SPECIAL ARTICLE

Cognitive impairments in psychotic disorders: common mechanisms and measurement

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Decades of research have provided robust evidence of cognitive impairments in psychotic disorders. Individuals with schizophrenia appear to be impaired on the majority of neuropsychological tasks, leading some researchers to argue for a "generalized deficit", in which the multitude of cognitive impairments are the result of a common neurobiological source. One such common mechanism may be an inability to actively represent goal information in working memory as a means to guide behavior, with the associated neurobiological impairment being a disturbance in the function of the dorsolateral prefrontal cortex. Here, we provide a discussion of the evidence for such impairment in schizophrenia, and how it manifests in domains typically referred to as cognitive control, working memory and episodic memory. We also briefly discuss cognitive impairment in affective psychoses, reporting that the degree of impairment is worse in schizophrenia than in bipolar disorder and psychotic major depression, but the profile of impairment is similar, possibly reflecting common mechanisms at the neural level. Given the recent release of the DSM-5, we end with a brief discussion on assessing cognition in the context of diagnosis and treatment planning in psychotic disorders.

Key words: Cognitive control, working memory, episodic memory, cognitive deficits, schizophrenia, psychotic disorders, generalized deficit, DSM-5

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The last four decades have produced an impressive body of research on cognition in schizophrenia, in part prompted by the evidence that cognitive function is a critical determinant of quality of life and everyday functioning in people with this disorder, potentially more so than the severity of symptoms such as hallucinations and delusions (1-3).

A strikingly consistent finding within the cognitive neuroscience literature is that patients with schizophrenia display deficits on a huge variety of neuropsychological tasks (4,5). Historically, researchers had hypothesized impairments in specific cognitive domains with pockets of intact functioning in these patients, but there has been a recent push to re-conceptualize the range of deficits in schizophrenia as reflecting a "generalized" or "global" cognitive deficit, implying that cognitive impairments across domains share a common neurobiological source (6-10).

One such common mechanism may be an inability to actively represent goal information in working memory as a means to guide behavior, with the associated neurobiological impairment being a disturbance in the function of the dorsolateral prefrontal cortex (DLPFC) and its interactions with other brain regions such as the parietal cortex, the thalamus, and the striatum, and the influence of neurotransmitter systems such as dopamine, GABA and glutamate (11-13).

In this paper, we provide a discussion of the evidence for such impairment in schizophrenia, and how it manifests in domains typically referred to as cognitive control, working memory (WM) and episodic memory (EM). We also briefly discuss how cognitive impairments manifest across psychotic disorders in both the non-affective and affective psychosis domains. We end with an overview of the assessment of cognition in the DSM-5.

COGNITIVE CONTROL AND GOAL REPRESENTATIONS IN SCHIZOPHRENIA

In recent years, cognitive impairment in schizophrenia has been conceptualized as a deficit in the function of proactive cognitive control (12,14-16), or the ability to proactively maintain goal representations that can be used to guide ongoing behavior.

This conceptualization builds upon earlier ideas on the use of context information in psychosis (e.g., 17-19), to argue for flexible mechanisms of cognitive control that allow humans to deal with the diversity of challenges they face in everyday life. In this theory, termed dual mechanisms of control (12,14,15), a distinction is made between proactive and reactive modes of cognitive control.

The proactive control mode can be thought of as a form of "early selection", in which goal-relevant information is actively maintained in a sustained or anticipatory manner, before the occurrence of cognitively demanding events. This allows for the biasing of attention, perception, and action systems in a goal-driven manner. Goal information refers to information about what one needs to accomplish in a particular task or situation, or the intended outcome of a series of actions or mental operations. In real life, such goals may include the need to avoid eating a piece of cake while on a diet, maintaining points one wishes to communicate in a conversation, or overriding habits (e.g., driving straight home) to accomplish a specific goal (pick up one's dry cleaning).

In contrast, in the reactive mode, attentional control is recruited as a "late correction" mechanism that is mobilized only when needed, such as after a high-interference event is detected. For example, such a reactive control mechanism

might be engaged if you encounter an unexpected distracting stimulus and need to retrieve the topic of your conversation, or if your mind wanders and you suddenly find yourself at a critical intersection, where one direction leads home and the other leads to the dry cleaners. Thus, proactive control relies on the anticipation and prevention of interference before it occurs, whereas reactive control relies on the detection and resolution of interference after its onset.

This dual mechanisms of control theory, similar to other theories about cognitive control, suggests that proactive control depends on actively representing information in lateral prefrontal cortex (20), using this information to coordinate activity with other psychological and neural systems (21,22), and that the updating and maintenance of such information depends on precise inputs from neurotransmitter systems such as dopamine into prefrontal cortex (20). As such, proactive control may be particularly vulnerable to disruption, since it is resource demanding, and dependent upon precise dopamine-prefrontal interactions. Thus, we have suggested that populations characterized by disordered prefrontal and dopamine function (such as people with schizophrenia) may rely more heavily on reactive control, as it may be more robust in the face of such dysfunction (12).

There is convincing evidence for an association between impairments in DLPFC activity and deficits of proactive control in schizophrenia (23-26), for both medicated (27) and unmedicated patients (17,28), as well as those at risk for the development of the disorder (29,30). These findings were strengthened by a meta-analysis of imaging studies of executive control and proactive control, which demonstrated reduced activity in DLPFC in schizophrenia (25). Further, growing evidence suggests a critical role for impaired connectivity between the DLPFC and other cognitive control related brain regions (31-36), as well as for GABAergicly mediated (37) impairments in neural oscillations that may support representations in DLPFC (38,39). A relationship between dopaminergic function and DLPFC activity in schizophrenia (40), and a positive impact of dopamine enhancement on cognitive control in psychosis (41,42), have also been documented.

WORKING MEMORY IN SCHIZOPHRENIA

Although many studies have focused on understanding cognitive control deficits in schizophrenia, an even larger amount of research has been devoted to the cognitive neuroscience of WM (43), leading to an overwhelming amount of evidence in support of WM impairments in schizophrenia (e.g., 5,44).

WM traditionally refers to temporary storage and manipulating information "on-line", typically in the service of some goal (45), but it is not a unitary construct. For example, Baddeley's model of WM suggests that it is comprised of a central executive resource system, two slave subsidiary systems (the phonological loop and the visuo-spatial sketchpad), and an episodic buffer (45).

There is relatively little evidence that WM deficits can be unambiguously attributed to dysfunction in either the verbal or visual-spatial buffer systems, as individuals with schizophrenia exhibit abnormalities on WM tasks with many different material types, with relatively little evidence for selective deficits for one material type over another (5,44). This has led to the suggestion that WM deficits in schizophrenia might primarily reflect deficits in the central executive resource system, or the active maintenance and manipulation of information over time, an interpretation consistent with a central role for deficits in the proactive control of behavior.

However, there is debate about the degree to which WM impairments in schizophrenia really reflect deficits in the maintenance of information, versus the initial encoding or representation of information. For example, in one meta-analysis (44), the effect sizes of WM impairment across studies did not change as a function of the delay period used, implying that deficits in the initial generation of representations could impact the stability of such representations, and therefore the ability to accurately maintain them over time. Consistent with this hypothesis, studies examining encoding deficits have demonstrated that patients with schizophrenia exhibit deficits even in the absence of a delay (e.g., 46). At the same time, a number of studies have provided evidence for deficits in the ability to maintain information across time in schizophrenia, even after controlling for encoding differences (e.g., 46,47).

Prefrontal recruitment during working memory in schizophrenia

Similar to the literature on cognitive control and DLPFC function, there is a robust functional neuroimaging literature demonstrating the presence of abnormalities in prefrontal cortex recruitment associated with WM dysfunction in schizophrenia.

The majority of findings suggest that regions comprising the dorsal frontal-parietal network are affected in patients and may be contributing to WM abnormalities. Specifically, reductions in DLPFC (Brodmann's area 9/46) activation have been documented while patients perform WM tasks, suggesting that patients exhibit task-related "hypofrontality" (17,48). These findings have also been confirmed through quantitative meta-analytic studies (49,50). Such DLPFC deficits are present even in medication naïve individuals (17), and also occur, albeit to a lesser extent, in the first-degree relatives of individuals with schizophrenia (e.g., 29), suggesting a potential role as an endophenotypic marker.

Further, as with proactive cognitive control, there is evidence suggesting a key role for impaired connectivity between DLPFC and other WM related regions (e.g., parietal cortex, thalamus and striatum) in explaining WM impairments in

schizophrenia (51-55), as well as evidence for altered gamma and theta oscillatory activity in prefrontal regions associated with WM impairments in this disorder (e.g., 56-58).

The above discussion focused on decreased DLPFC activity associated with proactive control and WM. However, there have been discrepant findings with regard to whether individuals with schizophrenia show decreased or increased DLPFC activity during WM (59-61). To explain this, some work has focused on the idea that WM capacity may be dependent on the level of recruitment of DLPFC, which is thought to operate according to an inverted U model (62). Such a model suggests that, with increasing WM demands, there is a concomitant parametric DLPFC signal increase. However, as WM load demands reach and exceed capacity limitations, DLPFC signals begin to drop, presumably due to information load exceeding available computational resources (62).

In line with this hypothesis, evidence suggests that patients with schizophrenia may exhibit a shifted inverted U function, such that capacity limitations are reached faster (i.e., with lower WM load levels), which may result in over- or under-recruitment when compared to healthy controls, depending on the level of WM load at which the groups are compared (63-65). In other words, at low difficulty levels, patients may find performance more effortful and may have to recruit more prefrontal cortex resources than healthy controls to accomplish the same task, leading to findings of "hyperactivity" in prefrontal cortex. Consistent with this model, a meta-analysis (50) demonstrated that the magnitude of WM performance differences between patients and healthy controls was positively correlated with the magnitude of activation differences in dorsallateral prefrontal regions.

Another way to understand the mixed directions of WM related DLPFC activation in schizophrenia is to think about the temporal course of WM. If WM impairments in schizophrenia also reflect impairments in proactive control and DLPFC mediated function, then more specific predictions can be made about the timing of altered brain activation in WM tasks in schizophrenia. A failure to use proactive control would suggest that patients may show reduced activity during encoding and/or maintenance in lateral prefrontal regions. When a response is needed, they may need to try to retrieve the memoranda, potentially resulting in increased activation in brain regions associated with memory retrieval or response selection.

A number of studies that examined the time course of activity during WM trials have shown evidence for reduced activity during encoding and maintenance periods in DLPFC, as well as other WM related brain regions (12,66-69). Further, studies that have specifically examined retrieval related activity have found evidence for increased activation among individuals with schizophrenia in either the same or different regions that showed reduced encoding/maintenance related activation (12,65). Thus, it may be useful in future research to more specifically tease apart the components of WM, as well as to examine the role of overall level of performance.

EPISODIC MEMORY IN SCHIZOPHRENIA

Similarly to WM, EM is not a unitary construct, but instead involves a number of different functional components and associated neural systems. The current literature on EM posits critical roles for both the medial temporal lobe, with a particular focus on the hippocampus, and prefrontal regions.

A common theme in theories regarding the role of the hippocampus in EM is the idea that it is critical for the rapid binding of novel configurations of information (e.g., 70,71). Consistent with such theories, numerous imaging studies have shown activation of the hippocampus during the encoding or retrieval of novel relational information (e.g., 72), and have shown that enhanced hippocampal/parahippocampal activity at the time of encoding predicts subsequent successful retrieval of that information (e.g., 73,74). Furthermore, work in amnestic patients demonstrates the importance of hippocampal structures in relational processing (e.g., 75).

More recent models of EM also suggest differential roles for hippocampal versus perirhinal regions of the medial temporal lobes in encoding of item versus relational memory (76). At the same time, there are also clearly important contributions from prefrontal regions. Damage to the prefrontal cortex can lead to EM deficits, among other cognitive impairments (e.g., 77,78). Further, activity during encoding in a number of prefrontal regions (e.g., Brodmann's areas 45 and 47) predicts subsequent memory when participants are asked to process verbal information using semantic elaboration strategies (79,80). In addition, there is work suggesting that DLPFC may contribute specifically to successful relational memory formation and retrieval (81-83).

As discussed above, much of the EM literature has argued that the hippocampus is critical for binding information in memory. A number of studies have examined whether individuals with schizophrenia have binding deficits by exploring whether they are more impaired on memory for associative information (e.g., the association of previously unrelated words or items) as compared to memory for individual items. For example, Achim and Lepage (84) conducted a meta-analysis comparing performance on associative and item memory tests in individuals with schizophrenia, and concluded that there was evidence for a 20% greater impairment in associative as compared to item memory. However, a number of the associative memory studies included in this meta-analysis were tests of source memory (i.e., memory for the time and place in which an event occurred) rather than associations of novel pairs of items, and the human neuropsychological and imaging literatures suggests that PFC function may make an important contribution to source memory (85).

More recently, clinical researchers have begun to use tasks derived from the animal literature on hippocampal function, such as the transitive interference test, which measures the ability to learn the relationships among hierarchically arranged stimulus pairs, as well as the transitive patterning test, in which individuals have to learn about relationships between items for correct selection. Individuals with schizophrenia are impaired on critical conditions of these tasks requiring relational processing, but not on conditions that require simpler associative reinforcement mappings (86-88), though not in all studies (89).

Other work has used eye-movement measures of relational memory, shown to be impaired in patients with hippocampal lesions (e.g., 90), to identify relational memory impairments in schizophrenia (e.g., 91,92). There is also work indicating impairments in both item and relational retrieval for information that was relationally encoded in schizophrenia (93). Still other work has provided evidence for greater deficits in recollection than familiarity in schizophrenia, which have also been interpreted as reflecting relational memory impairments (e.g., 94). It is certainly possible that this pattern of EM deficits in schizophrenia suggest hippocampally mediated impairments (95). However, as noted above, prefrontal structures also contribute to EM, and this may be particularly important for control functions, such as the ability to generate and apply effective memory strategies that help bind novel information into memory. Accordingly, a number of studies suggest that individuals with schizophrenia are impaired in their ability to generate effective mnemonic strategies, and that providing people with schizophrenia with effective memory strategies enhances EM function (for a review, see 96).

Importantly, a meta-analysis of brain activity alterations during EM performance in schizophrenia showed consistent evidence for reduced activation in both ventrolateral prefrontal cortex and DLPFC, but did not find consistent evidence for altered hippocampal activity (97). Recent work on relational memory encoding and retrieval has shown evidence for impaired DLPFC function associated with impaired relational memory function (98) and autobiographical memory (99) in schizophrenia, though other recent work has also implicated hippocampal function (100).

Taken together, these findings suggest potential roles for both hippocampal and prefrontal function in EM, and also suggest the possibility that cognitive control deficits may contribute to EM deficits in schizophrenia.

COGNITION ACROSS PSYCHOTIC DISORDERS

A key question is whether the nature and/or severity of cognitive impairment found in affective psychoses is similar or different to that found in schizophrenia. If qualitatively different, this would argue for a fundamentally different role for cognition in those psychoses. However, if the pattern or profile of cognitive impairment is similar, such a result would be consistent with the hypothesis that there are common dimensions of psychopathology across the affective and non-affective psychoses (101).

Both empirical and meta-analytic studies have fairly consistently shown that the degree of cognitive impairment in schizophrenia is worse than in bipolar disorder (for a review, see 102) and psychotic major depression (103), with an effect size typically in the range of 0.3 to 0.5 (103-107). The literature on the comparison of schizoaffective disorder to schizophrenia is mixed, with some studies finding very similar magnitudes of cognitive impairments in these two disorders (108-110) and others reporting worse impairment in schizophrenia (107,111).

Despite the evidence of a larger magnitude of cognitive impairment in schizophrenia as compared to affective psychoses, the literature is fairly consistent in demonstrating that the profile of cognitive impairment is similar across schizophrenia and affective psychoses (112,113). In other words, the relative severity of impairments across different cognitive domains tends to be very similar in bipolar disorder, psychotic major depression and schizoaffective disorders as compared to schizophrenia (e.g., 104,105,109,114).

Perhaps one of the clearest examples of such a result was provided by Reichenberg et al (114). These researchers compared individuals with consensus research diagnoses of schizophrenia, schizoaffective disorder, major depressive disorder with psychotic features, and bipolar disorder with psychotic features. The individuals with schizophrenia and schizoaffective disorder were overall more impaired than the individuals with psychotic affective disorders, and the prevalence of cognitive impairment was higher in schizophrenia and schizoaffective disorder. However, the individuals within all four groups showed the same relative pattern of impairment across cognitive domains, with the greatest impairment in verbal memory, and the least impairment in visual processing and general verbal ability.

Depp et al (104) provided another compelling example in their study comparing patients with schizophrenia or bipolar disorder and healthy controls. The profile of impairment was very similar in the two patient groups, with the most impairment in information processing speed and the least in crystallized IQ. In addition, there is evidence that the factor structure of cognition is very similar across schizophrenia and bipolar disorder (115,116). There are, however, some exceptions to these results, and some studies that have shown differences across psychotic disorders in the pattern of cognitive impairment (e.g., 111).

Thus, the bulk of the evidence suggests that all psychoses (affective and non-affective) are associated with some level of cognitive impairment. This impairment may be equally severe in schizophrenia and schizoaffective disorder, but less severe in individuals with psychotic bipolar disorder and psychotic major depression. However, the profile or pattern of cognitive impairment across affective psychoses is very similar to that seen in schizophrenia. This finding is consistent with the idea that there are common mechanisms

that lead to cognitive dysfunction across psychotic disorders and with a growing emphasis on identifying core neural systems that contribute to impairments cutting across traditional diagnostic boundaries (117).

MEASURING COGNITION IN THE DSM-5

As reviewed above, there is ample evidence that a large percentage of individuals with schizophrenia and other psychotic disorders suffer from impairments in a range of cognitive domains (e.g., 114), and growing evidence that the level of cognitive impairment predicts functional abilities (social, occupational, living status) (e.g., 118,119-121).

Despite the importance of cognition in understanding function in schizophrenia and other psychotic disorders, the DSM-5 psychosis committee did not propose to include cognitive deficits as a criterion A symptom of schizophrenia or any other psychotic disorder. This is because cognition may not be useful as a differential diagnosis tool. As described above, the profile of cognitive impairments is similar across the non-affective and affective psychoses (103-105,109,114,122), though the level of impairment may be greater in non-affective psychoses (103-106). However, the wealth of data suggests that this separation is not sufficient to justify inclusion of cognition as a criterion A symptom of schizophrenia.

Nonetheless, it remains clear that cognitive function is important for understanding functional status in schizophrenia (121,123,124), as well as other psychotic disorders, including bipolar disorder (125-128), and that cognitive deficits are not well treated by current antipsychotic medications (e.g., 129). Thus, the DSM-5 psychosis committee included a dimensional assessment of cognition, in order to highlight the potential need for additional treatments specifically targeting cognitive remediation in schizophrenia and other psychotic disorders (e.g., 130,131).

This assessment is a single dimension that collapses across all potential aspects of cognitive impairment. Ideally, one might have a separate dimensional rating of most major domains of cognitive impairment in psychosis separately, as it is possible to see dissociations across the level of impairment in one domain versus another within an individual (e.g., relatively impaired in WM, more so than in EM). However, this is not feasible from a practical standpoint, and the pretense of at least a single global dimension serves to highlight the need to attend to cognitive impairment when conceptualizing treatment and prognosis for an individual with psychosis.

Information about cognitive function is not something that is typically possible to assess as part of the standard psychiatric interview. Ideally, one would obtain a formal clinical neuropsychological assessment in individuals with psychosis to fully understand the nature and severity of their cognitive impairments. Such assessment may be of particular value early in the course of illness, when considering plans for further education and vocational functioning. If it is not possible to obtain a full neuropsychological evaluation, a number of studies have shown that several different brief assessment approaches provide clinically useful information concerning a patient's general level of cognitive impairment (7,8,132-136). However, brief screening instruments developed for use in the detection of frank dementia, such as the Mini-Mental Status Exam, are not sensitive to the types of impairments that are typically observed in patients with schizophrenia and therefore their use is discouraged in this context.

The growing research on other methods for assessing cognitive function (e.g., self-report, clinician interview) suggests that they have limited correlation with objective measures of cognitive performance (137), though they may still have utility in predicting functional status (137-144). If a formal assessment of cognition is not possible, it is still important for the clinician to use the best available information to make a judgment about the individual's cognitive function, including the clinician's interactions with the patient and/or reports of family members or clinical staff. However, it is likely that, without objective assessments, such ratings may have less than optimal reliability and validity, though hopefully they will still serve to highlight the critical need for treatments that address this debilitating aspect of psychotic disorders.

CONCLUSIONS

Individuals with schizophrenia show significant deficits in a number of different cognitive domains, including cognitive control, WM and EM, and the pattern of deficits is similar to those observed in affective psychotic disorders. Given the emerging re-conceptualization of cognition in schizophrenia (or all psychotic disorders) as reflecting a core neurobiological abnormality, we suggest that an impairment in proactive control can influence performance in a wide variety of cognitive domains, and therefore may represent a common mechanism contributing to these deficits.

Further, we suggest that, at the neural level, a common denominator to such deficits may be an impaired function of DLPFC, its connectivity with other brain regions, and the neurotransmitter systems that support precise updating and maintenance of goal representations which enable proactive control.

We do not mean to imply that all aspects of cognitive impairment in schizophrenia can be fully explained by these mechanisms. Schizophrenia is a complex disorder, and it is clear that it would be an oversimplification to suggest that a single mechanism could explain the diversity of impairments found in this illness. Nonetheless, we think it important to raise the possibility that there is a common core mechanism that can help explain at least a subset of impairments, and which may serve as a target for therapeutic interventions that could broadly enhance cognitive function and outcome in this illness.

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