Gamma oscillations and schizophrenia

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In the last 2 decades, it has become apparent that brain regions communicate by coordinating the firing of populations of neurons. When neurons synchronize their firing, their rhythmic input is reflected in the extracellular field potential as brain oscillations. Rhythmic brain activity in animals and humans can be recorded using noninvasive techniques such as electroencephalography (EEG) by placing recording electrodes on the surface of the scalp and, more rarely, intracranially at the surface of a brain region, such as the temporal lobe or hippocampus. Human EEG was developed as early as the 1920s by German psychiatrist Hans Berger and has been in constant use since then. However, in the last 25 years, advances in signal processing and methods for the analysis of EEG spectra have intensified interest in the use of quantitative EEG for research purposes. Additionally, more recently developed magnetoencephalographic (MEG) techniques have shown great potential for measuring weak magnetic fields generated by rhythmic currents in the brain. With these methods, rhythmic activity of various frequencies such as delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz) and gamma (30–200 Hz) can be detected. These neural oscillations are correlated with and are believed to play a role in normal cognitive processes including memory, attention, perceptual binding and consciousness.[1]

Investigating possible dysfunction in rhythmic activity in psychiatric and neurologic disorders has recently emerged as a potentially powerful approach to help determine what is wrong with neural circuits in these conditions. To date, the most intensively studied disorder in this respect is schizophrenia. However, evidence for disordered rhythms has also accumulated for other conditions including epilepsy, autism, attention-deficit hyperactivity disorder, Alzheimer disease and Parkinson disease.[2–5]

Although there are many possible mechanisms implicated in the pathophysiology of schizophrenia, an exciting proposal is that the symptoms of the disorder stem from a dysfunction in communication between different brain regions (i.e., the disconnectivity hypothesis). In the field of schizophrenia, the major focus of research into rhythmic brain activity has been specifically on gamma oscillations because of their potential role in information transfer between brain regions. What is the role of gamma oscillations in the normal brain? The idea that gamma oscillations may be important in combining information from different brain regions came initially from the classic work of Singer and colleagues who showed that gamma oscillations serve to synchronize intercolumnar input in the cat visual cortex.[6] It was proposed that neurons in different parts of the visual cortex fire at nearly the same time (i.e., in phase) during a cycle of gamma frequency oscillations to convey different attributes of the scenery and to help form a unified representation. Hence, gamma oscillations are thought to be key in the "binding" of cell assemblies to convey "oneness."

Exciting basic studies in experimental animals also point to the role of gamma oscillations in spatial and working memory. For example, it has recently been shown that in rats performing in a T-maze, hippocampal gamma oscillations are elicited particularly at the specific point when the animal needs to remember a given route selection. This probably serves to synchronize different hippocampal subregions to help phase spike firing and favour the exchange of information.[7] Recently, Colgin and colleagues[8] showed that information transfer between the entorhinal cortex, which conveys information about the position of the animal, and the CA1 area occurs at a fast-gamma frequency (65–145 Hz), whereas information from the CA3 to CA1 subfields, which is important in memory storage, occurred at a slower gamma frequency (25–50 Hz), suggesting that the sharing of different information between different brain regions occurs at distinct gamma frequencies.

In addition to the role of gamma oscillations in the sharing of information, studies in the prefrontal cortex suggest that gamma oscillations may also have a role in segmenting information during a working memory task. Working memory is a process in which one can keep several memory items in "mind" for a given amount of time. It is now established in humans that there is a very strong linear correlation between the power of gamma oscillations and working memory load in the prefrontal cortex. So why does the amplitude of gamma increase with larger memory load? A recent study

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performed in monkey prefrontal cortex suggests that this might be necessary for keeping memory items separate and in sequence by coding them on different phases of the gamma cycle.[9] The role of gamma oscillations in working memory is interesting in light of the fact that working memory is well known to be perturbed in schizophrenia. In a detailed analysis of working memory in early-onset schizophrenia, Haenschel and colleagues[10] showed that the power of gamma oscillations was reduced during encoding, maintenance and retrieval of working memory in patients with schizophrenia and that memory load in these patients saturated faster than in controls.

In addition to memory tasks, gamma oscillations elicited by other tasks or stimuli are also perturbed in patients with schizophrenia. In humans, EEG or MEG recordings of gamma oscillations can occur spontaneously or be elicited by a sensory stimulation such as an image or a sound such as a click. In chronic[11] and early-onset[12] schizophrenia, gamma oscillations evoked in the auditory cortex by trains of clicks are reduced in power (amplitude) compared with controls. Reductions in gamma power are also found in patients with schizophrenia following a visual stimulus that necessitates visual "binding" or perceptual organization.[13] In addition to a reduction in power, patients with schizophrenia show gamma oscillations of slower frequency in response to visual gestalt stimuli compared with controls.[14] A recently published study has also examined gamma synchrony in response to stimuli related to emotional perception in patients with first-episode schizophrenia. When presented with images of fearful or happy faces, patients with schizophrenia were found to exhibit reduced gamma synchrony in the right temporal and frontal regions compared with controls, and this reduction predicted poor performance on measures of social cognition.[15]

Overall, reductions in power or synchrony of evoked gamma oscillations have been reported in chronic,[11,14,16,17] first-episode[15,18,19] and early-onset[10,12] schizophrenia. These findings in patients may not be due to medication because reduced gamma-band activity has been found in unmedicated patients with schizophrenia[20] and in unmedicated first-degree relatives of people with schizophrenia.[21] However, it should be noted that the typical antipsychotic, haloperidol, reduced auditory-evoked gamma activity in healthy controls.[22] It is unclear at present if deficits in gamma activity actually cause deficits in cognitive function in schizophrenia, because the findings are correlational. However, using gamma activity as a biomarker for the progression of cognitive deficits or as an endophenotype in schizophrenia appears promising. The relation between reduced gamma activity and symptoms of schizophrenia is still under investigation. Although associations between aspects of reduced gamma activity and severity of specific symptoms in patients with chronic schizophrenia have been reported,[14,17] the specificity and reproducibility of these findings remain to be established. Notably, little association between symptom severity and observed reductions in gamma synchrony were found in a recent study with patients with first-episode schizophrenia.[15]

What can alterations in gamma oscillations tell us about the nature of changes occurring at the level of the neuronal network? Gamma oscillations are the product of the interplay between inhibitory γ-aminobutyric acid (GABA) interneurons and excitatory principal cells.[23,24] Hence, any changes in GABAergic function, glutamatergic input to interneurons and membrane properties will contribute to gamma oscillation dysfunction. There is evidence that GABAergic interneurons in the cortex and hippocampus are affected in schizophrenia.[25,26] In the prefrontal cortex of patients with schizophrenia, the GABA-synthesizing enzyme GAD67 and GABA transporter 1 have been reported to be reduced specifically in one subtype of interneuron containing the marker parvalbumin.[26] Parvalbumin-containing interneurons mediate rhythmic inhibition of pyramidal cells and are probably major players in the generation of gamma oscillations.[27,28] Interestingly, neuregulin-1, a protein whose gene is implicated in the etiology of schizophrenia, has recently been shown to markedly increase hippocampal gamma oscillation in rats and mice, and this may be mediated via high levels of neuregulin receptors (ErbB4) shown to be present on parvalbumin-containing GABAergic interneurons.[29] Hence, it appears likely that the disruption in gamma oscillations in schizophrenia in cortical regions is mediated in part by changes in GABA transmission. Modelling studies suggest that any changes in the kinetics of GABAergic responses will alter the power and frequency of gamma oscillations.[23] However, changes in GABAergic inhibition are likely not the only culprits because interneurons are embedded in extensive excitatory circuits that may also be affected in schizophrenia. Studies with animal models have shown that lowering glutamatergic input to interneurons can severely curtail the power of gamma oscillations.[27] Finally, in addition to changes in synaptic transmission, interneurons and principal cells are endowed with a myriad of ionic channels that provide these cells with the capacity to respond, or "resonate," appropriately at gamma frequency to sustain fast-frequency oscillations. Any changes to these ionic channels will greatly contribute to gamma oscillation perturbation.

If gamma oscillation perturbation is associated with cognitive impairment in schizophrenia, could "repairing" gamma oscillations reverse cognitive deficits? An exciting recent study has reported that increasing $GABA_A$ receptor function with a benzodiazepine derivative was able to increase frontal gamma power and reverse working memory deficits in patients with schizophrenia.[30] In addition to pharmacologic manipulation, other techniques to reverse impairment of gamma oscillations can be contemplated. For example, Barr and colleagues[31] have recently shown that repetitive transcranial magnetic stimulation (rTMS) over the dorsolateral prefrontal cortex increases gamma oscillations during a high-demand working memory task in healthy individuals, suggesting that rTMS may be useful as a cognitive enhancing strategy. Another potential approach still in the realm of animal experimentation might be the use of newly developed optogenetic techniques. Optogenetics involves the transfection into cells of ionic channels or pumps that can be activated by light. This allows for manipulation of neural activity within specific cell types in vivo in the millisecond time range. For example, using these techniques, Sohal and colleagues[28] showed that

activating parvalbumin interneurons in the neocortex of mice in vivo triggered gamma oscillations, while inhibiting these interneurons suppressed the oscillations. Optogenetic technology has already been suggested as a possible therapeutic approach in the future,[32] although it would probably be very difficult to implement for the treatment of human psychiatric disorders. In the more immediate future, optogenetics may provide a powerful research tool to gain new insights on ways to restore gamma oscillations in schizophrenia.

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