Memory Impairment in Schizophrenia: Perspectives from Psychopathology and Pharmacotherapy

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Objective: To describe the concept of memory impairment in schizophrenia and the clinical implications of this concept in terms of patient assessment and neuroleptic drug use.

Method: Narrative literature review.

Results: Individuals suffering from schizophrenia normally exhibit some degree of memory impairment. Recent work in psychopathology indicates that the impairment is comprehensive, involving the sensory, short-term, and long-term memory stores. Memory impairment appears to be a primary symptom of the disease, and its underlying causes are likely organic. A number of medications, however (for example, traditional neuroleptics and drugs that have pronounced anticholinergic activity), may cause or exacerbate impairment. In particular, anticholinergic agents used to treat extrapyramidal symptoms, a common complication of neuroleptic drugs, appear to have a deleterious effect on memory.

Conclusions: Memory impairment is an important consideration in the clinical assessment and management of patients with schizophrenia. The use of atypical antipsychotics like risperidone appears to have no impact on memory function; because risperidone is associated with a low incidence of extrapyramidal side effects, it can obviate the need for anticholinergic medications—thus offering greater hope of nondebilitative intervention. The advent of medications that are safer (on cognition) could also lead to generally better outcomes by facilitating compliance with drug regimens and rehabilitation programs.


Key Words: schizophrenia, cognition, atypical neuroleptics, risperidone, clozapine, seroquel, memory

Impairment of memory function in schizophrenia has been demonstrated in at least 2 dozen studies conducted over the past 20 years (1). The deficit is apparent whether the investigative paradigm is drawn from experimental psychology or involves such "ecologically valid" measures as the Rivermead Behavioral Memory Test (2). Furthermore, the impairment appears not to be selective, but rather to involve each major subcomponent of the memory system. Clinically, impairment of memory is now accepted as one of the major disabilities associated with schizophrenia. Because the impairment is a relatively stable characteristic of the disease, it also serves as a reliable predictor of long-term disability and treatment outcome (3–6).

Despite the growing literature in this area of schizophrenia research, a number of important issues remain unresolved, particularly concerning the effect of pharmacological treatment on memory function. While the adverse effects of anticholinergic medications are by now well established (7–11), the role of the various neuroleptic agents used to control psychosis is less certain. There is some evidence, although it is inconclusive, to suggest that typical neuroleptics like haloperidol may further exacerbate memory dysfunction (12). Preliminary studies involving more recent treatment modalities (for example, the antipsychotic risperidone [p S35]), suggest that these newer drugs offer a less-debilitating alternative to older therapies (13).
Lessons from Psychology

Modern psychology has made an enormous contribution to our understanding of memory function in schizophrenia. Testing procedures originally designed to investigate memory in healthy subjects have provided a valuable tool-kit for examining its breakdown in psychiatric populations. The various techniques now available have allowed researchers to pinpoint, with remarkable accuracy, precise domains of cognitive disturbance. Much is known, therefore, about the pattern of memory breakdown in schizophrenia. A comprehensive review of work in this important area was recently cowritten by the present author with I Lussier (12); in the rest of this section, the principal results of this review are summarized.

Sensory Memory

Relatively few studies have directly addressed sensory memory function in schizophrenia. The most compelling finding involves a masking paradigm in which the presentation of a target stimulus is followed immediately by a second stimulus, the mask. The length of exposure to the target is gradually reduced until it is no longer acknowledged by the subject. In healthy controls, the threshold of perception occurs at about 100 ms. In patients with schizophrenia, the threshold is 2.5 times greater (14). Another procedure that has been employed to examine sensory memory requires the subject to report the number of lines briefly presented in 1 of 3 orientations—horizontal, vertical, or unaligned—and in 1 of 2 conditions—with or without visual interference. In work conducted by Place and Gilmore (15), subjects with schizophrenia performed less well than normal controls on the interference task, as expected. Surprisingly, however, the schizophrenic group outperformed the normal group in the noninterference condition; moreover, unlike the control group, they showed no evidence of deteriorating performance over the course of the test. The investigators surmised that among the controls, performance was impaired by the formulation of perceptual organization strategies that, although relevant to the immediate task, were inappropriate because they interfered with subsequent test items. If this hypothesis is correct, the subjects with schizophrenia failed to generate organization strategies of any sort.

Work in this area would thus suggest that, while individuals with schizophrenia exhibit some impairment of sensory memory, this deficit involves not the actual formation of sensory impressions, but rather their immediate processing.

Short-Term Memory

Studies addressing short-term memory in patients with schizophrenia have produced somewhat inconclusive results. Deficits have generally been reported for delayed response tasks, which measure the maintenance of visuospatial representations over time. Park and Holzman (16), for example, found that in a task involving visual stimuli, subjects with schizophrenia performed less well than either manic-depressive or control subjects. In tests of serial recall, however, results have been mixed (16,17), as they have been for tasks involving the Brown-Peterson interference test (18).

Long-Term Memory

Studies of long-term memory often employ an explicit-recall task, which requires the retrieval, with or without cueing, of previously learned material. Subjects with schizophrenia consistently show a performance deficit on such tasks, whether the material in question is verbal or nonverbal (19,20). Moreover, recall is impaired not only for recently learned items, but also for older “retrograde” material (21,22). Schwartz and others (23), for example, have shown that among those with chronic schizophrenia, there is a disturbance of the temporal ordering of information, suggesting a possible disturbance of episodic memory.

In comparison with recall tasks, performance on recognition tasks tends to be relatively more preserved in patients with schizophrenia, although scores within the normal range are not necessarily attained (19,24). Such spared performance is perhaps not surprising, given the less elaborate search strategies demanded by the recognition task paradigm. There is thus some question as to whether these results are indicative of differential functioning of the underlying neural systems or whether they simply reflect psychometric tasks of unequal difficulty (25).

Impairment of long-term memory may also be demonstrated in tasks requiring the implicit recall of previously learned material. Studies have generally shown that implicit recall is preserved in schizophrenia. Previous work conducted with I Lussier (26) found that implicit memory, as measured in a stem-completion task, was intact in both drug-naive and neuroleptic-treated patients. Some studies, however, have produced contradictory results (27).

Semantic memory is also known to be impaired in schizophrenia. Although the performance deficit is relatively minor, it has been demonstrated repeatedly and in a variety of paradigms, from tests of semantic fluency (28) to tasks involving naming, word-to-picture matching, and definition (29,30). Most investigators, however, have attributed the functional deficit not to the semantic store itself, but rather to some disturbance of semantic processing. Studies of semantic priming in schizophrenia tend to support this interpretation. In a study using a lexical decision task, for example, Henik and others (21) found that, by lengthening the interval between prime and target, a normal priming effect could be induced in subjects with schizophrenia. This result suggested to the authors that the semantic network is preserved in schizophrenia, but that its activation is somehow impaired.

Studies of procedural learning in schizophrenia have tended to show that this component of the memory system is relatively unimpaired (31). Goldberg and others (32), for
example, found similar learning rates for patients and controls on a 4-disc version of the Tower of Hanoi. It has been noted, however, that the characteristic learning curve of subjects with schizophrenia is jagged, rather than smooth, suggesting an abnormal pattern of learning. Furthermore, the establishment of an automated cognitive routine appears much later in individuals with schizophrenia than in controls (12).

The evidence presented here provides a compelling picture of memory impairment in schizophrenia. Functional deficits have been demonstrated in each of the 3 major subsystems—sensory memory, short-term memory, and long-term memory. Nonetheless, the picture remains essentially descriptive: it illustrates the outward character of memory impairment, but it fails to illuminate its underlying nature. Two important questions thus need to be addressed: first, is memory dysfunction a primary cognitive deficit, or is it secondary to other disturbances; and second, is it rooted in demonstrable neuropathologies? We turn to these issues in the following sections.

Cognitive Basis of Memory Dysfunction

Some authorities maintain that the impairment of memory observed in schizophrenia is secondary to other, more fundamental cognitive deficits. Oltmanns (33), for example, has argued that the severe distractibility known to characterize schizophrenic behaviour interferes with normal cognitive functioning. By contrast, Nuechterlein and Dawson (34) have suggested that deficits of sustained and focused attention underlie the poor memory performance of patients with schizophrenia. Still others point to deficiencies of arousal, motivation, and higher executive function as primary sources of memory impairment (35–37). Although each of these variously implicated disturbances is demonstrably present in schizophrenia, it is doubtful that, whether singly or as a group, they can adequately account for the full range of observed memory deficits.

One argument in favour of this conclusion is that memory impairment in schizophrenia appears to occur independently of other functional deficits. For example, in a recent study, Gold and others (38) found that a majority of their subjects with schizophrenia scored less well on tests targeting memory function than they did on tests of general intelligence; in a significant portion of their cases, the full-scale IQ score was 15 or more points greater than the memory index. If memory impairment were secondary to other cognitive factors, such a discrepancy would not be anticipated.

The primary status of memory impairment may further be established through the application of statistical techniques to test-performance data. Kenny and Meltzer (28), for example, used an analysis of covariance to control for attention in a study of cognitive dysfunction in schizophrenia. Although they found evidence of impaired recall of both recent and remote material, this impairment was apparently independent of the observed attentional deficits.

Certain experimental results may also be invoked as evidence of the independence of memory impairment. One highly illustrative procedure exploits the distinction between effortful memory, which draws heavily upon attentional resources, and automatic memory, which does not. In recent work, Gold and others (39) reasoned that if attentional processes underlie deficient memory function, then subjects with schizophrenia should show greater variation from controls on tasks involving “effortful,” as opposed to automatic, memory. In a study of relatively chronic patients, however, they found that memory impairment was independent of the attentional demands of a particular task. This again suggests that memory impairment is an independent factor in schizophrenia. It should be noted that work conducted by Shoqueirat and Mayes (40), which involved patients with acute rather than chronic schizophrenia, did not replicate this result. Whether this is indicative of functional differences among schizophrenic types is uncertain.

On balance, the evidence appears to favour the interpretation of memory impairment in schizophrenia as a primary, rather than secondary, functional deficit. This conclusion should not be taken to imply, however, that the observed performance deficit is strictly and solely a reflection of memory dysfunction. There is undoubtedly a complex interplay among cognitive functions, and any processing defect, whatever its origin, must surely influence behaviour. The crucial point, then, is simply that there exists in schizophrenia an impairment of memory which cannot be accounted for exclusively in terms of other functional deficits.

Etiology of Memory Dysfunction

A separate but equally important issue concerns the etiology of memory impairment in schizophrenia. Although it has been argued that such impairment results principally from pharmacological treatment (41), the literature does not generally support such an extreme view: first, the evidence concerning the effects of medication is at best equivocal, and second, there is growing evidence of underlying neuropathologies.

Effects of Neuroleptics

The effects of the various medications used in the treatment of schizophrenia on cognitive functioning are uncertain. It is known, however, that cognitive function improves with clinical amelioration, and that this latter, in turn, may result from pharmacological treatment. At issue, then, is whether the remediation of cognitive function results directly from pharmacological intervention or secondarily from the improved clinical profile. The question has proven difficult to resolve, in part because, for reasons both practical and ethical, medication is not a variable that can be experimentally
controlled. Nonetheless, a small number of studies have attempted to sort out the various factors. Those which have addressed the specific case of memory have tended to produce somewhat inconsistent results. In one study, Cleghorn and others (42) found that patients treated with neuroleptics tended to show improved measures of verbal recall, but decreased measures of visuospatial recall. Landro (1), however, found no difference of performance on memory tasks when comparing medicated and nonmedicated patients.

The dose–response relationship is a complex issue. There was no correlation between serum neuroleptic levels and memory in the studies conducted by Tune (43) and Perlick (11). Taken together, the findings of these studies suggest that either anticholinergic or antiparkinsonian agents may produce long-term memory impairment measured with classical tasks which are correlated with serum anticholinergic levels. Another study (44) analyzed the relationship between drug dosage and measures of cognitive disturbances involving attention in treating patients with chronic schizophrenia. A correlation between high neuroleptic dosage and cognitive disturbances in these patients was observed. It is clear that more studies are needed to address this question (43–47).

A further difficulty in attempting to unravel the effects of medication on memory function is that many patients treated with traditional neuroleptic agents (for example, haloperidol) also receive anticholinergic medication for the treatment of extrapyramidal side effects. Moreover, a number of the therapies used in schizophrenia are known to produce pronounced cholinergic blockade. These include clozapine, thioridazine, mesoridazine, and chlorpromazine, as well as a number of tricyclic antidepressants (48). The deleterious effect of anticholinergic medications on learning and memory has been demonstrated in both normal and neurologically impaired populations (7). Nonetheless, in a recent study of monozygotic twins discordant for schizophrenia, Goldberg and others (49) concluded that the observed memory impairment in the affected twins could not result solely from the effects of anticholinergic medication. Significantly, the investigators found evidence of impairment of additional systems thought to be unaffected by anticholinergic activity. Moreover, the magnitude of impairment observed in 3 drug-free twins was judged to be “strikingly similar” to that of the remainder of the group. These observations led the authors to conclude that while the possibly adverse anticholinergic effects of medication could not be discounted, they were unlikely to account for the full extent of memory impairment.

In a review of 30 studies published since 1966 on the effects of neuroleptics on various cognitive and psychomotor tasks (50), King grouped the studies according to the cognitive effects reported: 10 studies indicated no neuroleptic effect on task performance, 6 reported a performance deficit, and 14 studies reported a positive effect, that is, an improvement in performance. The author offered several reasons for the discrepant findings. First, the eventual negative effects of neuroleptics are usually observed in subjects taking phenothiazine sedatives. Second, normal subjects are more prone to suffer the deleterious effects of neuroleptics than are schizophrenic patients. For example, in certain tasks assessing attention and vigilance processes, schizophrenic patients generally produce altered baseline or initial performances that improve once neuroleptic treatment has begun. In the same experiments, normal subjects instead see their baseline performance worsen. Finally, in King’s opinion, the differences observed among the studies reviewed are more a function of experimental conditions than of the cognitive functions targeted.

In another review, Cassens and others (51) reclassified 50 tasks used in 32 studies according to the cognitive parameters assessed by the different tasks. The effects of neuroleptics on these parameters were examined as a function of 1) the cognitive field targeted, 2) the duration of neuroleptic drug treatment, and 3) the dosage administered.

On the basis of the reclassification of the 50 tasks, Cassens concluded that neuroleptics can affect any of the following 6 major cognitive spheres: attention-vigilance (12 tasks), motor dexterity (7 tasks), abstract thought and problem solving (5 tasks), memory and learning (8 tasks), and verbal behaviour (6 tasks). These authors concluded that, among schizophrenic patients, the negative effects of neuroleptics are generally observed after acute drug administration and mainly in tasks calling into play vigilance, attention, and (most importantly) motor skills. In the case of prolonged treatment, the higher cognitive functions, with the exception of motor skills, are generally not affected. As for the beneficial effects of neuroleptics, these are usually observed after prolonged drug administration in sustained-attention and visuomotor tasks.

**Atypical Antipsychotics**

In view of the uncertain effects of anticholinergic drugs and the anticholinergic effects of traditional neuroleptics on cognitive function, there is considerable interest in the effect of the newer atypical antipsychotic agents that do not cause the severe extrapyramidal effects for which anticholinergics are prescribed (52). Clozapine is less likely than typical neuroleptics to cause clinically extrapyramidal side effects. One study, however, failed to find differences between clozapine and haloperidol or flupenthixol on several sensorimotor tests (53). Another found that clozapine significantly worsened visual long-term memory (49). Findings and interpretation are still mixed (53–55). Clozapine has been shown to release dopamine through in vivo microdialysis and to act as a cholinergic agonist (56). Usually, neuroleptics produce volume-increasing basal ganglia nuclei. This effect might be linked to the procedural learning impairment caused by the neuroleptic used. Clozapine has low D₂ receptor affinity and is able to produce a reverse effect (57). Recent work led by
the present author (p S35) investigated the effect of the drug risperidone on attention and memory in patients with schizophrenia. Risperidone is currently the only first-line, atypical antipsychotic that is associated with a low incidence of the extrapyramidal side effects for which traditional neuroleptics are notorious. This effect is dose-dependent at a dosage of 6 mg per day. A test involving 3 memory tasks was administered on 3 different occasions: at the onset of treatment and after intervals of 6 weeks and 6 months. The tasks consisted of a word- and digit-span test designed to measure short-term memory and 2 tests of long-term memory, one involving explicit recall, the other, implicit recall. No difference was found on any of the tasks over the 3 trial periods, suggesting that this novel treatment has no adverse effects on memory function. The average dosage of risperidone was 5.81 mg per day. Similar results have been reported by Goldberg (13), who found in a recent study that neither working nor long-term memory was impaired in clinical trials using risperidone. The same study found that clozapine, another atypical antipsychotic, had an adverse effect on both working memory and long-term visual memory.

Future Directions

Clearly, more studies are needed to determine the precise influence of various neuroleptics on the cognitive system. Such studies should take into consideration the pharmacologic properties of individual drugs, since receptor affinities may vary from drug to drug and yield significantly different effects on cognition. For instance, each neuroleptic agent exerts a different effect on both the dopaminergic and serotonergic systems, with its own affinities for the D₁, D₂, D₃, D₄, D₅, and 5-HT₂ receptors. In a recent study (58) comparing the effects of 2 drugs with markedly different receptor profiles (haloperidol and clozapine) on tasks involving procedural learning, patients on haloperidol demonstrated some degree of impairment in the performance of a mirror drawing task. This appears to indicate that haloperidol, but not clozapine, can induce a functional deficit in the striatum (51–58).

Future studies, such as those cited above, could lead to useful insights as to the potential advantages of the newer antipsychotics. For example, an agent like risperidone—which has a very high affinity for the 5-HT₂ receptor and quite a low affinity for cholinergic receptors—may have a sparing effect on various components of cognitive function.

Neuroanatomical Correlates

Work in neuropsychology has established the involvement of the temporal-hippocampal system in memory function (59). Subjects with left temporal lobectomy, for example, have been shown to exhibit poor story recall (61). If memory impairment in schizophrenia is a primary deficit with an organic basis, then anatomical or functional abnormalities of the temporal-hippocampal system would be predicted. In fact, such abnormalities have been reported. A number of studies (61,62) have found morphometric changes in both the anterior hippocampus and the parahippocampal gyrus. Magnetic resonance imaging data from the twin study cited earlier (49) indicated a volumetric reduction of the anterior hippocampus in the affected twins (63). Other work (64) has indicated a probable dysfunction of the medial temporal lobe structures. A recent review (65) of structural brain abnormalities in schizophrenia concluded that underlying the disease was a “functional disorganization of prefrontal-temporal-limbic cortical connectivity” that was likely of developmental origin.

Clinical Considerations

What are the clinical implications of memory impairment in schizophrenia? At present, this question can be given no adequate answer, in part because we lack a clear picture of its clinical character. The reason for this is suggested in an argument put forward by Green (66) and made in the broader context of cognitive dysfunction generally. On the one hand, patients with schizophrenia, as a group, score poorly on virtually every cognitive measure available. On the other hand, there exists considerable variation among individuals with respect to the distribution of deficit: on any given cognitive task, only about half perform in the subnormal range. Individuals suffering from schizophrenia thus tend to present an enormous variety of cognitive symptoms, and simply noting that these exist may have little diagnostic value. Much the same can be said in the particular case of memory (67). Thus, for the present, a reliable clinical profile of this particular aspect of the disease remains simply one of many professional desiderata. The potential value of such a profile, however, is clear enough: memory impairment is a known predictor of treatment outcome. Verbal memory, for example, has been shown to be among the strongest predictors of eventual community functioning (3). This is thought to be related to its critical involvement in the acquisition of psychosocial skills, as well as learning and retention skills, both of which are central to many rehabilitation programs (3).

If functional outcome is related to impairment of memory, questions concerning the amenability of the latter to treatment naturally arise. What are the current prospects for the amelioration of memory function in schizophrenia? Given the probable developmental origin of the neuropathologies underlying memory impairment, the outlook in this direction is bleak. With prudent pharmacological intervention, however, stabilization of the dysfunctional processes is a realizable goal.

Conclusions

Impairment of memory is one of the principal cognitive symptoms of schizophrenia. Cross-disciplinary research involving both clinical and experimental work has yielded a
compelling portrait of a functional deficit, which, in all likelihood, is organically based. Nevertheless, many questions remain unanswered. We do not know, for example, whether the impairment is primary or whether it to some extent follows upon other dysfunctional processes. Neither can we say with any real certainty what the direct effects of the various neuroleptic agents currently used in the treatment of schizophrenia might be. Indeed, we do not even possess a reliable profile of memory deficit as it presents in the typical clinical case.

The consequences of memory deficit for the patient, however, may be catastrophic. In the first instance, they are manifest simply as an added burden to the already difficult circumstances of life with a debilitating condition. Beyond this, however, is the far greater consequence that the deficit may interfere with programs aimed at rehabilitation. If modern medicine is unable to ameliorate the impairment of memory function in schizophrenia, then surely all attempts must be made not to exacerbate it. At present, the greatest danger in this regard lies in the clinical use of anticholinergic medication. Other adjunctive drugs also need to be taken into account regarding memory—notably benzodiazepines, which are abundantly prescribed for schizophrenia. Sadly, the use of such medications is often made necessary by the adverse effects of older “typical” neuroleptic drugs. If the more recent atypical antipsychotics like risperidone obviate the need for such intervention—and the evidence, at present, is that they do—then this alone may represent an important, if modest, step in the direction of an effective “cognitive” therapy. Where choices are available, the clinician should consider selecting drugs with clinical profiles that do not appear to have an impact on cognition or necessitate the use of other medications. With the growing body of research showing the clinical significance of cognitive factors in patients with schizophrenia, measures of cognitive functioning need to be strongly considered not only in the evaluation of these subjects, but also in the overall treatment and rehabilitation process.

Clinical Implications
• Every new neuroleptic should be studied for its effect on cognition.
• Procedural learning can be used to assess striatal functions.
• Clozapine has a different effect than classical neuroleptics on caudate nucleus volume and procedural learning.
• Clinicians should consider the cognitive adverse effects of neuroleptics.

Limitations
• Adjunctive drugs, such as benzodiazepines and antiparkinsonian medication, may be factors in memory impairment.
• Schizophrenia is a heterogeneous disorder.

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Résumé

Objectif : Décrire le concept de déficit mnésique dans la schizophrénie et les incidences cliniques de ce concept sur l’évaluation des patient(e)s et l’utilisation de neuroleptiques.

Méthode : Examen de la littérature consacrée aux exposés de cas.

Résultats : Les individus atteints de la schizophrénie présentent normalement un certain degré de déficience de la mémoire. De récents travaux de psychopathologie révèlent que la déficience est globale, touchant les stocks de mémoire sensorielle, à court terme et à long terme. L’atteinte de la mémoire semble constituer un des principaux symptômes de la maladie, et ses causes sous-jacentes sont probablement organiques. Un certain nombre de médications (les neuroleptiques classiques et les médicaments dont l’activité anticholinergique est prononcée) peuvent toutefois causer ou exacerber la déficience. En particulier, les agents anticholinergiques qui servent à traiter les symptômes extrapyramidaux, une complication fréquente des neuroleptiques, semblent avoir un effet nocif sur la mémoire.

Conclusions : Le déficit mnésique est un élément important de l’évaluation clinique et du traitement des individus atteints de schizophrénie. L’utilisation d’antipsychotiques atypiques, comme la rispéridone, semble n’avoir aucune incidence sur la fonction mnésique; parce que la rispéridone est liée à une faible incidence d’effets secondaires extrapyramidaux, elle peut permettre d’éviter la nécessité de médications anticholinergiques — accroissant ainsi l’espoir d’une intervention non débilitante. La découverte de médications plus sûres (à l’égard de la cognition) pourrait également donner de meilleurs résultats en facilitant le respect des schémas posologiques et des programmes de réadaptation.