Corticocortical Connectivity, Autonomous Networks, and Schizophrenia

by Ralph E. Hoffman and Thomas H. McGlashan

Abstract

Dr. David hypothesizes that increased, not decreased, corticocortical connectivity causes schizophrenia. He cites studies suggesting excessive semantic priming and cross-hemispheric interference in this disorder to support his hypothesis. These findings, David suggests, reflect excessive transmission of information between neurons or within neural systems. However, considerable caution should be exercised in making neuroanatomic inferences on the basis of cognitive studies alone. There is an increasing consensus that information is represented by the brain as patterns of neural activation, where the same neuron or group of neurons participates in many different representations. Our simulations, which reflect this consensus, suggest that persistent or intrusive activation patterns do not emerge from too many neural connections, but from too few. This condition causes subgroups of neurons to disregard information processing by other neurons and to produce autonomously their own output, which interferes with the functioning of the system as a whole. Direct neuroanatomic or neurochemical studies of the cerebral cortex are needed to fully assess hypotheses regarding abnormal corticocortical connectivity in schizophrenia.


The majority of projections to a particular cortical region derive from other cortical regions (Braitenberg 1978). The anatomy of these connections is highly dynamic: new connections are formed and old connections lost throughout childhood, adolescence, and adulthood in the mammalian brain (Hüttenlocher 1979; Rakic et al. 1986; Benowitz et al. 1989; Recanzone and Merzenich 1991). In a recent Schizophrenia Bulletin article, we reviewed empirical evidence that suggests, but by no means proves, that excessive reductions of corticocortical connections cause schizophreniform psychosis (Hoffman and McGlashan 1993). David (1994, this issue) suggests an alternative hypothesis, namely excessive corticocortical connectivity. A consequence of this neuroanatomic pathology, he proposes, is “dysmodularity,” where cortical modules interfere with each other because of a breakdown of informational encapsulation. The result is the cognitive disturbances associated with schizophrenia.

While we find Dr. David’s ideas both intriguing and challenging, we remain proponents of the hypothesis that schizophrenia is associated with neural networks with impoverished connections.

David (1994, this issue) notes that automatic cognitive processes are relatively spared in schizophrenia, whereas more complex processes seem to be more obviously affected. Automatic processes, in general, are attributed to modular or submodular circuitry, whereas more complex processes most likely involve the integration of multiple modules. We agree that higher order cognition, such as language processing, problem solving, and social cognition, tends to...
be impaired in schizophrenia. However, this impairment is not necessarily evidence for underpruning since overpruning could also disturb higher cognitive processes. Indeed, very little is known about how underpruning of cortical synapses would express itself clinically or cognitively. A clue may be offered by Cragg (1975), who reported increased cortical synaptic density in brains of mentally retarded individuals, a finding replicated in a single case study by Hüttenlocher (1979). Mental retardation is expressed as impairments in higher level cognition, though neither dysmodularity as described by David nor a resemblance to schizophrenia is evident.

Second, one cannot infer that excessive interference effects in performing the Stroop test (Stroop 1935) and enhanced linguistic priming associated with schizophrenia (Kwapil et al. 1990; Liddle and Morris 1991) provide evidence of excessive connectivity per se. For instance, a neural network simulation demonstrated that schizophrenia-like cross-modal interference could be simulated by attenuating responses of neurons that specify task (e.g., reading words or identifying colors; Cohen and Servan-Schreiber 1992); cross-modal interference in this model was generated by failures in working memory that specify response set, not by underpruning.

Similarly, excessive semantic priming does not imply that functional connections are enhanced. To make this assumption is to accept the hypothesis that single neurons or small groups of neurons code for particular concepts (see, for instance, Anderson 1983). Overconnectivity would then induce greater spreading of activation with an excess of semantic associations. Although this model has intuitive appeal, there is no evidence that the brain is organized in this fashion. Current theorizing, instead, tends to assume that the same group of neurons code for many different concepts via different activation patterns (see, for instance, Hopfield 1982; Wang et al. 1990; Hinton and Shallice 1991); concepts that prime for each other are coded to do so by overlapping patterns of activation. Priming would then correspond to the persistence of shared patterns of activation that code for closely linked concepts. Assuming this “distributed activation” model of concept representation, it is not at all obvious whether or how excessive anatomic connectivity might cause a network to more persistently retain a particular activation pattern, thereby causing excessive priming.

David (1994, this issue) notes that certain studies of schizophrenia have demonstrated increased cognitive interference under conditions of bilateral stimulation. He suggests that this phenomenon reflects an excess of corpus callosal fibers. However, evidence for excessively thick callosal anatomy in schizophrenia has been quite contradictory (see Coger and Serafetinides 1990; Raine et al. 1990; Günther et al. 1991; Woodruff et al. 1993). And there is danger, once again, in making inferences about neuroanatomic aberrance based solely on cognitive aberrance. An example of how such intuitions can run amok was provided by our own neural network models. When simulating certain aspects of speech perception (based on Elman 1990), information was transmitted from a temporary storage module to an executive module. We found that intrusive activation occurred in this system when connections were lost. This phenomenon occurred because the loss of projections caused a reduction in baseline inhibition of the receiving module; this inhibition ordinarily suppresses the emergence of spurious activation patterns. Consequently, the loss of projections from one module to another caused ordinarily subthreshold transmissions to be expressed. We used this finding to simulate the emergence of hallucinated speech or “voices” in schizophrenia (Hoffman et al., submitted for publication).

The basic problem is that we do not know what concepts underlie neural computation of information. However, as we attempt to build even very simple computer models of neural processing, our intuitions are frequently disproved or fall far short of the phenomena that we are attempting to understand. Equating cognitive or perceptual interference with excessive neuroanatomic connectivity requires greater empirical backing. We are intrigued with David’s reference to his own study of schizophrenia patients, which indicates a correlation between greater levels of cross-hemisphere functional interference and anterior callosal size (David et al., in press), although this result seems to contradict findings by Raine et al. (1990). Perhaps additional studies such as these will shed new light on cross-hemisphere integration of neural processes in schizophrenia.

For now, we believe that the currently available, though limited, evidence favors the hypothesis that
there is reduced corticocortical connectivity in schizophrenia (see also Hoffman and McGlashan 1993). The most important evidence, as we see it, is as follows.

1. Reductions in phosphomonoester resonance and enhanced phosphodiesters in prefrontal areas in schizophrenia patients have been reported by Pettigrew et al. (1991) using 31P magnetic resonance spectroscopy (MRS). Developmental studies in animals suggest that these findings reflect reduced outgrowth in dendrites and axons combined with excessive elimination of these connective processes.

2. Postmortem immunochemical studies of cortical proteins have demonstrated reduced MAP2, MAP5, and synapsin 1 in the hippocampal regions and reduced synaptophysin in the prefrontal cortex in tissue samples from schizophrenia patients (Arnold et al. 1991; Dudek et al. 1992; Glantz and Lewis 1993). MAPs play a critical role in elaborating cytoskeletal proteins essential for creating and maintaining axons and dendrites. Synapsin I and synaptophysin are phosphoproteins specifically associated with synaptic contacts. Reductions in these proteins support the hypothesis that synaptic density or the elaboration of neurites in the hippocampal regions or prefrontal regions in schizophrenia are curtailed.

3. Patients with adult-onset metachromatic leukodystrophy frequently present with a schizophrenic-like syndrome that includes voices (Hyde et al. 1992). Neurologic lesions in these patients involve primarily frontal subcortical white matter, but spare gray matter (Hyde et al. 1992). Such lesions are likely to impair communication between the prefrontal and hippocampal systems (Weinberger 1991). These patients may provide a naturally occurring model of neuroanatomic pathology in schizophrenia that reflects reduced connectivity of the prefrontal and hippocampal systems.

4. Goldman-Rakic and colleagues have found significant increases in the packing density of neurons and glial cells in postmortem prefrontal cortex of 13 schizophrenic brains compared to 11 age-matched controls (Selemon et al. 1993). Since there is no evidence that the absolute number of the cells is increased in schizophrenia, these data indicate a loss of surrounding neuropil, that is, the dense intertwining of axons and dendrites surrounding neurons and glial cell bodies. A reduction in neuropil volume is likely to produce parallel reductions in functional connectivity between neurons whose dendrites and axons occupy this microanatomic "space."

5. Phencyclidine (PCP) is the currently available psychotomimetic drug that induces symptoms best approximating those of schizophrenia. A PCP psychosis generally is accompanied by delusions, paranoid ideation, auditory hallucinations, and disorganized speech (Allen and Young 1978), and best replicates abnormalities in abstract reasoning, cognitive processing, and attention seen in patients with schizophrenia (Javitt and Zukin 1991). The pharmacologic effect of PCP derives from inhibition of excitatory synapses that use glutamate as a neurotransmitter. Corticocortical projections are probably glutamatergic (Conti et al. 1988; Iriki et al. 1991). Thus, PCP may achieve its psychotogenic effects by curtailing corticocortical transmission of information or functionally "uncoupling" cortical interactions.

No good method is currently available to directly measure corticocortical connectivity in the living human brain. David suggests electroencephalographic (EEG) coherence as a possible research strategy. One of us has applied coherence analysis to EEG measurements during perceptual activation in schizophrenia subjects and found some evidence of decreased interareal coupling (Hoffman et al. 1991). However, a limitation of this method is that decreased coherence between these two areas may reflect decreased signal transmitted to each of the areas from a third, common signal source rather than a direct reduction in corticocortical transmission.

This leaves postmortem studies as perhaps the best way to tackle the problem. A definitive study would be a direct count of synaptic density in key cortical areas of the brains of schizophrenia patients and appropriate controls. Unfortunately, quantifying synapses requires electron microscopy, which is very labor-intensive and vulnerable to the effects of tissue degradation during the postmortem interval. This leaves indirect methods, such as immunochemical quantification of phosphoproteins associated with synapses, dendrites, and axons, as one practical way to test this hypothesis (see Dudek et al. 1992; Glantz and Lewis 1993). Moreover, the MRS approach developed by Pettigrew and colleagues (1991) holds great promise as a method for assessing dynamic remodeling of corticocortical connections.

Meanwhile, we think that the
concept of reduced corticocortical connectivity offers an appealing way of understanding positive symptoms in schizophrenia. Such alterations could result in networks emerging as self-organizing and semiautonomous with respect to overall brain function. Neurocognitive interference would emerge, not because of the inappropriate or excessive transmission of information, but because certain networks that code for meaningful representations "go their own way." Therein could lie the key to understanding the alien, nonself experience of one's own mentation, a phenomenology that, in all its variations, we view as central to the experience of having schizophrenia.

References
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