Probing Prefrontal Function in Schizophrenia With Neuropsychological Paradigms

by Terry E. Goldberg and Daniel R. Weinberger

Abstract

In a recent series of studies we have attempted to clarify the nature of intellectual impairment in schizophrenia, and, in particular, how patterns of dysfunction implicate specific neural systems. First, we found that acute psychotic adolescent patients displayed the same pattern of IQ scores (Performance < Verbal) as adult chronic schizophrenic patients. We explored this deficit in problem solving by studying the performance of schizophrenic patients after receiving concrete and explicit instructions on how to do the Wisconsin Card Sorting Test, a task thought to be mediated by prefrontal cortex. We then studied the differential impact such a deficit in problem-solving strategies might have on a task thought to elicit both cognitive (prefrontal) and procedural or motor-skill (basal ganglia) processing. Procedural components appeared to be relatively more intact. We also addressed schizophrenic patients' ability to learn in other (extrafrontal) cognitive domains through verbal memory tasks and block design puzzles. Learning occurred under both conditions. We believe the overall pattern of deficit implicates primarily prefrontal neural systems, though a number of other neuropsychological functions are yet to be surveyed.

In the series of studies reviewed here, we delineate our preliminary efforts to clarify the nature of the intellectual impairment, i.e., the dementia, in schizophrenia. In our view, cognitive deficits are fundamental aspects of schizophrenia that may account for much of the long-term social disability associated with the disorder. As objective evidence has accumulated and pointed to brain dysfunction and structural brain pathology in schizophrenia, it has become possible to test the validity of intellectual impairment. Instead of comparing patients to controls on standardized test batteries, we primarily have pursued specific questions about the nature and course of cognitive deficits, about their relationship to brain pathology, and about how patterns of cognitive dysfunction implicate specific neural systems. Ultimately, we would like to know what areas of brain work and what areas do not. In particular, we have focused our interest upon the frontal system and its relation to subcortical diencephalic and basal ganglia systems of memory.

Neurocognitive Studies

Since recent studies have suggested that structural brain pathology exists at the onset of illness and is static in schizophrenia thereafter (Weinberger 1984), it is important to consider whether cognitive deficits show a similar pattern or whether they develop as the illness progresses. To examine the timing of intellectual deficit in the course of psychosis, we studied a sample consisting of 39 psychotic adolescent subjects (Goldberg et al., in press). Nearly all had been hospitalized for the first time. By focusing on adolescent patients at their first break, we hoped to reduce the influence of such confounding variables as lengthy neuroleptic treat-

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ment, lengthy hospitalization, and the duration of the disease process itself. Forty-one nonpsychotic adolescent psychiatric inpatients served as controls. All subjects were administered the Wechsler Intelligence Scale for Children-Revised as well as other academic and visual-motor tasks. Both groups were of low socioeconomic status. Full Scale IQ was below average. Performance IQ, however, was significantly lower in the psychotic group (72 vs. 93). It was notable that the IQ pattern in adolescent psychotic patients at a very early stage in their illness was similar to the pattern that has been displayed by chronic adult schizophrenic patients (Chelune et al. 1979; Kolb and Whishaw 1983; Lawson et al. 1988). It may be that performance subtests of the Wechsler (e.g., picture completion, picture arrangement, block design, object assembly, digit symbol) place a greater premium on the ability to solve novel problems in a nonroutinized manner. These results are consistent with the work of others (Foulds and Dixon 1962) and suggest that characteristic intellectual deficits seem at the very least to be present at the onset of the disorder, though it has been suggested that they are nonprogressive for many years thereafter (Klonoff et al. 1970). If this latter point is correct, it would parallel what is suspected about the neuropathological changes, namely, that they are static (Illowsky et al. 1988).

As a group, schizophrenic patients are known to do poorly on the Wisconsin Card Sorting Test, often thought of as the sine qua non of frontal lobe tasks. To investigate problem-solving skills assessed by the Card Sort, as well as the role of such state variables as attention, cooperation, and motivation, we examined the potential reversibility of this deficit (Goldberg et al. 1987). Three groups of patients with schizophrenia (n = 44) were administered the Wisconsin Card Sorting Test on six consecutive occasions. Two of the groups received incremental information on how to do the test in counterbalanced order. They were told the nature of the categories that could be matched and the nature of set shifts. Both groups then received explicit card-by-card instruction. A third group was administered the test in standardized fashion. Except while receiving card-by-card instruction, patients performed poorly on this test, regardless of group or occasion. While the patients’ performance could be normalized when they received explicit card-by-card instruction, they immediately returned to their poor baseline performance when structure was withdrawn. The deficit did not appear to be generalized as patients were able to learn word lists on a memory task. Moreover, they were not globally demented on Mini-Mental State examination.

Patients often behaved in a manner similar to patients with frank frontal lobe injuries; they displayed a dissociation between thought and action and were "impervious to error information" (Teuber 1972). Failure did not result from not knowing, but rather from not doing. Patients did not use information they obtained from their environment to change their behavior. We believe this failure may have broader implications for independent social behavior in that it may predict the inability of schizophrenic patients to use information from past experience to guide current behavior and shape future plans.

We (Goldberg et al. 1988a) extended our studies of problem solving to the administration of an artificial intelligence/skill-based/brain-teaser task in order to separate two possibly independent components of performance. One component is based on planning and reasoning; it involves surveying the nature of the problem and developing mental strategies to perform the task (and perhaps is mediated by prefrontal cortex). The other component is based on learning motor skills or procedures. The Tower of Hanoi, a puzzle in which disks must be moved from one peg to another, has been used to eliciting learning in amnestic patients who display markedly impaired memory for lists of items. Because the Tower may involve learning a skill, it has been thought to reflect procedural memory, as opposed to declarative memory for lists of items, including places, faces, and words. It is unclear what neural systems may mediate performance on the procedural aspect of this task, though the basal ganglia have been implicated in similar tasks (Mishkin and Petri 1984).

We administered the Tower to patients with schizophrenia. The patients required many more moves and trials per version than did normal control subjects, but they were usually able to reach a solution on the simple three-disk and even the more difficult four-disk versions of the task. It seemed that although patients with schizophrenia were once again not able to marshal systematic problem-solving strategies, they learned the task in an incremental manner, i.e., procedurally. Thus, in this paradigm, basal ganglia functions may be relatively more intact than frontal cortical functions.

Next, we wished to study more
closely learning in other cognitive realms in order to address the question of diffuse versus regionally selective deficits and to assess function in limbic neural systems. (Studies of IQ and the Tower of Hanoi test do not directly address declarative learning capacity for words, things, or episodes in schizophrenia.) We (Goldberg et al. 1988b) administered the Selective Reminding task to 31 schizophrenic patients to assess memory learning curves. The Selective Reminding task measures various components in the acquisition, recall, and recognition of new “declarative” information. A list of 12 words was repetitively presented to each subject 12 times. After each trial, subjects were reminded only of words they missed and then asked to recall all the words on the list. We found that schizophrenic patients were able to learn new verbal material. The learning curve indicated robust increases in performance over the 12 trials, though their absolute level of recall was below that of normal control subjects. Moreover, performance in recognition memory, in which recall factors were minimized, indicated that schizophrenic patients were able to acquire new information to a much greater degree than they were able to retrieve it. This seems consistent with our clinical experience, in that patients often fail to remember unless prompted. They know but need to be reminded.

From another standpoint, recall problems have been studied in patients with frontal damage. Learning curves of patients with lesions of the frontal convexity (Sass et al. 1987) were very similar to those noted in our patients. In fact, Jetter et al. (1986) found that patients with frontal damage displayed markedly impaired delayed recall compared to patients with extrafrontal lesions, while recognition performance was not significantly different between the groups.

We also found that recall scores, but not recognition scores, were highly correlated with a group of Brief Psychiatric Rating Scale symptoms that involve blunted affect, motor retardation, disorientation, and emotional withdrawal. These items may reflect loss of drive, motivation, and engagement with the environment, and anergia and result in “forgetting to remember” (Hecaen and Albert 1978), a characteristic of frontal as well as “subcortical” dementias. From a functional neuroanatomical viewpoint, our finding of the relative integrity of recognition memory suggests that those neural systems involved in this function, such as medial temporal and diencephalic structures, as well as orbitofrontal regions, may not be markedly dysfunctional in schizophrenia. In this context, relatively selective impairment in recall memory again implicates dorso-lateral prefrontal cortex, consistent with the results of the Wisconsin Card Sorting Test and Tower of Hanoi studies.

We (Goldberg et al. 1988a) also attempted to teach patients how to do another task they often find difficult: the Block Design subtest from the Wechsler IQ test. When instruction was focused on cognitive strategies involving attention to the “inner edges” of the designs, patients were not only able to master construction of items they previously failed but also passed more difficult succeeding constructions. These results indicate that patients’ deficits on this “extrafrontal” test, thought to involve posterior cortical regions (Lezak 1976), reflect performance factors that are not related to competence or ability. These results are not indicative of diffuse or generalized dysfunction.

Thus, of the four studies that assessed aspects of learning, the investigation using the Wisconsin Card Sorting Test provided the clearest evidence of nonremediable performance. It is the only selectively prefrontal test.

Comment

These studies have attempted to clarify some of the parameters of cognitive dysfunction in schizophrenia. We have focused on the question of differential deficits and on whether the deficits implicate dysfunction of diffuse or regional neuronal systems. We have been especially interested in working out the integrity of behavioral functions thought to be mediated by prefrontal areas, the diencephalon and medial temporal lobe, and basal ganglia. The Wisconsin Card Sorting Test, often considered to be the most sensitive test of frontal lobe dysfunction, elicited impairment in schizophrenic patients with regularity. We believe this deficit was both profound and “real.” It is typical of that seen in patients with coarse brain disease of the prefrontal cortex. In contrast to their performance on “prefrontal” tasks, schizophrenic patients displayed a robust learning curve on a repetitively presented word list, thus indicating that their cognitive deficits are not generalized. Recognition memory, which is thought to involve orbitofrontal-amygdaloid-hippocampal-thalamic circuitry, was relatively intact. Recall scores, however, were much lower and found to be related to a
psychiatric symptom factor that has been termed anergia. This profile is similar to that of patients with dorsolateral prefrontal cortex lesions who are apathetic, display poverty of planning, and recognize material at a markedly higher level than they recall it. On a task thought to involve both problem solving (mediated by prefrontal cortex) and procedural (mediated by basal ganglia) components, i.e., variants of the Tower of Hanoi, patients with schizophrenia were able to solve the puzzles, though it took them more moves to do so. We believe this pattern may also reflect relatively greater compromise in a prefrontal system that generates strategies than in the basal ganglia system used to set and maintain chains of action.

Even at a very early stage in the disorder, baseline intellectual performance is typified by impairment in problem-solving abilities. This pattern of performance on intelligence tests (Performance IQ < Verbal IQ) has been associated in a generic sense with brain damage. It is nonspecific and nonlocalizing; it may reflect a convergence of generalized factors, as well as more specific executive deficits; and it is typical of patients with chronic schizophrenia. The coterminance of these IQ patterns is consistent with the notion that intellectual dysfunction is not markedly progressive in schizophrenia. If this is correct, then the course of neuropsychological deficits would parallel the known course of neuropathological findings. This issue, however, requires further prospective investigation.

Note that we have concentrated our preliminary studies on prefrontal functions. We have not systematically surveyed all possible cognitive functions and the neuroanatomic substrates that mediate them. Thus, for example, many functions of posterior cortex have not been examined. We have recently started investigating (left) parietal function through lip reading and certain motor-sequencing tasks. Our early experience suggests that some of these functions may be impaired as well. Since posterior association cortices and prefrontal cortex are intimately linked, it may be difficult to distinguish which deficits are primary and which are secondary. These are ongoing and future research challenges.

In conclusion, while it is reasonable to assume that the symptoms that give rise to disability in schizophrenia are manifold and may differ from individual to individual, one important and quantifiable aspect likely involves cognitive impairment, especially that which compromises organizing one’s daily schedule, anticipating events, and goal-directed behavior. This perspective may have implications for treatment as well, be it psychoeducational or pharmacological. Structure, incremental construction of routines, and concrete direction (Bellack et al. 1987) may prove particularly useful in the former approach, while drugs that affect prefrontal neurochemical systems may be efficacious in the latter approach.

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