Original article

Cognitive impairment in psychotic illness: prevalence, profile of impairment, developmental course, and treatment considerations

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Despite effective pharmacological treatments for psychotic symptoms (eg, hallucinations, delusions), functional outcomes for people with psychotic disorders are often disappointing. Although it is not included in the diagnostic criteria for psychotic disorders, cognitive impairment is one of the strongest determinants of community functioning in this clinical population, and thus it is an important target for intervention. In this review, we discuss the major areas of research regarding impaired cognition in psychotic illness. The specific topics covered include: (i) the prevalence of cognitive impairment in psychotic disorders; (ii) the profile and magnitude of cognitive impairment in psychotic disorders; (iii) the developmental course of cognitive impairment; (iv) the longitudinal stability of cognitive impairment; and (v) treatment approaches to improve cognitive performance in people with psychotic disorders.

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Introduction

Psychosis refers to a constellation of symptoms categorized as positive (eg, delusions, hallucinations), disorganized (eg, odd speech and behavior), or negative (eg, anhedonia, avolition). These symptoms occur in primary psychotic disorders (eg, schizophreniform disorder, schizophrenia, schizoaffective disorder) and the affective psychoses (eg, bipolar disorder with psychotic features, major depressive disorder with psychotic features), but can also occur in certain general medical cognitions or following exposure to some medications, substances, or alcohol. Schizophrenia, arguably the most severe and persistent psychotic illness, has a lifetime prevalence of about 1%, while psychosis more broadly is estimated to impact roughly 3% of the population.[1] Beyond the clinical symptoms of psychosis, the majority of individuals with primary psychotic disorders or affective psychosis also exhibit significantly impaired cognition. These impairments are indicated by reduced performance on neuropsychological testing, and have serious consequences for functional recovery in this clinical population.

Although early descriptions of schizophrenia by Kraepelin did emphasize cognitive decline (ie, "dementia praecox" or premature dementia), the dramatic positive symptoms

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of psychosis have historically been the primary focus of treatment efforts. However, despite effective pharmacological treatments for positive symptoms, functional outcomes for people with psychotic disorders are often disappointing. Indeed, schizophrenia is a leading cause of disability worldwide.[2] Since the 1990s there has been a renewed interest in cognition in the psychoses, as well as a growing recognition that psychotic illnesses are cognitive disorders.[3,4] Notably, cognitive performance is one of the strongest determinants of community functioning in people with psychotic disorders.[5,6] Thus, cognition has been established as an important treatment target to improve functional outcomes in people with psychosis.

> Cognitive performance is a robust predictor of community functioning in people with psychotic disorders, and thus is an important target for intervention

In this review, we discuss a few of the major questions researchers have grappled with regarding cognition in psychotic illness. Specifically, what proportion of patients are impacted by cognitive impairment? What is the profile and magnitude of cognitive impairment? When do cognitive impairments occur during the illness course, and do they worsen over time? And finally, can we intervene to improve cognition?

Who is impacted by impaired cognition?

Cognitive impairment in primary psychotic disorders is ubiquitous, with approximately 80% of patients exhibiting clinically significant impairment (ie, at least one standard deviation below the population mean).[7-9] Notably, there is a subset of individuals who perform within normal limits[10] or in the superior range on neuropsychological tests.[11] However, even in the absence of clinically significant cognitive impairment, it has been argued that all individuals with a primary psychotic disorder perform at a level below what would be expected had they never developed a psychotic illness.[12,13] Evidence for this assertion can be found in studies of monozygotic twins discordant for schizophrenia[14] and studies comparing cognitive performance with expectations based on estimates of the individual's premorbid level of intellectual functioning.[11,15,16]

Compared with the vast literature in primary psychotic disorders, there are far fewer studies of the prevalence of cognitive impairment in the affective psychoses. The available evidence does suggest that cognitive impairment is common, with one study reporting approximately 60% of patients with affective psychoses exhibit clinically significant cognitive impairment.[9] However, the rates of cognitive impairment in affective psychoses are significantly lower than those observed in primary psychotic disorders.[9]

What are the cognitive deficits in psychotic illness?

To date, several comprehensive meta-analytic reviews have been published comparing cognitive performance of individuals with schizophrenia with that of healthy adults. These empirical reviews consistently show markedly impaired performance across a wide range of cognitive tests and domains in schizophrenia, with mean effect sizes in the large range.[17-20] Notably, effects tend to be somewhat larger for tests assessing memory[17-20] and processing speed,[17] and slightly smaller for measures of language and vocabulary[17-20] and spatial reasoning.[17,20]

Cognitive impairment in schizophrenia is not appreciably moderated by clinical factors such as duration of illness or positive symptom burden.[17] However, men may have more severe cognitive impairments, as larger effect sizes tend to be reported in studies with greater proportions of male patients.[17,18] While the Schaefer et al[17] review did not find a significant association between age of onset and magnitude of cognitive impairment, it has been reported elsewhere that more severe cognitive impairments are associated with youth-onset schizophrenia (ie, onset prior to 19 years of age), particularly for general intellectual functioning, processing speed, memory, and executive functions.[21]

While a similar pattern of diffuse cognitive impairment is observed in schizoaffective disorder, the magnitude of impairment may be marginally reduced compared with schizophrenia. When cognitive performance of individuals with schizoaffective disorder are directly compared with those with schizophrenia, better performance is evident in schizoaffective disorder across a wide range of cognitive tests. However, these effects are small (*d*'s<0.32), suggesting limited clinical significance.[22] Compared with

healthy adults, individuals with affective psychoses exhibit moderate to large deficits across cognitive tasks, with the largest patient-control differences observed for tests of attention, verbal fluency, and learning and memory.[22,23] However, the magnitude of cognitive impairment in affective psychoses is attenuated compared with schizophrenia.[22]

One notable limitation of the research reviewed above is a lack of consensus regarding how cognition is assessed, both in terms of the specific cognitive tests administered, and the breadth of cognitive domains assessed. This lack of consistency makes direct comparison of findings across diagnostic groups and across studies very difficult. This has also been a tremendous barrier for treatment research, particularly for clinical trials of cognitive enhancing pharmacological agents and psychosocial interventions.[24] In 2004, the National Institute of Mental Health (NIMH) launched the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative, which included a series of consensus meetings with experts from academia, industry, and government in multiple fields focusing on the methods that should be used in clinical trials to evaluate cognition-enhancing treatments for schizophrenia.[24,25] The MATRICS Consensus Cognitive Battery (MCCB),[26] an FDA-recommended compendium of cognitive tasks, was a key product of the MATRICS initiative.

Creation of the MCCB involved a multistep process[27] that included consensus meetings to identify the important cognitive domains and candidate tests for each domain,[28,29] evaluation of candidate tests and selection of the final test battery,[30] and co-norming the test battery on a representative sample of healthy adults.[31] Seven cognitive domains were identified for inclusion in the MCCB: Speed of Processing, Attention/Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning and Problem Solving, and Social Cognition. This seven-factor structure has since been supported with confirmatory factor analysis.[32] Of the 90 candidate tests evaluated, 10 were selected for the final MCCB battery based on factors such as test-retest reliability, utility as a repeated measure, relationship to functional outcome, tolerability (for patients), and practicality (for test administrators). The MCCB tests and their respective cognitive domains are listed in *Table I*.

DOMAIN	TEST	PERFORMANCE INDEX
Speed of Processing	BACS Symbol Coding Test (BACS SC)	Total number correct
	Category Fluency Test, Animal Naming (Fluency)	Total number of animals named in 60 s
	Trail Making Test, Part A (TMTA)	Time to completion
Attention/Vigilance	Continuous Performance Test, Identical Pairs (CPT-IP)	Overall d'
Working Memory	WMS 3rd ed., Spatial Span (WMS-III SS)	Sum of raw scores on forward and backward conditions
	Letter-Number Span Test (LNS)	Number of correct trials
Verbal Learning	Hopkins Verbal Learning Test – Revised (HVLT-R)	Total number of words recalled correctly over three learning trials
Visual Learning	Brief Visual Memory Test – Revised (BVMT-R)	Total recall score over 3 learning trials
Reasoning & Problem Solving	NAB Mazes Subtest (NAB Mazes)	Total raw score
Social Cognition	MSCEIT Managing Emotions	Standard score across all responses

Table I. MATRICS Consensus Cognitive Battery (MCCB) domains, tests, and performance indices. BAC, Brief Assessment of Cognition in Schizophrenia; WMS-III: Wechsler Memory Scale – 3rd Ed; NAB: Neuropsychological Assessment Battery; MSCEIT: Mayer-Salovey-Caruso Emotional Intelligence Test.

Adoption of the MCCB as a neuropsychological test battery in psychosis research is on the rise. At the time of this writing, ClinicalTrials.gov, an online registry of clinical trials across the globe maintained by the National Institutes of Health and National Library of Medicine, lists over 100 studies that employ the MCCB. Official translations of the battery are available for over 20 languages, and normative data on healthy adults have been collected in 10 countries in seven of the languages.

As a group, individuals with schizophrenia or schizoaffective disorder exhibit marked impairment across all seven MCCB domains, with performance ranging from about 1.0 to 1.7 SD below that of the healthy adult normative sample.[33] Relatively greater impairment is noted for the Speed of Processing and Working Memory domains, and relatively less impairment for Reasoning and Problem Solving. As the MCCB is adopted by an increasing number of clinical researchers, we expect profiles of MCCB impairment for different diagnostic groups to emerge. A recent study comparing MCCB performance in bipolar disorder with psychotic features, schizophrenia, and healthy adults found intermediate performance in the affective psychosis group.[34] Although the bipolar group was uniformly impaired compared with healthy adults on all MCCB domains with the exception of Social Cognition, the magnitude of impairment in bipolar was smaller compared with the schizophrenia group (ie, bipolar group performance approximately 0.5 SD below healthy adults).

What is the developmental course of cognitive impairment in psychotic illness?

Roughly coinciding with the renewed interest on cognition in schizophrenia, there was a shift in the conceptualization of psychotic illness from that of a neurodegenerative disorder to that of a neurodevelopmental disorder.[35,36] Evidence accumulated to indicate that subtle neurological and motor abnormalities preceded the onset of psychotic symptoms by many years,[37,38] raising questions regarding the developmental course of cognitive impairment in psychotic disorders. One question researchers have wrestled with is about the timing of cognitive impairment during the illness course. Specifically, are cognitive impairments present at the onset of psychosis, or perhaps does cognitive impairment precede the onset of psychosis?

To address the questions about the onset of cognitive impairment, we turn to studies examining cognition at early stages of the illness with recent onset (RO) psychosis (ie, individuals within the first few years of psychotic illness onset) and in samples at genetic high risk (GHR) (ie, first-degree relatives of schizophrenia probands) or clinical high risk (CHR, ie, individuals putatively prodromal for a psychotic illness). Results from a comprehensive meta-analytic review of 47 studies of cognition RO psychotic disorders indicate that marked cognitive impairment is already present at the onset of the illness.[39] Large effect sizes (SMD=-0.74 to -1.20) were evident in all of the ten cognitive domains assessed (ie, general cognitive ability, immediate verbal memory, delayed verbal memory, immediate nonverbal memory, processing speed, language, executive functioning, working memory, vigilance, motor skills, social cognition). Notably, the magnitude of these effects in RO psychosis mirror those observed in well-established psychotic illness.[17-20] Similar impairments are also evident in unmedicated RO psychosis samples,[40] indicating that cognitive impairments are not simply an artifact of exposure to psychotropic medications. The MCCB performance profile and magnitude of impairment in a sample of 105 people with RO schizophrenia was remarkably similar to that of individuals with chronic schizophrenia, although there was evidence for mild relative sparing of Working Memory and Social Cognition in the RO sample.[41] Longitudinal research, reviewed in the next section, adds further information concerning subtle declines in some cognitive domains occur during the course of illness.

Studies of groups at increased risk for development of schizophrenia address the issue of whether cognitive deficits actually precede the first psychotic episode rather than have an onset with psychotic symptoms. The initial attempts to address this issue focused on first-degree relatives of schizophrenia patients, particularly children born to a parent with schizophrenia. Given that first-degree relatives have a 10-fold increased risk of schizophrenia compared with the general population and often share some schizophrenia susceptibility genes with their ill family member, this group is at increased genetic risk and has been examined to detect cognitive deficits that may reflect aspects of genetic vulnerability to develop this disorder. A series of studies of GHR samples documented that an attenuated magnitude of cognitive deficits are present.[42,43] A meta-analysis

by Snitz, MacDonald, and Carter,[44] examining studies that included first-degree relatives of schizophrenia probands and demographically matched comparison samples, summarized this literature. First-degree relatives show a deficit in several domains of cognition, including processing speed, sustained attention, working memory, verbal memory, visual memory, and reasoning and problem solving, with deficits in sustained attention being among the largest.[44] These cognitive deficits are approximately half the magnitude of those typically found among schizophrenia patients. Furthermore, a longitudinal study of a sample of children born to a parent with schizophrenia found that those children who developed schizophrenia spectrum disorders by age 25 had shown sustained attention deficits at age 12.[45] Thus, the literature suggests that cognitive deficits occur at attenuated levels in GHR groups and may be genetic susceptibility indicators in those who have not yet experienced any psychotic symptoms.

Studies of CHR samples have started to add further evidence about the onset of cognitive deficits. Impairments across cognitive domains are evident, but the effect sizes tend to be smaller than those observed in RO psychosis and well-established psychotic illness. A meta-analysis of 19 studies reported small to medium effect sizes (g=-0.18 to -0.40) across the nine cognitive domains assessed (ie, general intelligence, verbal fluency, processing speed, attention, visual memory, verbal memory, working memory, executive functioning, and social cognition).[46]

Notably, like GHR samples, CHR samples are very heterogeneous, and only a subset of these individuals go on to develop a psychotic illness. Thus, the magnitude of cognitive impairment in the CHR group as a whole may be less helpful to address questions about the developmental course of cognitive impairment in psychotic illness compared with the magnitude of impairment for the CHR subgroup that later develops psychosis (CHR+). In some published CHR studies, researchers report later clinical status (ie, whether the individual transitioned to psychotic illness within a specified follow-up period or not). Fusar-Poli et al[46] report that in the seven studies included in the meta-analysis that reported follow-up clinical status, the CHR+ group evidenced significantly greater impairment in general intelligence, verbal fluency, verbal and visual memory, and working memory compared with the CHR group who did not transition to psychosis during the follow-up period (CHR-). A subsequent meta-analysis of nine studies comparing baseline cognitive performance in CHR+ to CHR- found significantly poorer performance on tasks of working memory (ES=-0.29) and visual learning (ES=-0.40) in the CHR+ group.[47] Finally, a 2-year longitudinal study comparing cognitive performance in CHR and healthy comparison subjects found that baseline cognitive impairment was especially severe among the CHR+ group.[48] Moreover, in the entire CHR sample, severity of cognitive impairment at the baseline assessment was associated with increased risk for subsequent conversion to psychotic illness and non-remission of CHR status over follow-up.[48]

A recent study comparing MCCB performance in a large sample of CHR (n=205), a RO psychosis group (n=28), a "help-seeking" comparison group (ie, individuals who did not meet CHR criteria, but were nonetheless seeking mental health services; n=89), and a healthy comparison group (n=60) found moderate impairment in Speed of Processing and Attention/Vigilance in the entire CHR group compared with the healthy comparison sample (d=0.63 to 0.69), while the RO psychosis group exhibited greater magnitude of impairment across domains (d=-0.72 to -1.09).[49] While the MCCB profile of the entire CHR group closely resembled that of the help-seeking comparison group, the MCCB profile for the CHR+ group (n=12) was extraordinarily similar to that of the RO psychosis group. These CHR+ participants significantly differed from the healthy comparison group in Speed of Processing (d=1.10), Verbal Learning and Memory (d=1.12), and MCCB overall composite score (d=1.12). Thus, the pattern and magnitude of cognitive impairment in this CHR+ group closely resembled impairment observed in individuals with an established psychotic illness.

Taken together, the results of the GHR and CHR studies conducted to date support the view that significant cognitive deficits precede the onset of psychotic symptoms. Attenuation of effect sizes in GHR and CHR samples compared with established psychotic disorders likely reflects heterogeneity of these high-risk samples with respect to future clinical outcomes (ie, eventual transition to psychotic illness, stability or remission of subclinical symptoms, etc), at least in part. However, although more data are needed, the available evidence suggests that the pattern and magnitude of cognitive impairment in CHR+ may not substantially differ from that observed in established psychotic disorders.

Does cognition progressively deteriorate over the illness course?

Having established that cognitive impairment precedes the onset of psychotic illness, consistent with a neurodevelopmental conceptualization of psychotic disorders, questions remain regarding the longitudinal stability of cognitive impairment. Does cognition progressively deteriorate over the course of illness, or are the impairments relatively stable? Although the studies reviewed above reporting effect sizes in CHR+, RO psychosis, and well-established psychosis do not suggest major differences in performance across phases of illness; only longitudinal studies can directly address questions about stability.

Evidence from longitudinal studies in CHR are consistent with stability, and in some cases slight improvement, of cognitive performance over short-term (2 years)[48] and long-term (10 years) follow-up periods.[50] Indeed, a meta-analysis of 25 longitudinal studies of CHR, RO psychosis, and healthy comparison subjects found no evidence for progressive decline over follow-up (range= 0.5 to 7 years) in the CHR group.[51] Thus, the cross-sectional studies described in the previous section indicate that impaired cognition is already present during prodromal phase of psychotic illness, and there is no compelling longitudinal evidence for significant progressive deterioration of cognition during the transition to psychotic illness.

Similar evidence for stability is evident in longitudinal studies of RO psychotic illness over 1 to 5 years.[51,52] Stability is also reported over longer periods. A 10-year follow-up of 171 RO psychosis patients who participated in the OPUS early intervention study reported no significant change in performance on tasks of processing speed, set-shifting, verbal fluency, and design fluency, indicating stability of cognitive performance over 10 years.[53] Likewise, two additional smaller-scale follow-up studies also support stability of cognition over 10 years in RO psychosis.[54,55] Thus, these longitudinal studies do not support progressive deterioration of cognition during the transition between the early and well-established (ie, chronic) phases of psychotic illness. Notably, these longitudinal studies did not involve interventions that specifically targeted cognition.

Finally, most longitudinal studies do not support progressive cognitive decline during the chronic phase of psychotic illness, but there is heterogeneity in the course. A meta-analysis of 53 longitudinal studies of cognition in chronic schizophrenia found no evidence for decline in cognitive performance over follow-up (mean follow-up period=12 months, median=4 months).[56] However, a study of cognitive trajectories over a 3.5-year follow-up period indicated heterogeneity of cognitive outcomes in a large sample with chronic schizophrenia.[57] Specifically, cognitive stability was reported for 50% of the schizophrenia sample (ie, mean change of 0.03 points per year on the Mattis Dementia Rating Scale), a modestly declining trajectory for 40% (ie, mean change of -0.43 MDRS points per year), and rapidly declining trajectory for the remaining 10% (ie, mean change of -2.11 MDRS points per year). A declining trajectory was associated with factors such as living in a board-and-care facility (ie, not living independently), greater negative symptom burden, and an earlier age of onset of psychotic illness. Regarding cognitive changes later in life, a meta-analysis of 14 longitudinal studies of cognition in older adults with schizophrenia reported small effect sizes (d=-0.10) for change in cognitive functioning over follow-up (mean follow-up period=2.21 years, range=1-6 years), indicating that cognitive performance did not appreciably decline.[58] However, marked cognitive decline late in life has been reported for people with a significant history of institutionalization.[59-61] These findings, along with those of Thompson et al,[57] suggest long-term stability of cognitive impairment for the majority of people with psychotic illness, but that a subset of individuals will experience progressive deterioration of cognitive functioning, especially in later life.

How can we treat impaired cognition in psychotic illness?

Previously, we established that cognition is an important treatment target, given the strong association between cognition and functional outcomes in people with psychotic disorders. In this section, we consider the status of research aimed to improve impaired cognition in psychotic illnesses. Most research efforts in this area fall into either relatively established approaches such as cognitive enhancing pharmacological agents or cognitive training programs, or relatively nascent approaches such as physical exercise or neurostimulation.

Results from large-scale studies and meta-analytic reviews indicate that antipsychotic medications can yield modest

beneficial effects on cognitive functioning in people with psychotic disorders, although the findings have been inconsistent regarding whether atypical antipsychotics confer greater effects than typicals.[62,63] Notably, detrimental effects of antipsychotics on cognition are also possible, and have been associated with very high D2 receptor occupancy level, very high dosing, polypharmacy, and co-occurring use of anticholinergic medications.[64,65]

Cognitive enhancing agents are pharmaceuticals that are posited to improve cognitive performance by acting on relevant neurotransmitter systems, typically the glutamatergic and cholinergic systems. The results of individual studies have been mixed, and a recent meta-analysis of 93 studies comparing cognitive enhancing agents to placebo reported a small (g=0.10) but significant effect of cognitive enhancers on overall cognition, but no significant effects on individual cognitive domains.[66] When individual neurotransmitter systems were considered, small positive effects were reported for glutamatergic (overall cognition g=0.19, working memory g=0.13) and cholinergic agents (working memory g=0.26). Major limitations of this literature are that many studies are underpowered to detect effects, studies investigating agents that act on neurotransmitter systems other than the glutamatergic and cholinergic systems are few, and the treatment durations are brief.[66,67]

Cognitive training (CT) refers to psychosocial interventions that aim to improve cognitive performance through repeated practice to retrain a particular cognitive domain (ie, a restorative approach) or to offset cognitive impairment via cognitive strategies or environmental accommodations (ie, a compensatory approach).[68] CT interventions can be administered individually via computer programs, and training effects can be bolstered through group discussions designed to generalize gains on the trained CT tasks to activities of daily life (ie, "bridging groups").[69] The results of clinical trials of CT have been promising regarding improvements on trained tasks, cognitive performance, and community functioning outcomes.[70-73] However, some studies report minimal transfer of CT gains to untrained cognitive tasks and community functioning.[74-76] A meta-analysis suggested that CT in the context of an active rehabilitation program may produce larger cognitive and community functioning improvements than CT alone.[73] Further research to identify predictors of treatment response and important aspects of CT that promote transfer of gains (eg, content area, delivery format, and intensity/dosing of CT, inclusion of a bridging component, timing of treatment during illness course, etc) is warranted.

Enhancing cognitive performance in psychotic illness through physical exercise and neurostimulation (eg, transcranial direct current stimulation, tDCS) is an exciting area of cognitive rehabilitation research. These methods have been investigated in isolation, and as part of a combined intervention with CT. Although the literature for these interventions is small, the results so far have been encouraging. A recent review of ten trials of physical exercise in schizophrenia reported small to medium effects on global cognition (g=0.33) and working memory (g=0.39), and medium effects for social cognition (g=0.71) and attention (g=0.66).[77] An empirical review of six studies comparing active tDCS stimulation to sham reports small positive effects of active tDCS for working memory and attention.[78]

Concluding remarks

In this review we established that: (i) impaired cognition impacts the vast majority of individuals with psychotic illness; (ii) the cognitive impairments are diffuse (ie, impairment is evident across many cognitive domains) and the effects are large in magnitude; (iii) cognitive impairment is present prior to onset of psychotic illness; and (iv) for the most part, is relatively stable over time. Cognitive performance is a robust predictor of community functioning in people with psychotic disorders, and thus is an important target for intervention. Cognitive rehabilitation for psychotic disorders is a growing area of research. To date, most research efforts have focused on cognitive enhancing pharmacological agents and cognitive training (CT). Some trials of glutamatergic and cholinergic pharmaceutical agents have yielded modest improvements in overall cognition and working memory. CT has demonstrated efficacy, but further research is needed to identify predictors of treatment response and the factors that promote generalization of treatment gains. Physical exercise and neurostimulation are exciting and promising new areas of investigation, and it is possible that combining these novel treatments with other modalities (eg, combining exercise with CT) may yield greater cognitive gains. ■

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