Network Synchronization/Desynchronization Defects in the Pathogenesis of Neuropsychiatric Disorders

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Abstract Classical theory maintained that all significant information transmission in the central nervous system was implemented by the movement of neurotransmitters at axon-to-dendrite synapses. It is now understood that this is an incomplete description. An alternative understanding incorporates other forms of information transmission and emphasizes the role of synchronization in organizing CNS activity. This expanded view has immediate implications for the clinical response to neuropsychiatric disorders. Treatment of neuropsychiatric disorders should not focus exclusively on neurotransmitters acting at chemical synapses. Rather, the focus should expand to include a generic examination of network dysfunction. CNS network defects will, it is hypothesized, result in abnormalities of synchronization that may be diagnostically disclosing.

1 Introduction: The failure of the Neuron Doctrine

Once it was simple. The Neuron Doctrine, it was supposed, provided an essentially complete specification of the mechanism of central nervous system (CNS) function. The Doctrine could be presented in five statements.

1. All information processing in the CNS is performed by neurons.
2. Neurons are anatomically discrete units; they do not form a reticulum.
3. All information transmission is unidirectional from axons of the pre-synaptic neuron to dendrites of the post-synaptic neuron.
4. All information transmission is mediated by all-or-nothing, regeneratively propagated action potentials.
5. All information is transmitted from neuron-to-neuron across the synaptic cleft by neurotransmitters.

In practice neuroscientists did not hold the Doctrine as stated above inflexibly. All recognized that there were exceptions to each of the five statements. Indeed even

Ramón y Cajal who introduced the concept of anatomically discrete neurons (as contrasted with Golgi's hypothesis of neurons forming a continuous syncytium) recognized that there would be exceptions to the principle of neural discontinuity (as cited by Bullock, et al[1]). Assessment of the frequency and magnitude of these exceptions and their operational significance to CNS function is, however, a challenging question that must be addressed. The exceptions are frequent, and they are highly significant because they lead to an expanded view of CNS operation which has immediate implications for the clinical response to neuropsychiatric disorders. As summarized by Bullock, et al[1] and Douglas Fields[2], emerging evidence indicates that the classical Neuron Doctrine is at best an incomplete description of CNS operation. Each of the five assertions made above have been challenged.

The list of exceptions to the Neuron Doctrine indicate that the search for organizing principles that provide a conceptual framework for interpreting CNS operation must expand beyond axon-to-dendrite neurotransmitter mediated communication between neurons. If not the Neuron Doctrine, what? Bullock's view, as presented by Douglas Fields[2] was that "the unparalleled abilities of the human mind arise not as a unique property of our neurons or brain circuitry but as an emergent property of the way its billions of neurons operate cooperatively." This is stated with such breadth that it is almost certainly correct, but it is not mechanistically specific. Most importantly it does not immediately suggest a potentially falsifiable hypothesis. The requirement for a hypothesis driven investigation is addressed by introducing the network synchronization hypothesis.

2 The Network Synchronization Hypothesis

A long intellectual development has lead to the concept of organization by synchronization. An important contribution to the development of the synchronization hypothesis was made by von der Malsburg in a theory of correlative brain function published as an internal report of the Max-Planck-Institut für Biophysikalische Chemie[3]. A parallel developmental history took the EEG as its starting point. Freeman's book "Mass Action in the Nervous System"[4] begins with the question "What are the neural mechanisms and what is the behavioral significance of the electroencephalogram (EEG)?" Freeman's analysis included an early, perhaps the first, mathematical account of the importance of neural synchronization in ongoing in CNS activity.

In the 1980's investigations of oscillating CNS activity took on an added interest because of the hypothesized role of synchronization in feature binding. The binding problem has been stated with exemplary concision by Revonsuo and Newman[5]. The binding problem is "the problem of how the unity of conscious perception is brought about by the distributed activities of the central nervous system." The problem is often examined in the context of visual processing. How do the distinct

elements of an object, its color, shape, distance, texture and direction and velocity of motion bind together to form a unitary percept? Building on earlier work, notably Bressler and Freemen[6], Singer[7] and Eckhorn[8] proposed that feature binding was accomplished by synchronized oscillations in the visual cortex.

The concept of integration by synchronization has subsequently been generalized beyond the specific context of sensory feature binding to provide a generic dynamical metaphor for CNS organization including cognition[9], [10]. Synchronization of EEGs and ERPs (event related potentials) are associated with attention, learning, memory and perception. (A large primary literature is identified in[11].) We must guard against an unduly simplistic conceptualization of the role of synchronized activity. The importance of a cautionary view becomes especially apparent when considering patterns of event related synchronization and desynchronization. Complicated patterns of synchronization and desynchronization can be seen simultaneously at different scalp sites in response to the same stimulus[12], [13], [14] With these complexities of mechanism and interpretation explicitly recognized, we can ask an empirical question: are abnormalities of synchronization and desynchronization associated with neuropsychiatric disorders? The answer is "Yes." A large literature is listed in[11] Table 3. General reviews are given in [15], [16], [17], [18].

3 Clinical Implications

At present, the principal treatment for psychiatric disorders is pharmacological. These treatments are directed to manipulating synaptic transmission by either facilitating transmission, for example by providing transmitter precursors, or by blocking transmitter receptor sites. The growing list of exceptions to the Neuron Doctrine indicates that synaptic transmission is only a part, possibly a small part, of CNS function. We should look beyond the chemical synapse and try to identify forms of treatment that will have a positive impact on network integrity. It is possible that some forms of treatment already in use act by enhancing network function. Fluoxetine (Prozac) is a widely prescribed serotonin reuptake inhibitor with antidepressant action. Paradoxically, tianeptine (Stablon) which is a serotonin reuptake enhancer also has antidepressant action. Though these drugs have opposite effects on serotonin transport, they have a common action in promoting increased innervation in the forebrain.[19]. This result is pertinent to the thesis of the present contribution because the resulting increase in serotonin fiber density in the forebrain would have an effect on network function.

The increased fiber density reported in [19] could be the result of increased arborization of exiting neurons. This is the possibility that they emphasize in the discussion of their results. Other investigations, however, suggest that neurogenesis may be a critical element in antidepressant action. For example, Madsen, et al.[20] have shown increased hippocampal neurogenesis in an animal model of electroconvulsive

therapy. Malberg, et al.[21] showed that chronic antidepressant treatment using several different classes of antidepressant medication increased neurogenesis in the adult rat hippocampus. Santarelli, et al.[22] carried the analysis further with animal studies showing that interventions blocking the neurogenesis effect of antidepressants also blocked the behavioral antidepressant action of these drugs. Similarly, aerobic exercise can have significant antidepressant action[23] and exercise can increase hippocampal neurogenesis to high levels[24]. Ernst, et al.[25] have argued that the antidepressant effects of aerobic exercise may be related to its impact on neurogenesis. Treatments that increase fiber density or create new neurons have an impact on the hardware available for network activity.

4 Conclusions

Neuropsychiatric disorders are disorders of networks. Treatment of neuropsychiatric disorders should not focus exclusively on neurotransmitters acting at chemical synapses. Rather, the focus should expand to include a generic examination of network dysfunction. Among other consequences, CNS network defects will, it is hypothesized, result in abnormalities of synchronization and desynchronization that may be diagnostically disclosing. Additionally, longitudinal time-frequency analysis of event related signals may provide an important technology for assessing the response to treatment.

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