Neuropsychiatric Abnormalities: A New Vista From Studies on Fundamental Properties of Neural Communication

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Postmortem studies indicate that neural circuit abnormalities in schizophrenia could be reflected in gamma-band synchrony. We review findings of recent studies that demonstrate abnormal synchrony in the gamma band of the EEG in chronic schizophrenia patients, and point to links between gamma oscillations and some of the core symptoms of schizophrenia.

In recent years, a number of researchers have suggested schizophrenia be viewed as a disorder of brain connectivity (e.g., Andreasen, 2000; Crow, 1998; Friston and Frith, 1995; Selemon and Goldman-Rakic, 1999). This view is intuitively appealing, as schizophrenia was conceptualized by Bleuler (1950) as a "splitting of the psychic functions" in which aspects of thought and personality were disintegrated.

In this article, we will review recent research on neural circuit function in schizophrenia using γ-band (30 Hz to 100 Hz) oscillations in the electroencephalogram as a probe. It should be appreciated that the neural circuits discussed here are not the "macro" circuits or major fiber tracts, but rather they are the elementary neural circuits of a neuron projecting to other regions and its interaction with inhibitory neurons.

**Neural Synchrony in the Gamma Band**
The nature of neural coding has been the subject of intense research in neuroscience since the publication of Gray et al.'s (1989) classic paper. These researchers suggested that synchronous neuronal firing might serve as a mechanism whereby individual stimulus features could be bound together into coherent representations of complex objects. An important corollary finding was that neural synchrony was often accompanied by high-frequency oscillations in the γ band, often near 40 Hz (Eckhorn et al., 1988; Gray and Singer, 1989).

Since these initial reports, evidence for neural synchrony in the γ band has been found not just in perception but in diverse processes such as working memory (Pesaran et al., 2002), selective attention (Fries et al., 2001) and motor control (Schoffelen et al., 2005). Current views propose that neural synchrony is a general mechanism for dynamically linking together cells coding related pieces of information into assemblies (Singer, 1999).

Neural synchrony cannot be directly studied noninvasively, so it is inferred from particular patterns of neural activity measured in the scalp-recorded EEG. A growing number of studies have provided evidence of neural synchrony in humans (Tallon-Baudry and Bertrand, 1999; Varela et al., 2001). Evidence for γ-band neural synchrony has been reported in perception, attention and working memory tasks, among others.

**Neural Circuitry Abnormalities in Schizophrenia**
Research into the neural mechanisms of synchrony has demonstrated that inhibitory interneurons are critical elements in the synchronization of networks of neurons (Whittington and Traub, 2003). Pyramidal cells drive oscillations among inhibitory interneurons, which in turn modulate the firing rates of pyramidal cells, leading to a synchronized γ-band oscillation in the whole network.

A possible link between neural synchrony and schizophrenia has been suggested by postmortem studies of the brains of people with schizophrenia. These studies have found abnormalities in the morphology and distribution of certain types of neurons in schizophrenia, particularly inhibitory interneurons (Benes and Berretta, 2001; Lewis et al., 2005).

A number of neural circuitry models have postulated a deficit in recurrent inhibition, either from a loss of interneurons, a blockade of the excitatory input onto interneurons or an abnormality of modulation of interneurons. All of these models may produce abnormalities in γ oscillations. There is considerable evidence that excitatory neurotransmission via N-methyl-D-aspartate (NMDA) receptors is abnormal in schizophrenia (Tsai and Coyle, 2002), and one possibility is that schizophrenic abnormalities of the NMDA-mediated glutamate projections from pyramidal cells to inhibitory interneurons (Woo et al., 2004) can impair oscillations, as shown in vitro (Grunze et al., 2003).
A reduction in the excitatory input to inhibitory interneurons will reduce their recurrent inhibition of pyramidal cells, thus disrupting the generation of γ-band oscillations (Figure 1). Chandelier cells are a class of interneurons that may be especially relevant to γ-band synchrony. These cells provide inhibitory input to the axon initial segment of pyramidal cells, so they are in an excellent position to control the timing of pyramidal cell firing and, hence, neural synchrony. In individuals with schizophrenia, recent studies have found abnormalities in the connections that chandelier cells make onto pyramidal cells (Lewis et al., 2005). In sum, there is considerable evidence that γ-band EEG oscillations might be sensitive to neural circuit abnormalities in schizophrenia.

Abnormal Neural Synchrony and Perception

In our laboratory, we have examined γ oscillations in schizophrenia in auditory and visual stimulus paradigms. Kwon et al. (1999) studied the responses to auditory steady-state stimulation. Steady-state stimuli consist of repetitive trains of simple stimuli presented at a constant rate, and analysis of the EEG responses to these stimuli can provide information regarding the operation of the stimulated corticocortical circuits. Click trains were delivered to subjects at stimulation rates of 20 Hz, 30 Hz and 40 Hz.

In healthy control participants, 40 Hz (γ band) stimulation elicited the largest response compared with the other stimulation rates, as is typically found. In contrast, the responses of the patients with schizophrenia were reduced but only for 40 Hz stimulation (Kwon et al., 1999). This finding was the first demonstration of abnormal neural synchrony particular to the γ band in schizophrenia and was of particular interest given the prevalence of auditory processing abnormalities in this disorder. Since γ-band synchrony has been classically linked to perceptual feature binding, we investigated γ oscillations in schizophrenia using a task designed to invoke visual feature-binding mechanisms (Spencer et al., 2003). In this experiment, participants discriminated between squares formed by illusory contours (Illusory Square) and a control condition (No-Square).

As can be seen in Figure 2, the stimuli in each condition are physically identical, but the rotation of the "pac-men" determines whether or not observers perceive a coherent object. In healthy controls, the Illusory Squares but not the No-Squares elicited a γ oscillation phase locked to the stimuli at occipital electrodes (Figure 3). For patients with schizophrenia, however, neither stimulus elicited an oscillation, even though the stimuli were correctly identified.

In a follow-up study, we examined response-locked γ oscillations in the same paradigm (Spencer et al., 2004). We reasoned that the neural mechanisms underlying conscious perception might be more correlated with reaction time than stimulus onset, as found in single-unit recording studies. We found that in healthy controls, the Illusory Squares elicited a response-locked γ oscillation approximately 250 ms before reaction time (Figure 3), also at occipital electrodes. No such oscillation was elicited by the No-Square stimuli. Thus, the response-locked oscillation may be a correlate of visual feature-binding processes involved in conscious perception.

For the group with schizophrenia, a response-locked oscillation was also elicited by the Illusory Squares at occipital electrodes. However, the response-locked oscillation occurred in a lower frequency range for the group with schizophrenia (22 Hz to 24 Hz) than healthy controls (34 Hz to 40 Hz). This difference in synchronization frequency suggests that synchrony was necessary for the coherent object to be perceived, but the cell assemblies coding the object were unable to synchronize in the normal γ range for the patients with schizophrenia.

One possible cause of this effect is reduced cortical connectivity and/or conductivity delays, as evinced by diffusion tensor and magnetization transfer imaging (Kubicki et al., 2005). Selemon and Goldman-Rakic (1999) have suggested that reduced connectivity is an important neural substrate of schizophrenia, and a study modeling γ oscillations found that increased conduction delays lowered the synchronization frequency of a cell assembly (Kopell et al., 2000). Evidence for a close relationship between the response-locked oscillation and core cognitive and neural abnormalities in schizophrenia was found in strong correlations between positive symptoms (visual hallucinations, thought disorder and disorganization) and the degree of phase-locking in the response-locked oscillation. These data are consistent with studies that have found correlations between thought disorder and disorganization symptoms and psychophysical measures of visual perception (e.g., Silverstein et al., 2000; Uhlhaas et al., 2004).

Conclusions and Clinical Implications

There is increasing evidence that schizophrenia is a disorder that impairs the communication of information within the brain. Recent studies suggest that γ-band synchrony is sensitive to core neural circuit abnormalities and symptoms of schizophrenia. Gamma oscillations in the EEG may, therefore, be a promising tool for studying the neural substrates of schizophrenia and other...
Neuropsychiatric disorders.
It will be important for future studies to further establish these links by examining whether γ oscillations are sensitive to symptom states and antipsychotic drugs targeting various receptor systems.

As this area of research is still in its infancy, it is difficult to predict how findings of abnormal γ synchrony might influence the treatment of schizophrenia in the near future. In the long term, as neurorehabilitation methods become more advanced, it might be possible to restore neural circuits to their healthy states of function using brain stimulation, such as through transcranial magnetic stimulation (a noninvasive method). Perhaps even direct stimulation of particular brain areas through implanted electrodes will help improve neural circuit function, as in the treatment of Parkinson's disease with deep-brain stimulation.

Another avenue of treatment suggested by this research is cognitive rehabilitation (Silverstein and Wilkniss, 2004). If the integration of information in the brain is impaired in schizophrenia, cognitive rehabilitation strategies might emphasize treatments that enable patients to improve integrative processes that presumably rely on γ oscillations. For instance, patients can be taught to better attend to entire aspects of percepts and social interactions, rather than seizing on one part as giving all the information needed.

In addition to formal cognitive training, many therapists will recognize the utility of working with patients to assist the integration of all the information available and alternative interpretations. Whatever the results of this research, we expect that the scope of treatments available to the clinician will only grow as our understanding of the neural bases of mental disorders continues to advance.

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