Cognition, schizophrenia, and the atypical antipsychotic drugs

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The Cognitive Deficit in Schizophrenia

Schizophrenia was originally called dementia praecox by Emil Kraepelin, the great 19th century psychiatric nosologist, who coined the term to categorize a group of young psychotic patients who went on to develop dementia. A decade later, Eugen Bleuler, noting that most patients who had similar psychotic and affective features did not become severely demented, renamed the illness schizophrenia and in the process decreased the central importance of cognitive impairment to the broader entity, although he, too, conceptualized schizophrenia as a neurocognitive disorder (1). Recognition of the central importance of cognitive impairment to schizophrenia further diminished in the 1950s, after the development of antipsychotic drugs such as chlorpromazine and haloperidol, which had, as their signature characteristics, the ability to improve delusions and hallucinations, although, at the same time, causing significant extrapyramidal side effects (EPS). The evolution of diagnostic schema for schizophrenia during the 1970s and 1980s further emphasized delusions and hallucinations (now generally referred to as positive symptoms), which, in about 70% of cases, respond to the haloperidol-like drugs (now called typical antipsychotics, for reasons explained below). However, these drugs were found not to improve cognitive function and, sometimes, to impair some aspects of cognition, such as memory and fine motor function (2–4). Research on the cognitive impairment of schizophrenia, nevertheless, went forward, and its major features were reliably described: (*i*) all domains of cognition, including attention, executive function, secondary (storage) memory, working memory, and semantic memory, may be affected (5); (*ii*) the pattern of deficits may vary widely among individuals with schizophrenia (5); (*iii*) the mean deficit in these domains may be 1–3 standard deviations below normal (5–7), although about 15% of patients with schizophrenia test within the normal range in all domains (8); (*iv*) for most patients, impairment is only slowly progressive after the first episode of psychosis (9, 10); and (*v*) some components of the deficit are present during childhood and early adolescence but usually in mild form (9, 11). This last feature led to the conclusions that an extensive decline in cognition must develop during the prodromal period (which usually lasts several months to several years before onset of psychosis), the first psychotic episode, or both and that prevention of the evolution of the cognitive deficit during these two periods might be of great value, if possible (12). Finally, it has been established that deficits in specific types of cognition are of key importance for work and social function in schizophrenia, more so even than positive or negative symptoms (withdrawal, avolition, anhedonia, and flat affect; refs. 13 and 14). Thus, there has been a true renaissance in the appreciation of the importance of cognition as the core of schizophrenia, from which most, if not all, aspects of the syndrome originate (1, 15, 16).

Antipsychotic Drugs and the Cognitive Deficit of Schizophrenia

Haloperidol, as well as the other classes of typical neuroleptics, produce equivalent improvement in positive symptoms. This action is most likely due to their ability to block dopamine D_2 receptors in mesolimbic areas, including the nucleus accumbens, olfactory tubercle, and stria terminalis (17). Blockade of D_2 receptors in the striatum is a major factor in causing acute and subacute EPS as well as tardive dyskinesia. Whether the worsening of negative symptoms and cognitive function sometimes produced by these agents is due to frontal cortical hypodopaminergia, as stated by Honey *et al.* (18), is not as well established, because there are very few D_2 or D_3 receptors in the frontal cortex. Clozapine was the first antipsychotic that did not produce EPS or tardive dyskinesia; this dissociation was the impetus for the term "atypical" antipsychotic (19). Numerous theories have been proposed as to the basis for the dissociation between antipsychotic efficacy and EPS, among them, relatively more potent blockade of 5-HT_{2a} receptors and weak blockade of D_2 receptors (20, 21). This hypothesis led to the development of other classes of antipsychotic drugs that share this pharmacologic core but with numerous differences in affinities for other monoamine receptors. Risperidone, the atypical antipsychotic drug studied by Honey *et al.* (18), was the first such drug, followed by olanzapine, quetiapine, ziprasidone, and iloperidone. There are at least six additional series of compounds reported in the literature that have atypical antipsychotic properties that seem to be related to this combination of pharmacologic features (16).

An important array of other advantages of clozapine, not all equally shared by the other atypical antipsychotic drugs, have been reported; of these, the most important are efficacy for positive symptoms in patients who fail to respond to the typical neuroleptic drugs (22) and improvement in negative symptoms, most likely, in our opinion, of both the "primary" and "secondary" types (23, 24). Our initial reports that clozapine was able to improve cognitive function in schizophrenia (4, 6, 25) have frequently, but not always, been replicated (see ref. 14 for review). Other investigators have reported significant beneficial effects of risperidone, olanzapine, and ziprasidone on cognition (see refs. 14, 26, and 27, for reviews; P. Harvey, personal communication). There seem to be differences in the domains of cognition improved by specific atypical antipsychotic drugs. For example, risperidone seems to be most effective in improving working memory (14, 28), the function tested by Honey *et al.* (18), whereas clozapine seems more likely to improve semantic memory and may actually impair working memory, at least transiently (4, 6, 14). Although the mean improvement in cognition with the atypical antipsychotic drugs in patients with schizophrenia almost always leaves cognition short of normal levels, there is little question of the

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fundamental importance of the demonstration that significant improvement in cognition, the central feature of schizophrenia, does, in fact, occur during treatment with these agents. Defining the neurocircuitry and neurochemistry of this improvement is, as Honey *et al.* (18) have suggested, of paramount importance to further progress in understanding and treating this illness.

Imaging the Cognitive Deficit in Schizophrenia

As shown by Honey *et al.* (18), functional magnetic resonance imaging (fMRI) is the current procedure of choice for identifying the neurocircuitry involved in mediating the cognitive effects of the atypical antipsychotic drugs, although positron-emission tomography (PET) study of regional cerebral blood flow may also provide useful information about the effect of antipsychotic drugs on the neurocircuitry of cognition. The present fMRI study of the effect of 6 weeks of treatment with risperidone on working memory in schizophrenic patients is a significant first step in describing the effects of the atypical antipsychotic drugs on the neurocircuitry of cognition. Working memory is a system for temporary maintenance and manipulation of information to guide behavior and is mediated by a neurocircuit, which includes the prefrontal cortex. Honey *et al.* (18) found that a network comprising bilateral dorsolateral prefrontal and lateral premotor cortex, the supplementary motor area (SMA), and posterior parietal cortex was activated by working memory task performance in both the patients with schizophrenia and normal comparison subjects. No significant differences in the pattern of activation were noted, indicating normal brain connectivity for this task in the schizophrenic patients, whether receiving typical or atypical antipsychotic drugs. However, it should be noted that the task chosen was sufficiently easy such that the patients performed as well as the normal controls. Risperidone increased functional activation during task performance in right prefrontal cortex, SMA, and posterior parietal cortex, as measured by increased blood oxygenation, compared with baseline on typical neuroleptic drugs; no such effects were noted in the patients whose medication status remained unchanged. The increased blood flow during risperidone treatment was not associated with improvement in working memory, but it must be remembered that because of the ease of the task, the patients were already performing at normal levels while receiving typical neuroleptic drugs. Whether the patients' performance of the task had, in fact, benefited from treatment with typical neuroleptic drugs cannot be determined from this study, but based on previous research, such an improvement is unlikely. This study provides further evidence that greater blood flow does not always indicate better performance. It has been shown that activation of cingulate and frontal cortical regions during initial learning of a task is greater than after skill acquisition. Minimal activation may mean highly efficient task performance. Thus, fMRI studies in patients with schizophrenia who showed an abnormal pattern of activation related to impaired cognitive function, who were normalized by atypical antipsychotics, and who were correlated with improved function would be more informative than demonstrating enhanced activation of a normal mechanism employed for cognitive problem solving by both normals and patients with schizophrenia.

Working Memory, Hypodopaminergia, and Cerebral Blood Flow

Honey *et al.* (18) speculate that the cognitive impairment in patients with schizophrenia is due to decreased frontal cortical dopaminergic activity, which may be further exacerbated by typical neuroleptic-induced blockade of cortical D_2 receptors. The researchers concluded that the increased regional cerebral blood oxygenation they noted may reflect the ability of risperidone to increase cortical dopaminergic activity, possibly by virtue of its ability to block 5-HT_{2a} receptors. Fletcher *et al.* (29), using PET, showed that, when performing a verbal fluency task in which patient performance was inferior to that of controls, those with schizophrenia had an abnormal pattern of left temporal lobe and anterior cingulate activation. This pattern was normalized by apomorphine, a directly acting dopamine agonist, but at a dose that might *decrea*se dopaminergic activity because of stimulation of dopamine autoreceptors that regulate the synthesis and release of dopamine. Verbal fluency is markedly improved by clozapine (4, 6), which, as discussed below, increases dopaminergic activity in prefrontal cortex, indicating the difficulty in relating cognitive changes to a simple dopaminergic model. We and others have shown that all the atypical antipsychotic drugs studied to date, risperidone included, increase prefrontal cortical dopaminergic activity in the rat or monkey (30–33). We have also found that clozapine and the other atypicals, but not the typical antipsychotic haloperidol, increase prefrontal cortical acetylcholine levels (34, 35). These effects of the atypical antipsychotic drugs to enhance dopamine and acetylcholine efflux on a region-specific basis must be evaluated in light of their agonist, partial agonist, and antagonist effects on various dopamine and cholinergic receptors (16, 32, 36). Thus, as mentioned above, clozapine did not improve verbal working memory in patients with schizophrenia (4, 6, 25). There are no studies yet with regard to the effect of clozapine on spatial working memory in humans, although the drug does reverse the impairment in spatial working memory produced by subchronic phencyclidine in monkeys (37). Haloperidol, however, exacerbates this impairment (38). It is, therefore, premature to conclude that increasing prefrontal cortical dopaminergic function is the basis for improvement in working memory or other cognitive functions, although it remains an attractive hypothesis.

Honey *et al.* (18) suggest that the typical neuroleptic drugs are more effective than the atypical antipsychotic drugs in occupying dopamine receptors in the prefrontal cortex. This suggestion may not be the case. We showed in rodents that atypical antipsychotic drugs had a greater affinity for extrastriatal than striatal D_2/D_3 receptors (39). Pilowsky *et al.* (40) subsequently reported single photon-emission computerized tomography results with I-epidipride as ligand that clozapine occupied D_2/D_3 receptors in temporal cortex to the same extent as did typical antipsychotic drugs. We have now obtained similar results in two olanzapine-treated patients by using PET with [^{18}F]epidipride. We observed 80–90% occupancy of temporal cortical D_2 with the expected 60–65% occupancy of striatal D_2 receptors in the patients who were receiving olanzapine (10 mg/day). Further research to determine whether this result is characteristic of other atypical antipsychotic drugs is warranted. Clozapine is a partial agonist at D_1 receptors (41) and a relatively potent D_4 antagonist (42), both of which are enriched in the prefrontal cortex. Thus, despite the increased release of dopamine in the prefrontal cortex, it is difficult to interpret its net effect on dopaminergic activity in the prefrontal cortex. The other atypical antipsychotic drugs, including risperidone, have complicated profiles with regard to affinities for D_1 and D_4 receptors, with no clear relation to atypicality per se (21, 43), but it is possible that their affinities for these receptors are important to their cognitive effects.

Cognitive Deficits and Choice of Antipsychotic Drug Treatment in Schizophrenia

There are several other issues raised by Honey *et al.* (18) that deserve brief comment. The researchers state that they would not randomize patients to risperidone, because they "considered it inappropriate to risk [. . .] denying atypical drug treatment to patients who might benefit from it" (18), thereby introducing a potential bias, which they rate as the most serious limitation of the study. In fact,

there is little evidence that it introduced any significant bias into this study of cognition, because, as many others have found, the cognitive deficit was independent of psychopathology. Thus, there was no difference in the baseline levels of working memory function between the two groups of patients or between the patients and the controls. Rather, as suggested above, the ease of this particular test of working memory was the factor that most significantly limited the overall value of this study in our judgement. More importantly, the authors did not seem to notice the contradiction between their reluctance to deny risperidone to patients who might benefit from it because of persistent positive symptoms or neuroleptic intolerance and their conclusion that they should avoid ''disturbing patients satisfactorily managed on typical drugs, by a randomized design'' (18). We would have expected that clinical investigators aware of the importance of working memory for schizophrenia and the ability of risperidone to improve this function would appreciate that ''satisfactory manage[ment] on typical drugs'' means only that positive symptoms and EPSs are well controlled. Patients treated with typical neuroleptic drugs, the vast majority of whom would be expected to be cognitively impaired (8), are denied the possibility of improvement in what is generally thought to be the core deficit in schizophrenia, i.e., cognitive dysfunction, which, as mentioned above, has important implications for work and social function as well as other features of the illness (13). Thus, in our view, it is shortsighted to continue to treat schizophrenic patients with antipsychotic drugs that lack the potential to improve cognitive impairment (44, 45). This conclusion would seem to be true, even though we lack sufficient evidence as to just how many patients with schizophrenia are significantly improved by atypical antipsychotic drug treatment. We have argued that the choice of antipsychotics should include identification of the specific cognitive deficits in patients with schizophrenia and knowledge of those domains of cognition that are most likely to be improved by an atypical antipsychotic drug (14). Further studies of the type reported by Honey *et al.* (18) should provide important data relevant to the neurocircuitry of specific cognitive deficits and to how atypical antipsychotic drugs modify those deficits.

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