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Cognitive Function in Schizophrenia—Do Neuroleptics Make a Difference?

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MORTIMER, A. M. *Cognitive function in schizophrenia—Do neuroleptics make a difference?* PHARMACOL BIOCHEM BEHAV **56**(4) 789–795, 1997.—Valid cognitive deficits in schizophrenia are now well characterised: general poor performance with disproportionate deficits in aspects of memory and executive function. Symptomatology, motivation, institutionalization, etc. cannot explain these deficits, which are of considerable importance for both the testing of theoretical models of schizophrenia and the determination of patients' functional outcome. The receptor blocking properties of neuroleptic treatments afford them the potential for interacting with monoaminergic, indoleaminergic, and cholinergic arousal systems in the brain and, hence, for modifying cognitive processes. However, the effects of conventional neuroleptics on cognition in schizophrenia are minor according to numerous studies. Atypical neuroleptics may, owing to their novel mechanisms of action, have the capacity to remediate cognitive impairment in schizophrenia: there is some evidence that clozapine has a "cognitive sparing" effect, but further research is needed in this area, particularly with other new drugs. Future studies should employ more appropriate methodology, particularly in terms of psychological/neurophysiological sophistication, patient evaluation, and applicability to real life, and should be hypothesis driven rather than purely empirical. © 1997 Elsevier Science Inc.

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THIS review sets out the evidence for cognitive impairments in schizophrenia and seeks to justify their importance, particularly with respect to pharmacological remediation. There follows an outline of the function of brain systems susceptible to neuroleptics and a summary of studies that have looked at cognitive changes brought about by both conventional and atypical drugs.

IS SCHIZOPHRENIA ASSOCIATED WITH COGNITIVE DEFICIT?

There is now virtually irrefutable evidence that the neuropsychology of schizophrenia comprises general cognitive impairment in many modalities, with outstanding impairments in memory and executive function.

General Cognition

One review of 94 studies on the performance of schizophrenic patients on neuropsychological tests concluded that acute, mixed, and chronic patients were increasingly difficult to distinguish from patients with organic brain disease (32). Subsequent studies have confirmed that schizophrenia is characterized by a compromise of intellectual function, ranging from a fall in IQ, through decline in a wide range of tests (21,44,55), to frank dementia (14,46,56). Evidence of independent dementia pathology in schizophrenic postmortem brain samples is, however, conspicuous by its absence (38,59). In view of these findings, the assumption that intellectual deterioration in schizophrenia is related to fixed structural abnormalities cannot be supported. It may be that some other process, for instance a neurochemical derangement that may be manipulated pharmacologically, is responsible.

One of the few studies to compare schizophrenics with patients suffering from affective psychosis (23) concluded that patients with schizophrenia consistently performed at lower levels on tests of psychomotor speed, attention, memory, and problem solving. These differences survived controlling for the effects of lower IQ in the schizophrenic group, which unlike in affective patients had fallen from premorbid levels. Disproportionate deficits, that is, significant compromise in the presence of intact general cognition, have provoked a great deal of interest given their potential for affording insights into anatomical or neurochemical substrates for schizophrenia pathophysiology.

Memory

There is good evidence that episodic memory and semantic memory are disproportionately impaired in schizophrenia

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(17,48,65,68), with preservation of implicit memory and procedural learning (10,26), a pattern of impairment that corresponds to the classic amnesic syndrome. The question of working memory deficits in schizophrenia is a vexing one. There is no evidence that "slave systems" are impaired in the absence of general cognitive deficit, nor that the "central executive" is impaired disproportionately, nor that "central executive" function corresponds to other aspects of executive function (Rubinzstein et al., in prep.). However, studies of executive function are frequently called upon when arguments for working memory dysfunction in schizophrenia are presented (28).

Executive Function

Poor performance on tests of executive ("frontal") function has been found repeatedly (29,47,52). Single case neuropsychological studies demonstrate the ubiquity of degrees of frontal impairment, and their disproportionate occurrence in schizophrenia even when there is no significant general cognitive dysfunction (65). However, executive function is not as well characterized as memory in terms of doubly dissociable components, and much work remains to be done to tease out which aspects are most relevant to schizophrenia and the brain systems which subserve them.

COGNITIVE DEFICITS, SYMPTOMS, AND STAGE OF SCHIZOPHRENIA

An obvious and influential point is that symptoms compromise cognitive performance, and it is certainly true that many patients in both acute relapse and chronic severe states are completely untestable. Furthermore, in older patients, the effects of "institutionalization" have been held responsible for cognitive deficit. However, several lines of evidence refute these propositions. Cross-sectional studies have found equivalent levels of impairment in different groups of cooperative schizophrenic patients despite wide ranges of age and illness duration (25,34,39), and substantial levels of cognitive impairment can be found at illness onset (3,36), even within samples of drug-naive patients (63). Comparable levels of deficit have been reported in both first-episode and chronic patients (36), while it appears that in the most severely affected patients (who are often the older group who became ill before neuroleptics were available) there is evidence of slow progressive cognitive decline (14). One recent study (71) found that in such a group of elderly patients, both general cognitive decline and negative symptoms were strongly determined by the duration of untreated illness prior to neuroleptic availability. Finally, the influence of symptoms on cognition is far from clear: although there is some evidence that overall symptom severity is a strong concomitant of neuropsychological deficit in schizophrenia (4), studies which have investigated cognitive improvement longitudinally from relapse have demonstrated both positive (67) and negative (7,24) findings despite ubiquitous symptomatic recovery. One study that explored the possible influence of symptoms on cognition (23) found that symptoms accounted for only 5% of the variance in schizophrenia, as opposed to 30% of the variance in affective disorder.

WHY DOES IT MATTER IF NEUROLEPTICS ALTER COGNITION IN SCHIZOPHRENIA?

The cognitive effects of neuroleptic drugs are important for both theoretical models of schizophrenia and for the practical matter of patient outcome.

A "levels of explanation" model of schizophrenia (19,54) suggests that symptoms or symptom classes can be the result of specific neuropsychological deficits, which in turn are the result of particular pathophysiological phenomena in the brain. For instance, it has been found that patients experiencing certain first-rank symptoms are impaired on an executive task that requires them to monitor their own self-generated actions (20,51). Similarly, poor performance on executive tasks has been associated with failure to activate the prefrontal cortex in functional imaging paradigms (1,45,72). Clearly, the manipulation of levels of cognitive performance by drugs, if indeed it does occur, should reflect prior changes in brain physiology and should bring about the relevant symptomatic adjustments as a consequence.

An alternative model of schizophrenia (8) sees cognitive impairment (here defined as attentional deficit and formal thought disorder) as a separate "domain" of schizophrenia pathology, other "domains" being other groups of symptoms, social and neurological abnormalities. There is an inherent problem in mixing up symptoms like thought disorder, which is rated impressionistically, with a neuropsychological deficit like attentional deficit, which can be measured psychometrically or neurophysiologically, within the same domain. Given this caveat, there is quite a good argument for relating thought disorder to executive dysfunction (74). One implication of models such as this is that symptoms and cognition may not be causally related to each other either way, although of course they may coexist or may be related to prior variables associated with each individually. Such models would predict that the effects of neuroleptics on symptoms and cognitive impairment may be independent of each other.

A third model (69) relates "dimensions" of behavioural psychopathology—inertia, aggression/anxiety, and anhedonia—to altered neurophysiology of the transmitter systems utilizing dopamine, serotonin, and noradrenalin, respectively. This model is obviously testable, because neuroleptics block receptors for these amines to varying degrees. The model would predict fundamental effects of neuroleptics on specific behaviours, but does not address the possibility of cognitive change, which presumably would be enabled secondarily by primary behavioural effects.

Apart from the issue of testing models of schizophrenia is the important practical question of patient outcome. An increasing body of research indicates that cognitive deficits are substantial correlates of psychiatric disability (40). Indeed, a recent review (30) found that verbal memory and certain aspects of executive performance—the Wisconsin Card Sorting Test and the Continuous Performance Task—were replicably and convincingly associated with functional outcome in terms of community functioning, social problem solving, and skill acquisition. By contrast, psychotic symptoms were not correlated with functional outcome in any study.

Because memory and executive functions are disproportionately compromised in schizophrenia, remediation of these deficits has the potential to overcome consequential rate-limiting steps in psychiatric rehabilitation and thus to improve outcome. Given the enormous costs of treatment and support for these patients, it is clear that any drug that remediates cognitive deficit—a "smart drug" for schizophrenia—would have major advantages.

WHY SHOULD NEUROLEPTICS MODIFY COGNITION?

All neuroleptics come into the general category of cerebral depressant drugs, which may impair performance on a wide variety of neuropsychological tests when given in acute doses.

However, any theoretical account of their expected cognitive properties must rest upon bringing together what is known about their neurotransmitter receptor blocking attributes with available knowledge of the function of these neurotransmitter systems in both normal and pathological situations. The latter aspect has recently been the subject of a comprehensive and thorough review (61).

Neurotransmitter systems relevant to the properties of neuroleptics are monoaminergic (noradrenaline, dopamine), indoleaminergic (serotonin), and cholinergic (acetylcholine). All are components of the ascending reticular activating system, which projects from the brain stem to the forebrain and whose function is overall one of arousal. Arousal, formerly a unitary concept, is the sum of the interplay between these systems. Animal work has shown that each neurotransmitter system has its own tonic pattern of firing and characteristic phasic responses to various environmental stimuli such as reinforcers and noxious events. It is thought that the forebrain effect of increased firing of noradrenergic, cholinergic, and possibly dopaminergic neurons, is to sensitise cortical regions to sensory stimuli, i.e., increase signal to noise, so that arousal increases. By contrast, application of serotonin to the neocortex blunts evoked responses, a "de-arousing" effect.

Animal behavioural work suggests that the noradrenergic system is essential for controlled, rather than automatic, responses to stimuli. Rats whose noradrenergic systems have been chemically destroyed are impaired on a continuous performance task when they are distracted by bursts of noise or irregular stimulus presentation, which arouses and/or alerts them beyond the normal test conditions. In humans, the noradrenergic system can be downgraded by clonidine, which impairs performance on both a continuous performance task and an executive task (Tower of London). The noradrenergic system seems to have a protective function of maintaining discriminability in stressful or arousing circumstances, sustaining alertness to the most salient stimuli.

The dopaminergic system is thought to activate behaviour in response to cues that signal the availability of incentives or reinforcers. In humans, low doses of amphetamine cause premature or impulsive responding to an attentional task, and dopamine depletion increases latency of responding, but neither have much effect on accuracy of response. Behaviour activated by the dopamine system includes basic functions such as eating and drinking, as well as newly learned responses. The mechanism seems to be the bringing about of a state of "motor readiness" or response preparation, so that cues are acted upon and that action occurs quickly. In addition, work with Parkinsonian patients whose L-dopa is withdrawn suggests that the dopaminergic system is involved in more complicated cognitive functions such as the planning and organising of sequences of behaviour, the modulation of an "executive network." Clearly, either up- or downgrading dopaminergic neurotransmission can have cognitive consequences.

Serotonin downregulation has been shown to improve memory, while upregulation can impair it, which is consistent with the "de-arousing" effects of reduced signal to noise ratios produced by serotonin in the forebrain. Massive serotonin depletion in animals leads to overarousal in terms of behavioural disinhibition, manifest as premature or impulsive responding on an attentional task.

The cholinergic system appears to have a very important and general arousing effect, which enhances stimulus processing in many cortical areas serving numerous cognitive functions. Depletion in experimental animals disrupts continuous performance task ability in the easiest paradigm. In humans, Alzheimer's disease, in which all cognitive functions are impaired, is characterized by marked widespread deficiencies in cholinergic function.

Several points are suggested by these data. The first is that there is ample evidence that neuroleptics should have the potential to modify cognition. The second is that any such modification will depend upon the pattern of receptor blockade of the individual drug. Therefore, modification by relatively pure blockers of one system may be more predictable than modification by a "dirty" drug such as chlorpromazine. Third, it is apparent that different tasks may well require different levels of arousal for optimum performance, depending upon which functions are under scrutiny: a drug acting on one system may improve performance on one task, impair it on another, or have no effects. Fourth, alteration of cognitive performance in patients in whom there is reason to suspect intrinsic neurotransmitter system derangement may well differ from the alteration seen in normal control groups. In conclusion, it is apparent that cognitive modification by neuroleptics in patients will be very difficult to predict; it is hardly surprising that studies have for the most part been empirical rather than theoretically driven.

In healthy volunteers, doses of sedating neuroleptics such as thioridazine impair performance on tests of attention more than less sedating drugs such as haloperidol and remoxipride (35). Impairment by neuroleptics is particularly marked in paced tasks, where the subject has no control over presentation of stimuli, as opposed to nonpaced tasks (5). The extrapyramidal side effects of these drugs are particularly relevant to motor paradigms. Regarding memory, it has been proposed that anticholinergic effects intrinsic to some neuroleptics, or the anticholinergic effects of drugs added to control Parkinsonian side effects, have amnestic results in healthy volunteers (42,58). One study (62) found that the atypical neuroleptic clozapine, which has pronounced antimuscarinic activity, produced such deficits in volunteers and that their EEG map became similar to that produced by anticholinergic antidepressant medication.

DO CONVENTIONAL NEUROLEPTICS CHANGE COGNITIVE PERFORMANCE IN SCHIZOPHRENIA?

General Cognition

The efficacy of neuroleptics in controlling psychotic symptoms is such that neuroleptic treatment has become mandatory for schizophrenia. Perhaps the necessity for lifelong therapy, the cerebral depressant effects described above, and concerns about long-term side effects have combined to generate quite a lot of work on the cognitive ramifications of neuroleptic treatment. Clearly, given their extrapyramidal effects, there is little point in assessing motor tasks where speed and accuracy are scored: the motor effects of the drugs will inextricably confound any therapeutic effects on mental performance. Despite this obvious problem, the literature contains many studies utilizing such tasks [see (49)]. However, several recent, comprehensive, and thorough reviews have all concluded that the chronic effects of conventional neuroleptics on a variety of cognitive functions in patients with schizophrenia are small (9,33,49,66). One study (64), in which dose was actually reduced by 80–90% in chronic stable patients, found no deleterious or favourable effects on cognition or symptoms after 6 weeks.

Memory

Anticholinergic medications are well known to impair memory (42), and it seems plausible that this effect, or the

intrinsic anticholinergic effects of some low potency neuroleptics, could contribute to the memory deficits in schizophrenia. However, one study (68) was unable to demonstrate any influence of anticholinergics on memory performance. Even so, it remains plausible that these effects contribute to the failure of typical neuroleptics to improve memory performance in schizophrenia (31). There are no studies of the effects of typical or atypical neuroleptics on narrowly defined working memory, i.e., slave systems ± central executive.

There is one study (58)—on haloperidol—that suggests improvement of a measure of semantic memory thought to be sensitive to frontal dysfunction; this improvement was lost when treatment was stopped and regained when treatment began once more.

EXECUTIVE FUNCTION

Executive function similarly seems impervious to typical neuroleptic treatment. Tests examined include the Wisconsin Card Sorting Test (12,43,64), the Stroop Test (11), the Digit Symbol Test (9,49), and verbal fluency (12,64). Verbal fluency is distinguished by two further studies, one showing improvement on neuroleptics compared with placebo (70) and the other showing deterioration (2). Some improvement has been found on the Continuous Performance Task, which measures sustained attention/vigilance, arguably including some aspects of executive function (57,66). Some very old work on maze tests [which require intact frontal function according to neurosurgical data (60)] suggests deterioration on neuroleptic treatment independent of motor effects (49). A recent hypothesis (22) proposes that neuroleptics interfere with the functional dopaminergic innervation from mesocortical systems to the frontal lobes, and that this is sufficient to compromise executive performance. This would predict that lower potency or atypical drugs, which do not block dopamine (D_2) receptors as strongly, would spare frontal functions. However, the evidence is overall that typical neuroleptics have trivial effects on these functions, although this may be owing to a "floor" effect where performance is so compromised by integral frontal dysfunction that the exhibition of neuroleptics has little to take from it.

THE POSSIBILITY OF PRACTICE EFFECTS IN SCHIZOPHRENIA

There is a dearth of literature on cognitive test practice effects in schizophrenia, possibly because so few instances of improvement have been reported. One study (31) tested nine stable treatment-resistant patients taking clozapine on nine executive and memory measures, repeating the tests 3 weeks later; no evidence of practice effects was found.

ATYPICAL NEUROLEPTICS AND COGNITIVE PERFORMANCE

Atypical neuroleptics are defined as effective antipsychotics that do not cause catalepsy in rats (41). Clozapine is the chief exemplar; other new drugs such as risperidone, seroquel, sertindole, olanzepine, zotepine, and ziprasodone can all cause extrapyramidal side effects, although they may be less frequent or milder. Apart from improved side effect profile, the new atypicals aim for increased antipsychotic efficacy over conventional drugs. The evidence for the superior antipsychotic efficacy of clozapine is not easy to refute (53). Novel mechanisms of action claimed to be associated with increased efficacy and better side effect profile of atypical neuroleptics include serotonin ($5\text{-}HT_2$) blockade, the balance between D_2 and $5\text{-}HT_2$ blockade, c-fos expression in the prefrontal cortex (16), and noradrenergic alpha-1 blockade (73). Despite the difficulties in predicting the cognitive results of such neurotransmitter manipulation, it could be predicted that superior relief of symptoms would improve cognitive performance on purely "common sense" grounds. Alternatively, levels of explanation models of schizophrenia would predict that the cognitive neuropsychological level is the functional substrate for neuroleptics and that symptomatic improvements should follow cognitive remediation brought about by these drugs.

Cognitive studies of atypical neuroleptics apart from clozapine are conspicuous by their absence, reflecting the recent introduction of these drugs. The clozapine studies have been relatively atheoretical in terms of any sophisticated appraisal of the neuropsychological deficits in schizophrenia and have been hampered by other methodological factors. These include the following: small patient numbers, short (weeks) therapeutic trials, normal control group, no control group, control group receiving single comparison drug in fixed dose, baseline data from acute phase of illness, baseline data from drug-free patients, groups not adequately matched at baseline, polypharmacy, and cognitive functions known to be impaired in schizophrenia not focused on. This has led one influential reviewer (50) to conclude that the question of cognitive improvement on clozapine remains to be answered. However, an historical summary of studies of cognition in relation to clozapine treatment follows below.

Classen and Laux (11) were unable to establish differences in motor function, reaction time, tests of verbal/spatial ability, and Stroop (executive) test scores between parallel groups of patients on normal therapeutic doses of haloperidol, flupenthixol, or clozapine. However, numbers were small (total n = 50) and patients were "acute inpatients" matched on age and sex only; there was no baseline assessment, patients being tested once after only 1 week's treatment.

Meltzer (50) studied 25 treatment-resistant patients who were tested on attention, working memory, executive function. and semantic memory. Both measures of semantic memory had improved at 6 months, and these improvements were independent of changes in psychopathology. There was no comparison group.

Hagger et al. (31) studied 36 treatment-resistant patients for 6 months. There were significant improvements from baseline in semantic memory and attention. However, baseline data were obtained from patients in near drug-free states, and the confounding effects of high symptom scores on baseline performance could not be excluded. Other tests of memory and executive function were unchanged. Improvements in Brief Psychiatric Rating Scale positive and overall scores were significant but very small (3.5 and 2.3 points, respectively). The authors' assertion that psychopathological changes predicted cognitive changes, when one or both scores had failed to alter significantly, is difficult to interpret. There was no comparison group.

Goldberg et al. (24) studied 15 assorted psychotic patients up to 15 months after beginning clozapine and found no change in a number of memory and executive tests, with deterioration on a test of visual memory (attributed to clozapine's anticholinergic effects). The problems of small numbers and adjunctive medications are obvious drawbacks, but the long follow-up, within-subjects design, and finding of a 40% decline in symptoms scores add some weight to these results.

Buchanan et al. (6) studied 38 treatment-resistant patients randomised to fixed-dose haloperidol or clozapine. The groups were well matched at baseline and were reassessed after 10 weeks: no measure distinguished the groups. Thirty-three patients either continued or commenced clozapine after the 10-week assessment and were evaluated a third time after 1 year.

There were significant improvements in semantic memory and executive function, and trends to improvement in long-term memory. Memory measures were significantly correlated with quality of life. There was no comparison group for this extension of the study. Cognitive changes were not related to symptoms or side effects.

Hoff et al. (37), in their study of 17 patients after 12 weeks of clozapine treatment, confirmed Goldberg's finding of a decrement in visual memory. However, there were improvements in concentration, speed, and spatial functions despite little symptomatic improvement. Small numbers and lack of a comparison group limit the generalizability of this report.

Daniel (13) compared clozapine and risperidone in 14 patients, utilizing a 6-week crossover design. Visual memory was superior on risperidone, as was Wisconsin card categories, while verbal fluency and continuous performance were superior on clozapine despite subjective sedation. Small numbers and short treatment intervals may have avoided other positive findings.

Dye and Mortimer (18) studied 29 stable chronic patients: 16 who started clozapine and 13 who remained on treatment as usual. At the time of reporting, four clozapine and six treatment-as-usual patients had been followed up for 2 years. This was a naturalistic study: patients were not randomised and the groups were not well matched for motor disorder at baseline. However, all other measures were comparable. For the clozapine patients, significant improvements on an ecologically sound test of long-term memory and three measures of executive function were demonstrated, but these improvements did not take place convincingly until after 12 months into the study. At 6 months, there were major improvements in positive and negative symptoms and very large improvements in social competence and behaviour problems. The authors concluded that there was no evidence for cognition to be identified as the primary substrate for the action of clozapine, but that disproportionately affected cognitive functions with the greatest room for improvement did show improvement as part of a general process of recovery.

CONCLUSIONS

Valid cognitive impairments in schizophrenia have become well characterized over the last 15 years. That schizophrenia is a disorder in which cognitive impairments occur is hardly surprising given the evidence (albeit circumstantial) for derangement of neurotransmitter systems responsible for differentiated components of arousal. However, that cognition can be substantially influenced by the exhibition of neuroleptics that act upon these systems is far from clear. Given the complexity of neuroleptic treatment in patients compared with the simplicity of animal experimental paradigms, it is difficult to predict how cognition ought to be affected, and even more difficult to imagine how cognitive changes will alter patient outcome in real life.

Despite the importance of cognitive deficits, there is not yet a culture of addressing cognitive impairment as a specific target for pharmacological treatment in schizophrenia. This can easily be understood given that proper intellectual assessment is not a routine part of clinical practice: deficits are overlooked in favour of symptomatology, which psychiatrists are more fully trained to elicit. In any case, the evidence that conventional neuroleptics have only minor effects on cognition is by now fairly well known. It has been suggested that dopaminergic and cholinergic agonists should be investigated as possible specific remedies for cognitive impairment (15), although this would risk antagonism of the antipsychotic effects of neuroleptics and worsening of Parkinsonism.

The case of clozapine is slightly different. Because clozapine is distinguished by poor blockade of D_2 receptors, it could be surmised that, compared with other neuroleptics, clozapine has a "cognitive sparing" effect. This would be particularly relevant to tasks that require self-generated action and that are timed (e.g.,verbal fluency), given the apparent role of dopamine in response readiness and motor preparation. However, the anticholinergic effects of clozapine would suggest adverse effects on memory, while blockade of cortical D_1 receptors would predict adverse effects on executive function (27). These hypotheses are partly supported by some studies, but as a whole the evidence is inconsistent. Nevertheless, it remains the case that clozapine is the only neuroleptic that has convincingly improved aspects of cognition in schizophrenia. There is a clear need for further psychologically sophisticated, hypothesis-driven studies of atypical neuroleptics, preferably with a neuroimaging component, to be carried out in the future.

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