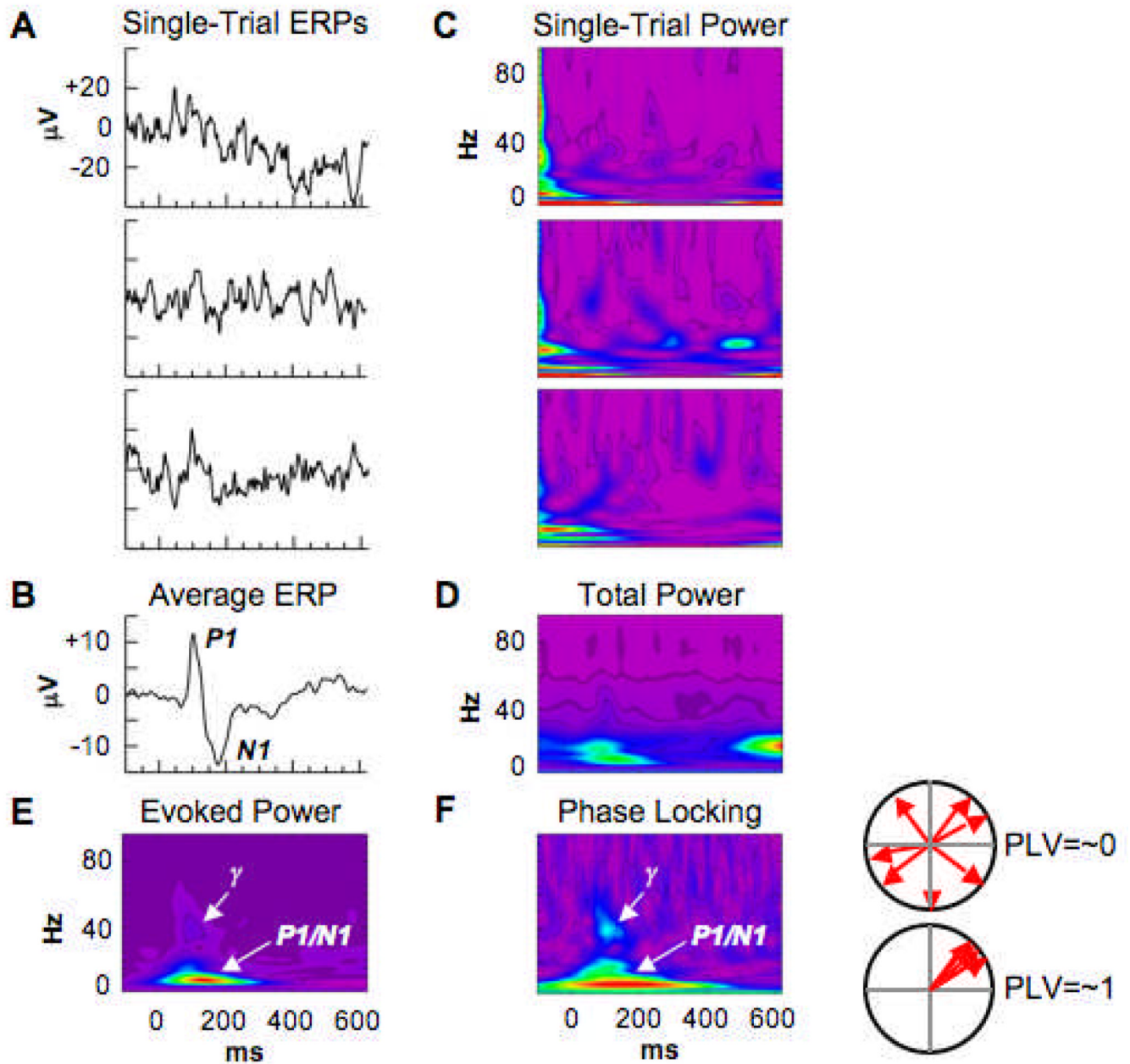
Fig. 1.
Types of time/frequency domain measures derived from single-trial epochs of EEG. The data were recorded at a parieto-occipital electrode (PO6) from a healthy subject performing a visual discrimination task (44). Stimulus onset is at 0 ms. **A)** Raw single trial ERPs. **B)** The average ERP is computed by averaging together the single trials (N=90 here). The P1 N1 components are clearly visible. **C)** Time frequency maps of spectral power for the corresponding single trials. Time-frequency decomposition was performed using the M orlet wavelet transform. **D)** Average of the single trial time-frequency power maps. This measure of "total power" represents both "background" (induced, or non-stimulus-locked) and stimulus-locked oscillations. **E)** Evoked power is the power of stimulus-locked oscillations (i.e., the average ERP). The P1 N1 components occupy the low-frequency rang (<20 Hz). The early evoked visual gamma oscillation (g) is apparent in the time-frequency map. **F)**

phase-locked represents the phase variability across trials and is insensitive to oscillatory power. Low phase locking values (PLV) indicate high phase variability (top circle plot) and high PLV indicate low phase variability (bottom circle plot). (Figure adapted with permission form Javitt et al., 2008, Nat Rev Drug Discovery).