Macroscopic fast neuronal oscillations and synchrony in schizophrenia

Odin van der Stelt*, Aysenil Belger, and Jeffrey A. Lieberman
Department of Psychiatry, School of Medicine, University of North Carolina, Chapel Hill, NC 27599

The study reported by Spencer *et al.* (1) in a recent issue of PNAS is part of a growing body of evidence (see review in ref. 2) for abnormalities in γ band (≈30- to 70-Hz) oscillations and synchronization in the electroencephalograms (EEG) of patients with schizophrenia. The authors assessed γ band activity while subjects with schizophrenia and healthy comparison subjects perceived and responded to visual Gestalt stimuli (i.e., the presence or absence of an illusory square). The results showed that the perception of the Gestalt stimuli was associated with synchronized γ band oscillations at occipital scalp electrodes that (*i*) occurred in a lower frequency range in individuals with schizophrenia than in comparison subjects, (*ii*) correlated with reaction time, and (*iii*) correlated with clinical symptoms within the patient group. Because γ band synchronization is commonly believed to represent a fundamental neural mechanism by which the brain transiently integrates, or "binds," different visual features into a unified meaningful perceptual function (3, 4), the authors concluded that impaired brain integration is a core pathophysiological feature of schizophrenia. These results confirm and extend results of previous studies of this research group (5, 6) and add to the evidence from postmortem neuropathological (7) and neuroimaging (8, 9) studies indicating that schizophrenia is characterized by impaired anatomical and functional connectivity of neural circuits.

Research of γ Band Activity in Schizophrenia: Conceptual and Interpretative Issues

This study (1) and previous investigations of brain oscillations and synchrony in schizophrenia (2, 5, 6) illustrate well how cognitive electrophysiological methods, in conjunction with recent developments in cognitive neuroscience, can be usefully applied to gain a better understanding of the brain mechanisms that underlie sensory, perceptual, and cognitive deficits in schizophrenia. In contrast to the more traditional analysis of components of the event-related potential, such as N1 and P300, which reflects only brain activity that is time-locked to a specific sensory, cognitive, or motor event, this research involves the analysis of neuroelectric and/or neuromagnetic data in both temporal and frequency domains. The possibility has been raised recently that impaired neuronal synchrony may provide a parsimonious explanation for the variety of neurocognitive deficits observed in schizophrenia, which include deficits in sensory gating, selective attention, working memory, vigilance, problem solving, and verbal fluency (10). Moreover, because neuronal synchrony can be observed in both humans and animals and can be studied at various levels of spatial analysis, from microscopic (e.g., single-unit recordings) to macroscopic (e.g., EEG) measurements (3, 4, 11), this methodology offers the possibility of linking the results of clinical studies to findings from basic neuroscience. For instance, the ability to induce and maintain network oscillations within the γ range is thought to rely on GABAergic interneuronal circuits (12), a concept that is consistent with cellular models of schizophrenia that implicate dysfunction of corticolimbic GABAergic interneurons (13).

Evidence suggests that γ band oscillations and synchronization are disrupted in patients with schizophrenia.

Although accumulating evidence suggests that γ band oscillations and synchronization are disrupted in patients with schizophrenia, a number of important conceptual and interpretative issues remain to be clarified. Initially, the precise functional significance of γ band abnormalities in schizophrenia is unclear, because γ band synchronization is associated with multiple rather than a single unitary information-processing function (14). Incidentally, the theoretical and operational definition of the primary function of γ band synchronization (binding) typically bears a strong resemblance to the concept of selective attention, which often has been used to explain schizophrenia symptomatology. In fact, several researchers postulate that the primary function of attention is concerned with solving the binding problem (15, 16). Similar to attention processes, γ band synchronization also has been demonstrated to enhance the effect of the affected neurons on postsynaptic targets (17), a mechanism that may mediate amplification of signals that represent behaviorally significant stimuli. Thus, it is not fully clear whether binding and attention are distinct, the same, or partially overlapping concepts. Additionally, it is uncertain whether abnormalities of γ band activity in schizophrenia depend on the clinical state of subjects or are more enduring trait characteristics of the illness. The possibility that reduced γ band synchronization reflects a trait or preexisting vulnerability to schizophrenia is suggested by a recent study (18) showing that γ band synchronization is reduced in first-degree relatives with schizophrenia spectrum personality symptoms.

The anatomical substrates of impaired γ band synchronization in schizophrenia remain to be determined, because the underlying intracerebral generating sources cannot be directly inferred from scalp-recorded EEG data alone. It is also unknown whether the γ band response observed in scalp EEG data reflects within-area or local synchrony or, perhaps more likely, synchrony among different brain areas (19). For instance, γ band activity at scalp occipital recording sites can be modulated by top-down influences from higher-order (e.g., prefrontal) cortical regions (20). Furthermore, the relationship between γ band activity and schizophrenia is not invariant but can be modified by stimulus and task-specific factors [e.g., sensory modality and familiarity (21)] as well as subject sample characteristics (illness duration, symptom severity, and smoking) (20, 22). The heterogeneity of results emerging across studies is likely partly due to a failure to account for the effects of such moderating variables. Furthermore, most studies of schizophrenia have focused on high-frequency, γ band activity and have neglected to

See companion article on page 17288 in issue 49 of volume 101.

*To whom correspondence should be addressed. E-mail: ovdstelt@med.unc.edu.

assess synchronous activities in lower-frequency bands (e.g., α, τ, δ), which also seem to have relevance for brain function and cognition (23) and for their disruption in schizophrenia (24). Finally, impaired neuronal oscillations and synchronization may not be specific to schizophrenia but also have been implicated in other psychiatric disorders, such as autism (25) and attention-deficit hyperactivity disorder (26). Accordingly, as with other neurophysiological abnormalities found in schizophrenia, such as impaired generation of the auditory P300, abnormalities of γ band synchronization probably represent a pathophysiological marker rather than a diagnostic marker for schizophrenia (27).

Conclusion

Spencer *et al.* (1) provide additional evidence indicating that schizophrenia is characterized by impaired brain oscillations and synchronization. We believe that the currently available data are of sufficient interest to warrant further research in this area. In conjunction with more conventional analyses of neuroelectric or neuromagnetic data in the time domain, the application of time-frequency analysis to assess oscillatory brain activity is likely to provide new insights into the primary cognitive and pathophysiological features of schizophrenia. Furthermore, if disruption of neuronal fast oscillations indeed reflects a basic pathophysiological mechanism in schizophrenia, a deeper insight into the mechanisms of generation of these brain oscillations, together with a greater understanding of their functional role in information processing, will potentially provide an ideal background upon which to design and test new pharmacological therapeutic interventions (12).

1. Spencer, K. M., Nestor, P. G., Perlmutter, R., Niznikiewicz, M. A., Klump, M. C., Frumin, M., Shenton, M. E. & McCarley, R. W. (2004) *Proc. Natl. Acad. Sci. USA* **101,** 17288–17293.
2. Lee, K. H., Williams, L. M., Breakspear, M. & Gordon, E. (2003) *Brain Res. Rev.* **41,** 57–78.
3. Singer, W. & Gray, C. M. (1995) *Annu. Rev. Neurosci.* **18,** 555–586.
4. Varela, F., Lachaux, J. P., Rodriguez, E. & Martinerie, J. (2001) *Nat. Rev. Neurosci.* **2,** 229–239.
5. Kwon, J. S., O'Donnell, B. F., Wallenstein, G. V., Greene, R. W., Hirayasu, Y., Nestor, P. G., Hasselmo, M. E., Potts, G. F., Shenton, M. E. & McCarley, R. W. (1999) *Arch. Gen. Psychiatry* **56,** 1001–1005.
6. Spencer, K. M., Nestor, P. G., Niznikiewicz, M. A., Salisbury, D. F., Shenton, M. E. & McCarley, R. W. (2003) *J. Neurosci.* **23,** 7407–7411.
7. Benes, F. M. (1997) *Schizophr. Bull.* **23,** 503–507.
8. Friston, K. J. (1998) *Schizophr. Res.* **30,** 115–125.
9. Kubicki, M., Westin, C. F., Maier, S. E., Frumin, M., Nestor, P. G., Salisbury, D. F., Kikinis, R., Jolesz, F. A., McCarley, R. W. & Shenton, M. E. (2002) *Am. J. Psychiatry* **159,** 813–820.
10. Green, M. F. & Nuechterlein, K. H. (1999) *Arch. Gen. Psychiatry* **56,** 1007–1008.
11. Basar, E. (1980) *EEG–Brain Dynamics* (Elsevier, Amsterdam).
12. Whittington, M. A., Faulkner, H. J., Doheny, H. C. & Traub, R. D. (2000) *Pharmacol. Ther.* **86,** 171–190.
13. Coyle, J. T. (2004) *Biochem. Pharmacol.* **68,** 1507–1514.
14. Karakas, S., Basar-Eroglu, C., Ozesmi, C., Kafadar, H. & Erzengin, O. U. (2001) *Int. J. Psychophysiol.* **39,** 137–150.
15. Reynolds, J. H. & Desimone, R. (1999) *Neuron* **24,** 19–29.
16. Treisman, A. M. & Kanwisher, N. G. (1998) *Curr. Opin. Neurobiol.* **8,** 218–226.
17. Fries, P., Reynolds, J. H., Rorie, A. E. & Desimone, R. (2001) *Science* **291,** 1560–1563.
18. Hong, L. E., Summerfelt, A., McMahon, R., Adami, H., Francis, G., Elliott, A., Buchanan, R.W. & Thaker, G. K. (2004) *Schizophr. Res.* **70,** 293–302.
19. Tallon-Baudry, C. (2003) *J. Physiol.* **97,** 355–363.
20. Gallinat, J., Winterer, G., Herrmann, C. S. & Senkowski, D. (2004) *Clin. Neurophysiol.* **115,** 1863–1874.
21. Lee, K. H., Williams, L. M., Haig, A., Goldberg, E. & Gordon, E. (2001) *Clin. Neurophysiol.* **112,** 1499–1507.
22. Crawford, H. J., McClain-Furmanski, D., Castagnoli, N. & Castagnoli, K. (2002) *Int. J. Psychophysiol.* **45,** 33–33.
23. Basar, E., Basar-Eroglu, C., Karakas, S. & Schurmann, M. (2001) *Int. J. Psychophysiol.* **39,** 241–248.
24. Winterer, G., Coppola, R., Goldberg, T. E., Egan, M. F., Jones, D. W., Sanchez, C. E. & Weinberger, D. R. (2004) *Am. J. Psychiatry* **161,** 490–500.
25. Welsh, J. P., Ahn, E. S. & Placantonakis, D. G., *Int. J. Dev. Neurosci.*, in press.
26. Yordanova, J., Banaschewski, T., Kolev, V., Woerner, W. & Rothenberger, A. (2001) *Clin. Neurophysiol.* **112,** 1096–1108.
27. Nurnberger, J. L. (1992) *Acta Psychiatr. Scand.* **86,** 1–4.