Neuroanatomy of Schizophrenia

by David L. Braff and Neal R. Swerdlow

Abstract

The articles that appear in this issue offer a framework of insights about the neuroanatomy of schizophrenia from three learned and creative perspectives. All three articles advance our understanding of schizophrenia from a single locus/specific "lesion" model to more advanced perspectives of neural circuit dysfunction models. Goldman-Rakic and Selemon review their own and others' work on structure-activity relationships of the frontal cortex and related working memory dysfunction. This important but sometimes cloudy and complex area is illuminated by their highly specific, informative research. Jones focuses on thalamic abnormalities hypothetically linked to abnormal oscillations in large arrays of cortical and thalamic neurons, a critically important concept in understanding the functional consequences of abnormal (thalamic) brain structure and function. Graybiel describes her interest in abnormal basal ganglia activity-dependent loops that may access the thalamus and set the tone of thalamo-cortical transmission. This view allows for us to understand the "upward" influences on basal ganglia function (and dysfunction) relevant to schizophrenia. These intriguing articles raise a number of issues that await increased data and continued integrating insights. These issues include (1) the timing of any initial lesions or dysfunctions (e.g., genetic with prenatal onset, environmental with prenatal induction, postnatal/genetic, or postnatal/environmental); (2) the extent and/or regional distribution of abnormalities within certain critical brain areas and how central nervous system (CNS) dysfunction "diffuses" along planes of physical proximity and functional connectivity; (3) the relationship of brain dysfunction to clinical/cognitive abnormalities observed in the group of schizophrenias; and (4) the relationship between specific forms of brain dysfunction and the boundaries of schizophrenia, including schizophrenia and schizotypal patients, and the unaffected relatives of schizophrenia patients. In particular, we must carefully consider why abnormal CNS functions in such populations as unaffected family members of schizophrenia patients do not lead to the disorder (i.e., what additional factors must be present for schizophrenia to be fully expressed).

Over the past decade, neuropsychiatric disorders, and schizophrenia disorders in particular, have increasingly been understood in terms of complex neural circuit dysfunction. These three articles (Goldman-Rakic and Selemon, Graybiel, and Jones—all 1997, this issue) reflect the historical tide of our evolving understanding of neural circuit dysfunction and schizophrenia.

Several critical issues about brain dysfunction must be addressed in any comprehensive model of the neuropathology and pathophysiology of this group of disorders. These issues include (1) the timing of any initial lesions or dysfunctions (e.g., genetic with prenatal onset, environmental with prenatal induction, postnatal/genetic, or postnatal/environmental); (2) the extent and/or regional distribution of abnormalities within certain critical brain areas and how central nervous system (CNS) dysfunction "diffuses" along planes of physical proximity and functional connectivity; (3) the relationship of brain dysfunction to clinical/cognitive abnormalities observed in the group of schizophrenias; and (4) the relationship between specific forms of brain dysfunction and the boundaries of schizophrenia, including schizophrenia and schizotypal patients, and the unaffected relatives of schizophrenia patients. In particular, we must carefully consider why abnormal CNS functions in such populations as unaffected family members of schizophrenia patients do not lead to the disorder (i.e., what additional factors must be present for schizophrenia to be fully expressed).

Among this trio of articles, two focus on the contribution of dysfunction in particular brain regions (Goldman-Rakic and Selemon on the prefrontal cortex, Jones on the thalamus) to the pathophysiology of schizophrenia, while a third (Graybiel) focuses on the contribution of the basal ganglia to interconnected circuit "loop"
dysfunction in schizophrenia. Hypotheses that emphasize the role of a single brain substrate (i.e., “hole” hypotheses; see Swerdlow 1991) carry the burden of accounting for many other brain abnormalities reported within the schizophrenia literature. Hypotheses that focus on dysfunction within multiple different brain regions (i.e., “whole” hypotheses) present challenges related to heterogeneity in causes and presentations of this group of disorders.

While each of these three articles presents novel and important information, in each case—with the prefrontal cortex, thalamus, and basal ganglia loops—we await convincing clarification of the four issues listed above: the timing, extent, and specific clinical correlates of the defining neuropathology in schizophrenia patients, and the status of such defining brain abnormalities in nonpsychotic boundary populations.

Goldman-Rakic and Selemon’s article on the functional and anatomical pathology of prefrontal pathology in schizophrenia uses a critical assumption of “working memory-frontal lobe hypotheses” to understand schizophrenia. This article addresses the limitations of a one-locus theory, and the Selemon et al. (1995) reference aptly reveals that postmortem studies show the posterior structural cortical areas (of the primary visual cortex) are also abnormal in at least some schizophrenia patients. Goldman-Rakic and Selemon’s definition of working memory is derived from, but not exactly the same as, Baddeley’s (1992). Baddeley hypothesized a visuospatial and verbal temporary storage bin and seems to require not only storage but also manipulation of information. Without manipulation, working memory may be equivalent to short- or long-term memory.

Goldman-Rakic and associates have advanced our knowledge of functional/structural interactions in the frontal cortex; their work has, to some extent, led us away from expecting a single lesion in one cortical area in schizophrenia patients. In fact, to take this line of reasoning further, based on the available data, we might not expect even a particular dysfunction (i.e., working memory) to be present in all schizophrenia patients, especially if the disorder is complex and heterogeneous.

Goldman-Rakic and Selemon state the commonly cited belief that evidence of prefrontal cortical dysfunction is “overwhelming” in schizophrenia patients. But just how overwhelming is this evidence, and are there equal levels of evidence for ventral striatal, lenticular, or temporal lobe dysfunction in schizophrenia? First, many of the original positron emission tomography findings that supported the hypofrontality hypothesis of schizophrenia were most compelling when anterior-posterior activity ratios were examined. One could say that these data support a “hyperoccipitality” hypothesis of schizophrenia. Also, a linchpin of the working memory/frontal connection is the body of cited imaging and neuropsychological studies. Still, when we conducted an extensive imaging study in outpatients, we found magnetic resonance imaging (MRI) evidence of volumetric abnormalities in frontotemporal and lenticular structures (Jernigan et al. 1991).

In a related study, schizophrenia patients had widespread neuropsychological deficits when a comprehensive Halstead-Reitan battery (Reitan and Wolfson 1985) was administered, including the Wisconsin Card Sorting Test (WCST; Heaton 1981)—commonly but probably inaccurately cited as somehow uniquely tapping dorsolateral prefrontal cortex (DLPFC) function. In fact, the WCST was a “middle of the road” test (14th out of 27 tests) for discriminating schizophrenia patients from a large cohort of normal controls (Braff et al. 1991). All of this leads us to be quite uncertain about the “overwhelming” evidence of DLPFC dysfunction in schizophrenia, especially if such abnormalities are viewed as being somehow unique or singular to the schizophrenia patient.

It seems clear from the Goldman-Rakic and Selemon article that additional independent evidence for dysfunction of the DLPFC and related working-memory abnormalities will be extremely important for our ongoing understanding of schizophrenia. What needs to be further defined are issues of DLPFC/working-memory dysfunction at the boundaries of schizophrenia, as well as any critical “extra” factors that may tip the DLPFC/working memory-impaired individual into the maelstrom of a serious psychotic disorder. Is this sequence of events related to the developmental timing of the DLPFC dysfunction, to the extent of the putative underlying lesion, or to both? Given the productivity of the Goldman-Rakic laboratory, these and many other answers will no doubt be forthcoming, but they must also be addressed through functional magnetic resonance imaging (MRI) and animal-model studies.

Jones focuses on thalamic and brain development and answers questions as to the timing and extent of neuropathology in schizophrenia. Clinical correlates and issues of heterogeneity/boundary populations are emphasized much less. A strength of this approach is that it is focused and singular in examining thalamic cell loss and at least raises the issue of whether this thalamic cell loss is primary or secondary to damage in cortical or other subcortical pathways. Although the clinical sequelae of such thalamic cell loss are not specified in great detail, there is an almost poetic reference to “loss of thalamic cells and/or corticothalamic inputs [that] could lead to disintegration of thought processes by failure in functional brain states dependent on collective oscillation of large
ensembles of cortical and thalamic neurons” (Jones 1997, this issue, p. 483).

The crux of this argument appears with the concept of vulnerability and discussion of a loop model of thalamocortical integration. An obvious next step in this work would be to specify how the developmental timing and extent of thalamic pathology relate to the diverse findings that Jones reports. For example, can a compelling case be made for a primary thalamic developmental abnormality resulting in the hippocampal and nucleus accumbens (Pakkenberg 1990) cell diminution cited by Jones?

A great strength of the Jones approach is the assertion that alterations in connectional patterns lead to activity-dependent changes in gene expression with somewhat and as yet ambiguous, functional consequences. A major next step would be to probe for the functional consequences of early thalamic lesions (or other manipulations) in animal models of disrupted cognitive functions in schizophrenia. Alternatively, coherence measures on functional brain imaging (Wu et al. 1990) may allow us to probe the integrated array of activity seen in disparate but connected areas of the whole, living primate brain.

Graybiel’s article is perhaps the least schizophrenia-dependent presentation. Still, her emphasis on the illness as a circuit disorder of activity-dependent loops is based on extensive literature. Graybiel extends her own pioneering efforts on understanding subcortical functioning into territory discussed by Penny and Young (1983), Alexander et al. (1986), Mogenson (1987), and Swerdlow and Koob (1987), and more recently by Baxter et al. (1992) (in the context of obsessive-compulsive behavior). “Loop” models ascribe function and dysfunction as a series of interconnected brain regions; these models are consistent with the pathology reported at every level of limbic corticostrato-pallido-thalamic circuit loops in schizophrenia (Swerdlow and Koob 1987). Similar to models proposed by Gray et al. (1991), Graybiel’s “wiring diagrams” attach particular psychological functions to these circuit elements.

Graybiel adds unique insights, particularly with regard to striatal connections and infrastructural organization. For example, she challenges a commonly held belief that assigns the basal ganglia into a “rote” or subsidiary role and takes the position that the basal ganglia directly access the thalamus and set the tone for the functional state of thalamocortical transmission. Graybiel’s emphasis on the basal ganglia as loop generators with connections to motor and motivational circuits ablates the old “subcortical dualism.” This view also points to an understanding that the basal ganglia influence both dorsal motor and ventral motivational circuits, which are linked to the hippocampus with its cognitive and declarative memory function.

Perhaps the most speculative section of Graybiel’s article relates to the symptom correlates, where she suggests that “the basal ganglia may . . . participate in the development of motor and cognitive patterns that differentiate self from others . . . [and] could contribute to both the negative and positive symptoms of the disorder. Motivated, goal-directed behaviors could be disabled, and planning, ordered action repertoires, and recognition of self versus other disrupted” (Graybiel 1997, this issue, p. 465). In so doing, Graybiel echoes the considerable evidence linking basal ganglia pathology to cognitive and motivational deficits (Elliott et al. 1995; Swerdlow and Koob 1987).

The role of the basal ganglia in executive ego function and the formation of self-concept is another critical issue discussed in the relationship to the symptoms of schizophrenia and other neuropsychiatric disorders (Swerdlow 1996). There is ample evidence from subcortical disorders such as Huntington’s disease that the striatum is a critical regulator of self-awareness. Graybiel proposes a specific contribution of iterative activity within basal ganglia loops and cognitive “binding” to the formation of the self. The next challenge will be to develop operational measures to test these models in infrahumans and humans. At the least, Graybiel reminds us that, as our field barrels toward the sanctum of as-yet undiscovered “molecular space,” we cannot overlook the insights currently available by clearly superimposing the maps of known psychological and anatomical substrates of these disorders.

References
Elliott, R.; McKenna, P.J.; Robbins, T.W.; and Sahakian,


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