Neurobehavioral Studies in Schizophrenia: Implications for Regional Brain Dysfunction

by Raquel E. Gur, Ruben C. Gur, and Andrew J. Saykin

Abstract

The application of neurobehavioral methods to the study of brain function in schizophrenia can provide useful information on the neurobiology of schizophrenia. Standard neuropsychological batteries were designed to assess behavioral correlates of regional brain function. Methodological considerations in the application of these tests to schizophrenia are discussed. Although there is considerable evidence for both frontal and temporal lobe dysfunction in schizophrenia, the field is likely to advance further through the systematic study of brain function. A combination of neurobehavioral and physiological data obtained simultaneously is a promising avenue to pursue, and the behavioral imaging method is presented as an example of one approach to data integration.

Neurobehavioral data have been called upon to contribute in the search for brain regions that may be dysfunctional in schizophrenia. Neurobehavioral methods link behavioral measures to regional brain function using theories and hypotheses based principally on animal data, behavioral sequelae of brain injury, and clinical-pathological correlations. We will not review this literature but rather examine the problems facing investigators in the field and suggest possible directions. The focus will be on frontal lobe and temporal lobe function in schizophrenia from this neurobehavioral perspective.

Linking regional brain function with behavioral dimensions is accomplished by application of behavioral measures to patients with brain disease and, more recently, neurophysiological "activation" procedures. Each of these strategies has its inherent advantages and limitations, but together they can help describe how a behavioral measure is "mapped" in the brain. They all serve the aim of understanding how behavior is regulated by brain mechanisms and networks.

Clinical Neuropsychological Batteries

The clinical application of neuropsychological tests has usually involved the administration of a standard set or "battery" of tests. There have been two major methodological trends in the selection of measures in neuropsychological research with clinical batteries, including studies of schizophrenia. These have been referred to as the "fixed" and "flexible" battery approaches (Incagnoli et al. 1986). Fixed batteries include comprehensive sets of tests and are typified by the Halstead-Reitan (Reitan and Wolfson 1985) and Luria-Nebraska neuropsychological batteries (Golden et al. 1980). In contrast, the flexible approach (Benton and Hamsher 1976; Benton et al. 1983; Goodglass 1986; Milberg et al. 1986) usually involves a core battery plus additional sampling of selected functional domains that may be used to test specific hypotheses (Luria 1966; Goodglass 1986; Milberg et al. 1986). Either approach permits comparison of performance of patients with schizophrenia to that of patients with other brain disorders.

Reprint requests should be sent to Dr. R.E. Gur, Neuropsychiatry Section, Dept. of Psychiatry, University of Pennsylvania, 205 Piersol Bldg., Philadelphia, PA 19104.
Neuropsychological batteries include a broad range of behavioral measures (language, memory, spatial skills, abstraction, reasoning, and sensorimotor integration). These batteries were originally designed for the diagnosis and behavioral characterization of the effects of brain damage in neurological and neurosurgical populations. In such cases, regional brain dysfunction can be inferred from the pattern of deficit.

**Effects of Structural Lesions of the Frontal and Temporal Lobes**

Structural brain lesions typically affect a functional system (Luria 1966) or network (Mesulam 1981). Anterior lesions affecting the frontal brain system can disrupt most higher level cognitive operations by causing a disorganization of goal-directed behavior, particularly related to attentional processing and conceptual flexibility (Stuss et al. 1982; Goldberg and Bilder 1987; Goldberg et al. 1987; Perecman 1987). Often identified as “executive” deficits, impairment of this type can affect multiple processes. Psychometrically, these deficits appear on measures such as the Wisconsin Card Sorting Test (WCST; Grant and Berg 1948; Heaton 1981), Trail-Making B (Reitan and Wolfson 1985), and measures of verbal or figural fluency.

In contrast, temporal lobe lesions, particularly of the medial temporal lobe (MTL) region, which includes the hippocampus and amygdala, are associated with deficits in memory and learning of new information (Squire and Butters 1984). In humans, this has been most closely studied in the context of surgical treatment of medically refractory seizure disorders (Milner 1975). During the acute postoperative phase after left MTL resections, patients frequently show deficits in verbal memory for prose passages and in learning lists of information. The California Verbal Learning Tests (CVLT; Delis et al. 1983) and the Wechsler Memory Scale (WMS; Wechsler 1945; Wechsler 1958) are sensitive to these acute changes (Milner 1975; Saykin et al. 1989). Similarly, after right MTL resections, deficits have been observed in nonverbal memory for designs, faces, and musical sequences.

**Effect of Subcortical Lesions**

Subcortical systems have been implicated in a number of diseases in man (Ricklin and Levita 1969). The basal ganglia in particular have been examined in imaging studies of schizophrenia because of the dopamine-rich connections to the frontal lobes and pattern of activity which covaries with the patient’s pharmacological status. Perceptual-motor integration, fine motor skills, spatial ability, and procedural memory are putative neurobehavioral functions of the basal ganglia. There are present no neuropsychological tests that are pathognomonic for basal ganglia involvement. In spite of this absence of specificity, many tests tapping the above abilities appear sensitive to basal ganglia dysfunction.

**Clinical Neuropsychological Studies of Schizophrenia**

Neuropsychological batteries have been widely applied in studies of patients with schizophrenia. The results have generally demonstrated diffuse impairment as indicated by cognitive, perceptual, and attentional deficits, regardless of what instruments were used (Heaton et al. 1978; Malec 1978; Seidman 1983; Goldstein 1986; Levin et al. 1989; Saykin et al., in press). Across studies, patients with schizophrenia have performed poorly on complex cognitive and perceptual tests, particularly in such tests that pose high demands on information-processing systems involved in the maintenance of attention and the exercise of rapid psychomotor speed (Goldstein 1986).

**Regional Brain Function in Schizophrenia**

There have been multiple regional hypotheses in the neuropsychology of schizophrenia, and no dimension has escaped attention—anterior/posterior, left/right, and cortical/subcortical. The involvement of anterior brain systems, particularly the frontal lobe, has been suggested by deficits in higher level abstraction and mental flexibility on tests such as the WCST and the Halstead Category Test (Flor-Henry and Yeudall 1979; Flor-Henry et al. 1983; Berman et al. 1986; Weinberger et al. 1986, 1988; Goldberg et al. 1987). The involvement of the left hemisphere has been implicated by deficits in verbal cognitive functions, such as low Verbal IQ relative to Performance IQ and impairment on language tests (Andreasen 1979a, 1979b; Andreasen and Grove 1979; Flor-Henry and Yeudall 1979; Newlin et al. 1981; Silverberg-Shalev et al. 1981). Subcortical and cortical dysfunction has been implicated by studies of attention and information processing (Minsky 1977, 1986). The extensive interconnectivity between the frontal lobes and the diencephalic limbic and reticular structures makes subcortical systems...
potential sites for the disruption of attentional processes through impaired selective gating of information (Skinner and Lindsley 1973). Mesulam (1981, 1985) has proposed a neural network for attention, which involves parietal, temporal, and frontal cortex as well as the cingulate gyrus and subcortical “limbic” regions. Attentional deficits, also noted in genetic studies of children of patients with schizophrenia, may provide a biological marker (Nuechterlein and Dawson 1984; Erlenmeyer-Kimling et al. 1989).

Methodological Limitations

There were numerous methodological problems in early psychometric studies (Heaton and Crowley 1981). Also, the conceptual basis for applying neurobehavioral methods was often superficial (e.g., an attempt to separate patients with “functional” schizophrenia from those with organic brain dysfunction). The general finding has been that the level of performance of schizophrenic patients falls between that of patients with known structural brain lesions and control samples.

The interpretation of the obtained deficits is complicated, however, by a number of psychometric problems, particularly the formation and analysis of quantitative profiles and the mapping of these profiles onto regional brain systems. As is evident, both frontal lobe functions including abstraction and attention and temporal lobe functions including learning and memory are impaired in schizophrenia; but this is a part of the general impairment that spares only a few simple functions. The question becomes how to test which function is differentially impaired (Chapman and Chapman 1989) and what are the implications of such differential impairment for hypotheses on regional brain dysfunction.

This is a complicated undertaking for several reasons. To establish that function A is differentially impaired, it is necessary to administer not only a test for function A, but the same sample has to receive tests for all other candidate functions as well as measures of general ability. This raises the logistical demand to tread carefully on a tightrope balancing the need for comprehensive evaluation against what is practical for a patient. Furthermore, as Chapman and Chapman (1989) emphasized, the various measures must have comparable reliability and task difficulty for normal subjects. Otherwise, we can be misled to infer that patients are impaired in test A and not B if we find a significant effect for A and not for B, when the only reason for this finding is that test A is more reliable and hence more sensitive to effects of pathology.

Another dilemma is how to deal with education. It could be argued whether education correlates with brain anatomical or metabolic measures, but without doubt education is an important factor in evaluating neuropsychological test performance. When studying the effects of a focal brain disease acquired late in life, such as a stroke, it makes sense to balance patients and control subjects for educational attainment. On the other hand, schizophrenia is a developmental disease affecting individuals while they are in the midst of achieving their educational goals and directly interferes with their attainment. Because reduced educational attainment is a part of the syndrome, it does not make sense to equate patients and controls for education. Indeed, matching patients to controls on education constitutes a “matching fallacy” (Meehl 1970). A more appropriate variable to use for balancing the samples is parental education. The effects of education do need to be examined, however, and in some cases partialed out, to interpret differences between patients and controls.

Finally, it is important to bear in mind that the disease itself affects behavior on many levels other than the cognitive performance assessed by neuropsychological testing. The patient’s motivation, cooperation, psychotic symptoms, and treatment must all be considered.

We have attempted to address these issues through two avenues. First, we examined the functional characterization of deficits in an unmedicated sample (Saykin et al., in press). Second, we began to perform regional analyses of the neuropsychological data using an algorithm for topographic display and analysis of the test scores (Gur et al. 1988a, 1988b, 1990).

Functional Analysis of Deficits

We have applied a battery that measures a range of behavioral functions and implicated brain regions. From this battery it is possible to test the hypothesis of frontal relative to temporal lobe impairment by contrasting performance of the same patients on the functions associated with these brain regions. Specifically, the frontal lobe hypothesis will predict that patients are more impaired on the WCST than on the memory and learning tests, whereas the temporal lobe hypothesis will predict the reverse.

In a sample of 36 patients and 36 normal controls, we found that
patients were impaired both in abstraction (WCST) and memory tests. The impairment in memory and learning, however, was significantly worse than the impairment on the WCST. This effect, which supports a selective temporal lobe deficit in schizophrenia, remained when variables that might affect performance were considered in the statistical analysis. Thus, it existed for both men and women, across the age range (which was 18-45), for all educational levels, and for both highly cooperative and less cooperative patients.

It is still of questionable validity to conclude on the basis of this effect alone that the temporal lobes are differentially affected in schizophrenia whereas the frontal lobe is not. How do abstraction and memory compare with other functions? Conceivably both could be superior or inferior to the general level of performance. Therefore, we compared each to the other functions using a profile analysis. We found that abstraction was significantly better in patients relative to their average neuropsychological performance, whereas memory and learning were significantly worse than all other functions.

But even this strong form of support for the temporal lobe hypothesis relative to the frontal lobe hypothesis does not settle the issue of identifying specific regional brain dysfunction. The memory deficit could be ubiquitous and robust and may indeed point to temporal lobe dysfunction, and yet a constellation of other deficits can suggest other brain regions that may be implicated. There is need for a systematic evaluation of the combined set of neuropsychological data in relation to current theory of brain-behavior regulation. This will permit the identification of impaired neural networks. The nature of the brain disease we expect to find in schizophrenia is not a focal lesion with circumscribed boundaries and effects, but more likely one involving neurotransmitter systems with distributed physiological effects. Given that, it would be a mistake to find an area of greatest abnormality and declare it as the "site of schizophrenia." Rather, we must continue to search systematically for networks. This requires the joining of neuropsychological test scores with hypotheses linking them to the integrity of all regions of interest. We have developed an algorithm, "behavioral imaging," which attempts to accomplish this task by providing standard regional interpretation of neuropsychological measures.

Behavioral Imaging

The process of testing neurobehavioral theories can be helped by quantification of hypotheses concerning regional brain involvement in the regulation of behavior. We have proposed an algorithm that applies such a quantification to standard neuropsychological test scores (Trivedi and Gur 1987, 1989). The algorithm yields values for specific brain regions, which reflect the prediction that the region is dysfunctional given a pattern of neuropsychological scores. The regional values can also be presented topographically to facilitate comprehension of the spatial distribution of implicated brain areas.

The algorithm applies weights for each test score x region, reflecting the rated sensitivity of the score for a lesion in this area. The weights are multiplied by the scores obtained, and the intensity of a pixel is a function of the summed product normalized for the sum of weights assigned for a given region (Gur et al. 1988b). The weights were supplied by expert neuropsychologists (Gur et al. 1990) and showed interrater agreement and intrarater reliability.

Initial testing of the algorithm in clinical cases and populations was encouraging (Gur et al. 1988a, 1988b). There was consistency between the "behavioral images" and the location of lesions in patients with unilateral cerebral infarcts (figure 1).

The topographic displays showed correspondence with clinical, computed tomographic, and metabolic data, and they were congruent with the clinical interpretation of the neuropsychological assessment. Patients with focal ischemic lesions have been a major source of information on the validity of neurobehavioral theories. This reflects the circumscribed nature of many infarcts and their tendency to occur in adult, hence neurally mature, brains. We are currently evaluating the algorithm in other clinical populations with focal and diffuse brain disorders.

As a preliminary step toward the application of this approach to schizophrenia, where diffuse brain dysfunction is expected, we are performing simulation studies to optimize the performance of the algorithm in focal diseases, particularly of the frontal and temporal lobes, which have been strongly implicated in schizophrenia. Figure 2 shows simulations of impaired performance on the WCST (a) and the CVLT (b).

As can be seen, all four experts place impaired performance on the WCST as reflecting primarily frontal lobe dysfunction and impaired performance on the CVLT as reflecting...
Figure 1. A behavioral image of a patient with a stroke in the distribution of the right middle cerebral artery.

Darker colors indicate greater impairment. Data are presented using the weights provided by each of the experts: Drs. Arthur Benton, Edith Kaplan, Harvey Levin, and Andrew Saykin. A top view is presented on the right and a lateral view of the left hemisphere (top) and right hemisphere (bottom) on the left.
Figure 2a–b. Simulation images for (a) the Wisconsin Card Sorting Test (perseverative responses) and (b) California Verbal Learning Test (total trials 1-5) for each expert.

Darker colors indicate ratings of greater sensitivity of each test to dysfunction in the region of interest.
primarily left temporal lobe dysfunction. A "behavioral image" of schizophrenia must await further verification and optimization of the algorithm.

Future Directions

In our search for brain mechanisms that may explain the pathophysiology of schizophrenia, neurobehavioral studies can play an important role. The neuropsychology of "mental" disorders is a relatively new field, and there is an opportunity to orient its course. There should be a generally accepted "core" procedure for obtaining neuropsychological data. The individuals administering this battery can be technologists, but they have to be supervised by qualified neuropsychologists and trained in the specialized application of neuropsychological tests to psychiatric populations. The main purpose of neuropsychological tests is not for differential diagnosis of schizophrenia. Its purpose is to assess and characterize the pattern of behavioral impairment and preserved abilities. It quantifies the pervasiveness of impairment and can help determine the degree of brain dysfunction. This is important for assessing progression, medication effects, and rehabilitation, for example.

In addition to the application of test batteries, such as those described above, there is potential for advancing the field using combined behavioral and physiological studies. The activation paradigm appears to be a more appropriate model for schizophrenia. It provides physiological data when individuals are engaged in neurobehavioral tasks that are known, in normal subjects, to activate specific brain regions. This paradigm has been applied to the study of schizophrenia to examine the laterality hypothesis (Gur et al. 1983, 1985) and the frontal lobe dysfunction hypothesis (Berman et al. 1986; Weinberger et al. 1986). It is only the beginning of what could become a productive line of research that will generate a more refined understanding of the neurobehavioral substrates of schizophrenia.

References


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The Authors

Raquel E. Gur, M.D., Ph.D., and Ruben C. Gur, Ph.D., are Professors of Psychiatry and Neurology, and Andrew J. Saykin, Psy.D., is Assistant Professor of Psychiatry, Neuropsychiatry Section, Department of Psychiatry, University of Pennsylvania, Philadelphia, PA.