Neurodynamics and Schizophrenia Research: Editors’ Introduction

by Ralph E. Hoffman and Thomas H. McGlashan

Abstract

The term, "neurodynamics," refers to interactions of large numbers of neurons that, in the short term, transform input information derived from their environments into meaningful outputs and, in the long term, use this information to alter their own architectures. This general concept may be useful in framing and investigating research questions that could advance our understanding of the nature, course, and treatment of schizophrenia. The mechanism of action of neuroleptics, the anatomic localization of schizophrenia, the stability of associated brain disturbances over time, and the distinction of state versus trait variables are briefly discussed as examples of issues whose understanding may be enhanced by a neurodynamic perspective.

In spite of intense research activity and the explosion of knowledge in the brain sciences, our ignorance of schizophrenia still seriously outweighs our understanding. Basic features of the illness remain unaccounted for: its waxing and waning course, age of onset, the neural basis for its many symptoms and cognitive disturbances, and its widely variable clinical outcomes. The ultimate goal—more definitive treatment—most likely awaits the attainment of an integrated perspective that reveals, at least in part, the nature of these different components of the illness.

This issue of the Schizophrenia Bulletin brings together reports from several research efforts that address these aspects of schizophrenia. Contributions by Scheibel and Conrad (1993, this issue), Waddington (1993, this issue), McGlashan and Fenton (1993, this issue), Pettegrew et al. (1993, this issue), and Hoffman and McGlashan (1993, this issue) address how the brain—and the mind—of a person destined to acquire schizophrenia may change over time; these changes include the induction of a biological vulnerability, the onset of active psychosis, and sequelae of the illness itself. The contribution by Ulas and Cotman (1993, this issue) reviews recent studies that suggest abnormalities involving excitatory amino acids in schizophrenia. Excitatory amino acids are key mediators of neural learning, neural development, and brain plasticity throughout the cerebral cortex, and therefore provide a neurochemical focus for exploring dynamic changes in behavior, symptoms, and brain function in schizophrenia.

Collectively, these articles emphasize that complex neuronal circuits are dysfunctional in schizophrenia. Such circuits, insofar as they involve the assignment of meaning to a phenomenal world, the generation of beliefs, and the production of language, must involve “higher level” neuronal assemblies in the cerebral cortex and limbic areas. Such networks do not consist of 1 or 10 neurons, but thousands or, more likely, millions of neurons. They are modulated by monoamine systems, but their functioning is ultimately dependent upon the extraordinarily complex interactions among these thousands to millions of neurons themselves.

Reprint requests should be sent to Dr. R.E. Hoffman, Yale Psychiatric Institute, Box 12A, Yale Station, New Haven, CT 06520.
How very large populations of neurons interact to accomplish mental “work” has become the subject of active study. Much of the current investigation has been accomplished through computer simulations of neural processes and the cognitive abilities achievable by these simulations. A set of new concepts has emerged from these studies, known as parallel, distributing processing (PDP). PDP studies have radically altered the conceptualization of brain functioning. Two of this issue’s contributions focus on these developments. Cohen and Servan-Schreiber (1993, this issue) describe their computer modeling of information-processing neural networks and their successful simulation of the performance of schizophrenic patients on common cognitive tasks. Their work not only provides clues to the pathophysiology of schizophrenia but also gives validity to PDP models, principles, and dynamics. Hoffman and McGlashan discuss how PDP computer simulations of dysfunctional states suggest mechanisms for many of the positive symptoms of schizophrenia.

These simulations make it clear that we must understand how neural circuits assemble and modify themselves to accomplish information-processing tasks in order to understand cognition in relationship to brain function. In other words, neurocognition cannot be investigated in isolation from neurodevelopment and neural learning. We refer to this combined perspective as “neurodynamic.”

The term neurodynamic is adapted from Pineda (1987) and is defined as a neural system that uses input information from its environment and its own prior outputs to transform itself and yield orderly outputs. Environment could include inputs from other circuits of the same nervous system as well as external information. Transformations could include the physiological incorporation of new information (learning) as well as fundamental alterations of functional anatomy. Orderly means that its outputs are considerably less random than its inputs. All intelligent nervous systems are neurodynamic in the sense that they depend on environmental inputs as well as their own outputs to organize themselves over time for useful information-processing work. Useful information-processing work requires that the nervous system distill input information in a fashion that disregards random noise and responds nonrandomly to signals. A neurodynamic perspective has prompted new types of neurobiological and computer simulation studies of information processing, neural learning, neurodevelopment, and neural plasticity. This perspective may also offer insights into the dynamic changes in cognitive and brain function that correspond to the induction of schizophrenic vulnerability, the onset of active psychosis, the organism’s own response to that psychotic process, and the interaction of these illness processes with normal cognitive and neural maturational processes. The following are examples of the types of questions relevant to schizophrenia research in which a neurodynamic perspective seems necessary.

**What Is the Function of Monoamine-Blocking Agents?**

It is clear that dopamine-blocking agents are often effective in reducing symptoms of schizophrenia. But it is not clear whether these drugs correct a primary defect of excessive central dopamine activity or compensate for problems occurring elsewhere in the brain or at another functional level. Clinical researchers have often assumed that dopamine upregulation leads to a breakdown in the inhibition of certain neural impulses (Bunney and Geyer 1990). On the other hand, animal studies of the prefrontal cortex, hippocampus, and striatum suggest that dopamine acts as an inhibitor (Bunney and Chiodo 1984; Rolls et al. 1984; Stanzione et al. 1984), causing postsynaptic neurons to be less responsive and perhaps more selective in their response to other inputs.

Cohen and Servan-Schreiber suggest that dopamine downregulation may not alter excitation or inhibition of neurons per se, but may reduce the response of neurons to excitatory and inhibitory inputs from other neural sources. Their research suggests that these changes may have especially profound effects on working memory during information-processing tasks and implies that downregulation of central dopamine yields impairments in working memory.

What if psychotic symptoms emerge, in part, from overactive working or contextual memory? Then reductions in psychotic symptoms may result if this system is somehow buffered via dopamine downregulation. This perspective further emphasizes the importance of studies highlighting neuroanatomic abnormalities in medial temporal regions, the site of working memory (see Scheibel and Conrad). Also consistent with this perspective is the Ulas and Cotman contribution, which in-
includes a description of possible interactions of neural processes mediated by glutamate and monoamine systems. Their work suggests that schizophrenia is a product of complex cortical circuitry and complex neuromodulatory feedback loops that recruit not just the dopamine system but others as well. Of particular interest is their discussion of differential effects of standard neuroleptics versus clozapine on glutamatergic functioning, a finding that may have significant clinical implications.

How Spatially and Temporally Localized Are Brain Disturbances Underlying Schizophrenia?

A neurodynamic perspective implies that efforts to localize neural circuit aberrations in schizophrenia to one or a few specific anatomic regions are likely to invite frustration and nonreplication. Certain areas of the brain do seem more involved than others in schizophrenia, that is, frontal, limbic, and medial temporal; however, it may be that all areas are involved to some extent. The brain may be a single integrated organ in which alterations in one circuit induce alterations in others. Waddington reviews the extensive anatomic and functional imaging studies in schizophrenia and notes that the diverse individual findings strongly suggest that anatomic changes accompanying the disorder are diffuse and variable. The fact that glutamate and other excitatory amino acids are so widely distributed throughout the cortical and limbic system (see Ulas and Cotman) suggests that abnormalities involving these neurotransmitter systems in schizophrenia are similarly widespread.

In “localizing schizophrenia in time,” the concept of neurodevelopment has become increasingly popular (Feinberg 1982/1983; Weinberger 1987; Crow et al. 1989; Hoffman and Dobscha 1989). At the same time, extraordinary progress has taken place over the last decade in the genetics, physiology, and neuroanatomy of normal brain development. Scheibel and Conrad present one of the most explicit statements of the neurodevelopmental perspective. Their work demonstrates how the extraordinarily complex process of neuroembryogenesis might go awry and result in hippocampal neurocircuits that are compromised at birth. The fact that the hippocampus interacts with so many distinct cortical regions suggests that a disturbance involving the former may have widespread and perhaps progressive effects on the latter. The 31P magnetic resonance spectroscopy studies summarized by Pettegrew and colleagues highlight the importance of both prenatal and late (i.e., childhood and adolescent) brain development in understanding schizophrenia.

How Stable Are Brain Disturbances in Schizophrenia?

The development of schizophrenia, at least in certain cases, may involve a failure to achieve a certain developmental level of cognitive functioning and also a loss of capabilities that were in place before the onset of active illness. Of course, a substantial number of schizophrenic patients have demonstrated long-standing adjustment difficulties or peculiar behaviors during adolescence before becoming psychotic for the first time. On the other hand, as originally observed by Kraepelin (1919/1971), their long-term level of functioning may decline significantly as a consequence of their illness.

McGlashan and Fenton describe the longitudinal course of symptom and subtype phenomenologies in schizophrenia. They reiterate Kraepelin’s assertion that the disorder includes a phase of deterioration that may be seen as another form of brain development, albeit a pathological form (see also contribution by Waddington). They contend that this process occurs early, usually at or before onset. The process also appears to be time limited; clinical stabilization is usually achieved within 5 years. The work of Pettegrew and colleagues lends in vivo biochemical support to the notion of accelerated neural tissue turnover and loss in schizophrenia. Their work offers exciting leads for the biological identification, tracking, and understanding of both the neurodynamic consequences of schizophrenia and its antecedents.

Are Distinctions Between State Versus Trait Overdrawn?

The longitudinal malleability of neural network structure and function suggests that the traditional distinction between state and trait variables may be an oversimplification. Entering an active schizophrenic state, for example, may in and of itself cause enduring damage that then becomes “trait-like.” A recent review of outcome literature of patients treated around the time of the introduction of neuroleptics supports this hypothesis (Wyatt 1991). Those patients who suffered prolonged psychotic episodes before neuroleptic-induced remissions had a worse
long-term outcome than those patients whose psychotic episodes were interrupted more quickly. Thus, the duration of exposure to active psychosis may have long-term deleterious effects even after the psychotic state ends.

A neurodynamic perspective provides a framework for thinking about such phenomena: brain maturation does not end with childhood or adolescence (see Hoffman and McGlashan). It is highly likely that our brains are constantly re-casting neural connections (albeit at slower rates) throughout adulthood (Buell and Coleman 1979; Benowitz et al. 1989). This raises the possibility that active schizophrenia may affect the brain, causing further pathological changes in cognition, brain function, and perhaps even brain structure.

Conclusion

Although these and other such questions may once have represented conundrums, a neurodynamic perspective can offer potentially useful solutions and research approaches. It is in the spirit of asking such new (though in some cases also very old) questions to which this issue of the Schizophrenia Bulletin is devoted. Although these articles do not offer a single coherent picture of brain dysfunction in schizophrenia, they suggest the need for researchers to think in terms of complex, highly interactive cortical systems that evolve over time.

References


An Invitation to Readers

Providing a forum for a lively exchange of ideas ranks high among the Schizophrenia Bulletin's objectives. In the section At Issue, readers are asked to comment on specific controversial subjects that merit wide discussion. But remarks need not be confined to the issues we have identified. At Issue is open to any schizophrenia-related topic that needs airing. It is a place for readers to discuss articles that appear in the Bulletin or elsewhere in the professional literature, to report informally on experiences in the clinic, laboratory, or community, and to share ideas—including those that might seem to be radical notions. We welcome all comments.—The Editors.

Send your remarks to:

At Issue Research Projects and Publications Branch
National Institute of Mental Health
5600 Fishers Lane, Rm. 18C-06
Rockville, MD 20857