Schizophrenia and cognitive function

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Schizophrenia and cognitive function
Gina Kuperberg* and Stephan Heckers†

Schizophrenia is often associated with cognitive deficits, particularly within the domains of memory and language. Specific cognitive deficits have recently been linked to psychotic phenomena, including verbal hallucinations and disorganized speech. Impairments of working and semantic memory are primarily due to dysfunction of the frontal cortex, temporal cortex, and hippocampus. Cognitive skills in schizophrenia predict social functioning and may serve as outcome measures in the development of effective treatment strategies.

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Abbreviations
DLPFC dorsolateral prefrontal cortex
fMRI functional magnetic resonance imaging
MT medial temporal area
PET positron emission tomography
WM working memory

Introduction
Schizophrenia is a severe mental disorder characterized by a variety of signs and symptoms. The clinical phenomena associated with schizophrenia can be grouped into positive and negative clusters. The positive cluster includes the phenomena that are not present in the normal individual: for example, hallucinations, delusions, disorganized speech or positive thought disorder. The negative cluster describes the absence of certain functions that are present in the normal individual: for example, apathy, avolition, and poverty of speech. More recently, factor analytic studies have suggested that these phenomena cluster into three ‘syndromes’: psychomotor poverty (encompassing many of the negative symptoms), reality distortion (hallucinations and delusions), and disorganization (positive thought disorder and disorganized, non-goal-directed behavior). Since its earliest conception as ‘dementia praecox’ (i.e. early-onset dementia), impaired cognitive function has also been considered a core feature. Clear evidence to suggest that cognitive dysfunction is intrinsic to schizophrenia, however—rather than the result of chronic illness, institutionalization or medication—is only now emerging: cognitive deficits are present in adolescents at risk for schizophrenia and in untreated first-episode schizophrenic patients [1]. Moreover, cognitive performance does not deteriorate over the first few years of illness when patients are treated [2,3].

Research into cognition and schizophrenia over this past year has taken several different approaches. Here, we review behavioral studies of cognitive dysfunction, regional brain activation during task performance, the effect of cognitive impairment on social functioning, and the effect of psychotropic medication on cognition in schizophrenia (see Table 1).

Impaired cognitive function
Schizophrenic patients show deficits in a variety of cognitive domains including executive function, attention, memory and language. There is increasing evidence that such deficits are not global and generalized but rather are specific and selective, manifest by distinct patterns of association and dissociation of performance across different cognitive tasks.

Table 1
Recent studies (reference number in brackets) of cognitive deficits in schizophrenia, their correlation with clinical features, and their neural mechanisms.

<table>
<thead>
<tr>
<th>Deficits in</th>
<th>Clinical correlates</th>
<th>Neural mechanism</th>
</tr>
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<tbody>
<tr>
<td>Working memory [4,5,78]</td>
<td>Thalamus [27]</td>
<td></td>
</tr>
<tr>
<td>Episodic memory [10*]</td>
<td>Striatum [28]</td>
<td></td>
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<tr>
<td>Semantic memory [6,9*]</td>
<td>DLPFC [20,21,23,24**,25]</td>
<td></td>
</tr>
<tr>
<td>Sentence processing [18**]</td>
<td>Thought disorder [18**]</td>
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CCTCC, cortical-cerebellar-thalamic-cortical circuit.
A distinct pattern of cognitive deficits in schizophrenia could theoretically reflect a single cognitive deficit. For example, the correlation of reaction-time facilitation and error interference on the Stroop task (a measure of selective attention) with performance on the Speaking Span test (a measure of working memory) could indicate a common cognitive disturbance [4]. Similarly, Cohen et al. [5] have demonstrated that schizophrenic patients show selective patterns of impairment on three different tasks (a version of the Continuous Performance Task, the Stroop test, and a lexical disambiguation task), with the poorest performance seen in experimental conditions that were most sensitive to context. Moreover, a significant cross-task correlation within these 'context-sensitive' conditions was taken to support the theory that schizophrenia is characterized by an impairment in using representations of context to govern appropriate behavior.

A dissociation in performance, either between two related tasks or between experimental conditions within the same task, is also consistent with the existence of selective deficits. For example, dissociations have been described between semantic as opposed to phonological fluency [6] and in verbal as opposed to non-verbal auditory working memory [7]. A deficit in the Stroop test but not in two other interference tasks [8] suggests that schizophrenic patients with the disorganized syndrome are impaired in their ability to suppress irrelevant verbal responses. In addition, schizophrenic patients have been described in the pattern of retrieval from both semantic and episodic memory. Semantic memory has been conceptualized as an associative network in which world knowledge and the meaning of words are stored. Following presentation of a series of words, the pattern of recall depends upon both the strength and the number of associative links with other words in the network. Schizophrenic patients recall fewer words than normal controls in a retrieval task. More interestingly, over and above this poor overall performance, patients show an abnormal pattern of word recall, suggesting a specific impairment in either the structure or modulation of this associative network [9].

Schizophrenic patients are also impaired when asked to provide details of a previous episode, or when asked to identify the origin of an event. When schizophrenic patients performed or watched the pairing of objects, they showed an overall recognition deficit and were specifically impaired when asked to recall details of the pairing episode [10••]. This provides evidence that memory deficits in schizophrenia are associated with an inability to link the separate aspects of events into a cohesive, memorable, and distinctive whole.

Cognitive deficits are not necessarily found in all schizophrenic patients. This raises the issue of whether heterogeneity in cognitive performance reflects heterogeneity in symptomatology. Some of the paradigms used in studies describing specific qualitative differences between normals and schizophrenics have face validity with particular symptoms of schizophrenia. For example, one might predict that patients with positive thought disorder (disorganized speech) may have specific deficits in semantic function, while those with auditory hallucinations may have particular problems with auditory source memory.

This paves the way towards a 'symptom-orientated approach' to the study of cognitive deficits in schizophrenia. In such an approach, a particular symptom is taken as the point of reference; patients with and without this symptom are recruited, and the hypothesis posed relates to the theoretical link between the proposed cognitive deficit and this clinical phenomenon.

Verbal hallucinations might occur when internal thought (or 'inner speech') is misattributed as arising from external sources. Johns and McGuire [11••] report that hallucinators are particularly likely to make errors when articulating derogatory words — a finding consistent with the pattern of deficits revealed on a source monitoring task [12] and with the clinical observation that auditory hallucinations are often derogatory. Misattribution errors may arise from an abnormal attribution 'bias', as opposed to abnormal perceptual encoding [13]. A cognitive bias caused by the emotional content of the material may be influenced by top-down processes; for example, by one's beliefs about one's relationship with one's surroundings, such as 'metacognitions' about controllability and danger [12]. An alternative hypothesis — that verbal hallucinations arise from abnormalities in speech perception — is supported by the finding that patients with, but not without, auditory hallucinations show deficits in speech tracking and sentence repetition [14].

It has been hypothesized that positive thought disorder reflects a specific deficit in processing meaning. At the level of individual words, this hypothesis has been explored using semantic priming paradigms [15]. Semantic priming is the decrease in the reaction time to name a target word, if the word presented just before the target is semantically related. The results of semantic priming studies in schizophrenia have been mixed, showing both increased, normal and decreased priming effects. These contradictory results may reflect the psychometric parameters and paradigms used, and have been interpreted as consistent with abnormalities in semantic processing. For example, increased direct and indirect priming (where subjects are more likely to associate relatively weakly 'linked' words with one another) in healthy subjects with elevated scores for schizophrenic language disturbances [16] has been interpreted as evidence for an activated (or disunited) semantic associative network. On the other hand, reduced priming to medium or highly associated words in positively thought-disordered patients may reflect a deficient pattern of activation within the semantic network [17]. Clinically, positive thought disorder is characterized not just by abnormal word associations, but by phenomena such as...
areas such as the parietal cortex \[22•,25\] and the superior with increased responses in distant yet highly connected becomes less accurate \[21,22•,23\]. Although this finding abnormal when WM load increases and performance function lies within the normal range and only becomes performance. DLPFC function may be dependent upon sensory information — in schizophrenia \[20\]. Several the internal representation, maintenance and updating of has been linked with impaired working memory (WM) — impaired dorsolateral prefrontal cortex (DLPFC) function schizophrenia \[20\]. A recent prospective study, for example, linked Schizophrenia and cognitive function \[38•\]. Frontal dysfunction in schizophrenia may be associated with increased responses in distant yet highly connected areas such as the parietal cortex \[22•,25\] and the superior temporal gyrus \[22•\]. Moreover, a recent PET study revealed abnormally high levels of hippocampal blood flow in schizophrenia: patients failed to show a normal modulation of hippocampal activity during word retrieval \[20••\]. There is increasing evidence that three brain regions that make strong connections with the frontal lobe — the thalamus, the striatum and the cerebellum — are also abnormal in schizophrenia. First, thalamic glucose metabolism during verbal learning is reduced in schizophrenia subjects, primarily in the region of the mediodorsal nucleus \[27•\]. Second, both treated and untreated patient groups show decreased striatal metabolic rates during a verbal learning task \[28\]. Third, studies of verbal learning and story recollection suggest that the cerebellum, via connections with both the DLPFC and the thalamus, is also part of the abnormal circuity in schizophrenia \[20,30•\].

Recent studies of eye-tracking dysfunction in schizophrenia provide further evidence for the involvement of both frontal and temporal regions \[31,32••,33,34,35•,36\]. First, the observed pattern of impaired pursuit eye movements and intact catch-up saccades implicates the frontal eye fields or their efferent or afferent pathways \[35•\]. Second, a series of recent studies has described a motion perception deficit with impaired velocity discrimination, suggesting the involvement of the motion processing area MT (medial temporal area) in the temporal lobe \[31,32••,33\].

In summary, perturbations of brain activity in schizophrenia are not localized to one brain region but to neural networks, primarily involving the frontal and temporal lobes as well as subcortical regions. It has been proposed that the functional connections between these regions may be abnormal in schizophrenia. This hypothesis has been tested using novel statistical approaches. For example, structural equation modeling (path analysis) of a semantic processing study using PET showed differences between schizophrenia and control groups in the neural interactions amongst frontal regions, between frontal and temporal regions, and between the frontal lobe and anterior cingulate cortex \[37•\]. When PET data from a memory study were analyzed for the effects of one neural system over another (so-called effective connectivity analysis), the normal anterior cingulate modulation of frontal-temporal interaction was found to be disrupted in schizophrenia \[30•\].

**Implications of cognitive dysfunction**

**Do cognitive deficits predict social functioning?**

There has been a renewed interest \[39\] in predicting how the schizophrenic patient will function in the community, on the basis of both symptoms and cognitive deficits \[40–43\]. After reviewing studies that evaluated cognitive measures as predictors and correlates of functional outcome for schizophrenic patients, Green \[39\] suggested that deficits in verbal memory and vigilance are the best predictors for impaired social functioning in the community. Subsequent studies have provided further evidence that cognitive deficits contribute directly to impaired social functioning \[40,41\]. Cognitive dysfunction is not the only predictor for social functioning in schizophrenia. A recent prospective study, for example, linked community functioning to the degree of disorganization \[43\]. Cognitive dysfunction is a valuable measure in the study of schizophrenia however, as it allows for objective

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**Mapping cognitive dysfunction in the brain**

Studies involving functional neuroimaging during several different cognitive tasks suggest that schizophrenia is associated with a widespread dysfunction within a network of brain areas involving the frontal and temporal cortex, the hippocampus, and subcortical regions. Impaired dorsolateral prefrontal cortex (DLPFC) function has been linked with impaired working memory (WM) — the internal representation, maintenance and updating of sensory information — in schizophrenia \[20\]. Several recent studies have given new insights into the precise rela- tionship between DLPFC dysfunction and WM performance. DLPFC function may be dependent upon task ‘difficulty’: during tasks with a low WM load, DLPFC function lies within the normal range and only becomes abnormal when WM load increases and performance becomes less accurate \[21,22•,23\]. Although this finding reconciles the divergent results of some previous studies, discrepancies still remain: both decreased \[21\] and increased \[23\] recruitment of DLPFC have been described during high-load WM tasks, and both right \[21\] and left \[23\] DLPFC may be involved. Moreover, deficits on different WM tasks are associated with distinct patterns of dysfunction: for example, WM deficit for words but not tones \[10••\] is associated with an impaired recruitment of left inferior frontal cortex \[24••\].

Frontal dysfunction in schizophrenia may be associated with increased responses in distant yet highly connected areas such as the parietal cortex \[22•,25\] and the superior temporal gyrus \[22•\]. Moreover, a recent PET study revealed abnormally high levels of hippocampal blood flow in schizophrenia: patients failed to show a normal modulation of hippocampal activity during word retrieval \[20••\]. There is increasing evidence that three brain regions that make strong connections with the frontal lobe — the thalamus, the striatum and the cerebellum — are also
The effect of medication on cognitive function

Psychotropic medication can, in theory, either impair or improve the cognitive skills of patients with schizophrenia. Moreover, some psychotropic medications may have selective beneficial effects on particular aspects of cognitive function. For example, there is preliminary evidence that several of the atypical antipsychotic drugs (such as risperidone and clozapine) improve cognitive skills more efficiently than typical antipsychotics (such as haloperidol) [44,45]. Indeed, cognition is emerging as a valuable outcome measure in the development of new atypical antipsychotic medications. Specifically, risperidone has been associated with improved verbal WM and clozapine with improved verbal fluency and verbal learning [44,45]. The mechanisms for the differential effects of psychotropic drugs is unclear [44], but could involve specific targets in the dopaminergic, noradrenergic, and cholinergic systems [46].

Neuroimaging studies provide an important link in the study of the neural mechanisms mediating the effects of antipsychotic medication on cognition: a recent fMRI study demonstrated that risperidone enhances brain activation during WM task performance in right prefrontal cortex, supplementary motor area, and posterior parietal cortex after substitution for typical antipsychotic drugs [47]. However, it is unclear how the differences in brain activation should be interpreted, because the task was sufficiently easy for the patients to perform at normal levels.

Conclusions

In recent years, we have seen the examination of cognitive function in many areas of schizophrenia research, perhaps reflecting our growing understanding of schizophrenia from a neurocognitive perspective. Cognitive dysfunction is a direct predictor of poor social functioning and can be ameliorated by corresponding antipsychotic drugs. Deficits are found in many behavioral domains, and are mediated by widespread but distinct abnormalities in brain function. The existence of specific patterns of cognitive dysfunction — many linked with particular clinical phenomena — suggests several important avenues of future research. Are specific associations and dissociations of cognitive dysfunction reflected by parallel patterns of neuroanatomical dysfunction? Can these, in turn, be linked to individual symptoms of schizophrenia? Do different drugs have selective effects on symptoms and cognition? If so, what is their mechanism of action? Addressing such questions has direct implications for the prognosis and treatment of the individual patient: it will pave the way towards the development of more rational approaches to treatment, whereby specific symptoms and cognitive deficits can be targeted and remedied.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

** of outstanding interest


In this paradigm, subjects were asked to monitor spoken sentences for target nouns (e.g. guitar), which were linguistically-violated compared with words in normal sentences. Compared with both other groups, thought-disordered patients showed significantly smaller differences in reaction time, suggesting that they were relatively insensitive to all linguistic violations. In this study, syntactic violations (exocategorization violations) were also semantically violated. Thus, further studies are required to determine whether positive-thought-disordered patients are specifically impaired in processing semantic aspects compared to syntax.


Fusing PET and fMRI data, this JST study demonstrated that DLPFC blood flow increased during learning and recoding words when the working memory load was low, but declined from the normal range with increased word list length. The DLPFC response was closely related to task performance in schizophrenia.


Using fMRI, the authors' working memory deficits in schizophrenia are associated with an impaired activation of language-associated areas in the left hemisphere in both patients and control subjects.


This study found that the normal hippocampal blood-flow increases during conscious recollection but show widespread frontal blood-flow increases and be better than normal recall accuracy during effortful retrieval.


This PET study reveals that hippocampus lacks the normal hippocampal blood-flow increases during conscious recollection but show widespread frontal blood-flow increases and become better than normal recall accuracy during effortful retrieval.


The authors summarize recent PET studies of a neural network including cortex, thalamus, and cerebellum during the performance of several memory tasks; in each of the studies, schizophrenia was associated with decreased blood flow in all or some of the three brain regions.


In this study, 15 patients with chronic schizophrenia showed deficient processing of velocity information; providing evidence for an impairment of motion-sensitive areas such as MT (in addition to frontal areas).


Twelve neurocopic smear first-episode patients showed impaired pursuit initiation, low steady-state pursuit gain, and preserved integrity in the processing of motion information, providing support for fronto eye field dysfunction in schizophrenia.


This PET study employed a statistical model (structural equation model) to determine the interaction between brain regions as a semantic processing task. Connections between frontal and temporal regions that were high positive in the control group were highly negative for the patients, and vice versa.


This PET study employed an anatomical model of connectivity to determine the interaction between brain regions as a semantic processing task. Connections between frontal and temporal regions that were high positive in the control group were highly negative for the patients, and vice versa.

