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Review

Cognitive impairment and functional outcomes in schizophrenia: a narrative review

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This narrative review re-examines the background and evidence related to cognitive impairment and outcomes in schizophrenia. This area has gained much enthusiasm and research interest over the years, with the focus on recovery of patients with schizophrenia. Hence, knowledge sharing is imperative when incorporating evidence-based medicine into day today clinical practice.

Schizophrenia – introduction

Schizophrenia is possibly the most devastating disorder treated by psychiatrists (1). With a worldwide prevalence of approximately 1%, its economic cost has been estimated to be 65 billion USD per year (2) in (1).

Cognitive impairment is a core dimension of schizophrenia, (1,3) which has been demonstrated to be predictive of functional outcomes, (4,5) and to improve with interventions such as cognitive remediation (6-9), although not with the pharmacological agents currently available (10). Several pharmacological agents which remain in early-stage trials at the current time are reported to show promise in improving cognition (11).

Schizophrenia – description

The eleventh edition of the International Classification of Diseases (ICD-11) describes schizophrenia as being characterised by disturbances in multiple mental modalities which include thought, perception, self-experience, cognition, volition, affect and behaviour. The cognitive disturbances specified in the description are in the domains of *attention, verbal memory, and social cognition*. Psychomotor disturbance is described as variably present (12).

As the ICD-11 produced by the World Health Organization is the diagnostic guideline currently used in many if not most areas of the world, the increased prominence attributed to cognitive impairment in this description of Schizophrenia is significant. This is especially so when contrasted with the description of schizophrenia in the previous edition of the International Classification of Diseases (ICD-10), which mentions only that "certain cognitive deficits may evolve in the course of time" (13).

ICD 11 gives an increased prominence to cognitive symptoms of schizophrenia compared to ICD 10 based on cumulative evidence in this regard across the globe.

Schizophrenia – cognitive impairment in relation to diagnosis

Neither ICD-10 nor ICD-11 nor DSM-5 include cognitive impairment in the diagnostic requirement for schizophrenia (12-14).

The ICD-11 makes several important references to cognitive impairment. In the specifier for diagnostic threshold or 'boundary with normality', the ICD-11 states that multiple and persistent symptoms are typically present in association with cognitive impairment and difficulties with psychosocial difficulties in schizophrenia. In the specifier for course features, the ICD-11 states that cognitive symptoms tend to persist more than positive symptoms and are associated with functional impairment (12).

The DSM-5 specifies a wide array of cognitive impairments as associated features which are supportive of a diagnosis of schizophrenia. It lists decrements in neurocognitive domains such as attention, memory, language, and processing speed, and also mentions deficits in social cognition (14).

Cognitive impairment in schizophrenia – introduction

One of the earliest reported studies assessing disability associated with schizophrenia is a collaborative study conducted by the World Health Organisation (WHO) and published in 1980 (15). In 1996, a review article highlighted *verbal memory and vigilance* as being important for functioning while identifying that psychotic symptoms were comparatively less important (16). In the 2000s cognitive deficits in schizophrenia gained increased attention, (17) with several studies aiming to identify the specific cognitive deficits in

schizophrenia, (18,19) and these cognitive deficits soon being identified as potential targets of intervention, towards achieving improved functional outcomes (8,19).

Cognitive (neurocognitive) impairment in schizophrenia – description

A review of research data from 1980-2006 demonstrated that *"the cognitive deficits demonstrated in schizophrenia are significant and characterised by generalized cognitive impairment"* (3). Furthermore, it was noted that the reporting of cognitive deficits had remained stable over decades and was similar across the world despite cultural and linguistic differences (3), with only a 'significant minority' of patients with schizophrenia having normal neuropsychological functioning (20).

Although these deficits are widespread, they are unevenly distributed among the various domains of cognitive functioning. It is reported that "patients with schizophrenia scored significantly lower than controls across all cognitive domains" with patients demonstrating "larger impairments in processing speed and episodic memory" (3). In more detailed analyses it is described that "the magnitude of difference between patients and controls is greater for processing speed and aspects of sensory, verbal and working memory, than for attention, executive function, language, motor and spatial abilities, or general intelligence", and that *"processing speed might be the single most sensitive cognitive indicator of schizophrenia"*, although the "broad-based nature of the deficit continues to receive support" (21).

A recent study conducted in southern Sri Lanka reported findings similar to those reported worldwide with cognitive impairments correlating positively with earlier onset of illness, advancing age and shorter duration of formal education (22).

Intelligence Quotients and schizophrenia

Lower premorbid Intelligence Quotient has been shown to have a strong association with an increased risk for schizophrenia (23).

Social cognition in schizophrenia

Social cognition is not usually listed amongst the conventional cognitive functions which are synonymous with neurocognition (24). Examples of social cognition include empathy, connectedness with others, and the ability to infer the thoughts of others and react emotionally to them. Deficits in social cognition are present in schizophrenia and are identified as causative of significant impairments in day-to-day functioning (25). Deficits in social cognition are demonstrably present both prior to the onset of psychotic symptoms in schizophrenia, and among first degree relatives of patients with schizophrenia (26), in a pattern similar to that demonstrated for the neurocognitive deficits in schizophrenia (27).

Structural correlates of cognitive functioning in schizophrenia

Structural brain correlates of the cognitive dysfunction in schizophrenia are more recently being identified (28), with neurodevelopmental abnormalities believed to underlie both the onset of psychopathology and cognitive dysfunction (29).

Cognitive impairment in schizophrenia – onset

The cognitive decline in schizophrenia may precede the onset of psychosis by as much as a decade (30). Retrospective studies have demonstrated the neurocognitive deficits and deficits in social cognition in schizophrenia to be present in the premorbid phase and the prodrome as well as after the onset of psychotic symptoms (27). These deficits are also demonstrable among healthy relatives at high genetic risk of schizophrenia, suggesting these neurocognitive deficits and deficits in social cognition might be considered a trait marker for schizophrenia (27).

It is thought that cognitive deficits may have stabilized even prior to the first episode of psychosis, although this remains disputed (27). It remains unclear how much cognitive deficits progress after the onset of psychosis (30). One longitudinal study reports the deficit in processing speed as beginning in childhood and progressively worsening until the early teenage years, and verbal deficits as emerging in childhood but remaining static thereafter (31).

Another meta-analysis reports the now widely accepted view that mild cognitive deficits are present in the premorbid period, with a sharp decline in cognition 'at or near' the first episode of psychosis, with deficits remaining largely stable thereafter into the more chronic stages of the disease (32).

An earlier age of onset of psychosis is associated with higher levels of cognitive deficit (33). This may be due to the additive impact of hampered education and scholarship (27).

Impact of cognitive impairment in schizophrenia

The impact of neurocognition and social cognition and their impairments on clinical and functional outcomes have been the subject of much interest and research, especially as the unitary diagnosis of schizophrenia is associated with a heterogeneity of outcomes (5,21,34).

Impact of cognitive impairment in schizophrenia on clinical outcomes

Verbal memory is the neurocognitive function with the strongest demonstrated association with clinical outcome, with patients who do not achieve remission of schizophrenia demonstrating larger deficits in verbal memory than patients who do achieve remission (5).

The relative risk of dementia is significantly increased among patients with schizophrenia, in a manner that is not explainable by the established risk factors for dementia alone (35).

Impact of cognitive impairment in schizophrenia on functional outcomes

Deficits in both neurocognitive functioning and social cognition have a greater impact on functional outcomes than the clinical symptoms of schizophrenia (16) in (5).

It is worthy of note that verbal memory, which is the most impaired cognitive function in schizophrenia is also the strongest predictor of functional outcome (36) in (5).

Cognitive function is predictive of patients having the skills for independent living, (4) in (5) and of their ability to maintain social functioning and be functional members of their society (37) in (5).

It is evident that cognitive impairment is also negatively correlated with return to occupational functioning following the onset of schizophrenia, (38) in (5) and to later work success (5).

Schizophrenia – measuring outcomes: introduction

Following recognition of the central role of cognitive impairment as a determinant of functional outcomes (16), and functional outcomes being established as a key determinant of recovery (39), much attention was paid to assessing cognition (40), functional capacity, and real-world functioning in schizophrenia (41).

An accurate assessment of cognitive impairment is required to facilitate the selection of patients for appropriate interventions, such as cognitive remediation and psychosocial rehabilitation, and to assess for post-intervention improvement (4,5).

It is important also to distinguish between what a patient is capable of, which is 'functional capacity' or functional competence, and what they do, or real-world functioning (42). Assessments of functional capacity do not provide information on whether these actions are performed in real-life. This is because internal factors such as depression and lack of motivation, and external factors such as lack of resources or opportunity do not affect performance in the office or laboratory setting as they do in the real world (42).

A multi-centre study has demonstrated that even neurocognitive test performance is influenced by factors such as motivation and effort, suggesting they may need to be accounted for if more accurate measurements of cognitive impairment are to be made (43).

Functional capacity is typically assessed in office or laboratory-based simulations, during which observers assess patients engaging in simulated activities. Such measures are known as performance-based tests (42). Performance-based tests typically require time, trained observers, and special resources to simulate real-life situations (41,42). Performance-based assessments of functional capacity correlate highly with neurocognitive test results (42,44). However, tolerability (patient perception of pleasantness), and practicality (assessors' perceptions of convenience) are the variables which need to be considered (41).

Objective assessment of cognition is conducted via neurocognitive tests also known as neuropsychological tests of cognition. These are typically administered by trained staff and assess specific domains of cognitive functioning (41). "Interview-based clinician assessments of neurocognition" correspond poorly with neuropsychological tests of cognition (45), which are unreliable and hence best avoided.

Real-world functioning and outcomes are assessed by patient self-report and informant report which are obtained either by interview or questionnaire (41,44,46). Patient self-report has been found unreliable in the assessment of real-world functioning (47,48), with patients having higher cognitive abilities found to underestimate real-world outcomes (47) and patients with greater cognitive impairment overestimating their functioning (47).

In contrast with patient self-report, informant report has been found to have a much higher correlation with tests of functional capacity (44) in (42). Therefore, informant report is the preferred method for obtaining information on real-world functioning. Case managers' and caregivers' ratings of real-world functioning have been demonstrated to correspond highly with performance-based assessments of functional capacity (42,47), thus underlining the usefulness of informant reports. However, reliance on informant report is not without drawbacks such as

the possibility of there being no available informant with adequate recent knowledge of the patient (49).

'Validity' or the capacity of a measure to assess the variable it was designed to measure (50), 'test-retest reliability;' the ability of a measure to generate the same results if repeated after a brief lapse of time (51), and 'inter-rater reliability' or the ability of a measure to generate the same response from a subject despite evaluation by different assessors are properties expected of any psychological measure (51).

'Feasibility' or ease and speed of administration, 'repeatability' with minimal impact from practice effects, and 'sensitivity to change' are considered important qualities in outcome measures used in research and clinical trials (42,52), but are arguably of even greater significance in clinical settings where patients need to be selected by staff for interventions and later evaluated for improvement (42,52). Clinical staff who lack training in the administration of neuropsychological tests (44), may be disincentivised to allocate or prescribe therapies or medication for cognitive enhancement.

Schizophrenia-measuring outcomes: scales and measures
Identifying accurate outcome measures is essential to the success of any clinical trial or intervention aiming to improve outcomes in schizophrenia (21). An accurate assessment of cognitive impairment is required to facilitate the selection of patients for appropriate interventions, such as cognitive remediation and psychosocial rehabilitation, and to assess for post-intervention improvement (3,4)

The Brief Assessment of Cognition in Schizophrenia (BACS) demonstrates validity, reliability, and sensitivity as a neurocognitive test in schizophrenia (53).

The Montreal Cognitive Assessment is an accurate measure of general cognitive abilities in patients with schizophrenia (54). It has been validated for screening patients with schizophrenia for cognitive impairment, demonstrating good correlation with the Brief Assessment of Cognition in Schizophrenia (BACS) in assessing cognitive impairment, and the Brief University of California San Diego Performance-Based Skills Assessment (UPSA-B) in assessing functional outcome (55). However, using a lower cut-off of 24 rather than 26 for this purpose has been suggested (54).

The Mini Mental State Examination is a cognitive assessment in widespread use worldwide over five decades (56). Despite good specificity, it lacks sensitivity in detecting mild cognitive impairment and identifying change in cognition (56) limiting its suitability for assessing cognition in schizophrenia (57).

The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) has demonstrated concurrent validity and reliability in screening for cognitive impairment in schizophrenia (58-60). However, it lacks content validity for this purpose, as it does not assess executive functioning or working memory which are affected in schizophrenia (61). As a copyrighted neuropsychological test requiring 30-45 minutes and administer (62) in (61), it is not in widespread use although validated in Sinhala (63).

The Independent Living Skills Survey is a measure of real-world functioning, which is available for either self-report or informant report (64).

The Schizophrenia Cognition Rating Scale (SCoRS) and Clinical Global Impression of Cognition in Schizophrenia (CGI-CogS) are interview-based measures specifically designed to assess cognition and functioning in Schizophrenia (46). Both were used in the MATRICS research initiative (41,65).

The Cognitive Assessment Interview which was developed from SCoRS and CGI-CogS, is also an interview-based measure of cognition and functioning in schizophrenia. It has the added advantage of being brief in comparison with the parent measures but has lower correlation with assessments of functional capacity (24).

SCoRS is a broad assessment of cognition, assessing seven domains of social cognition and neurocognitive functioning with recognised impact on functional outcomes in schizophrenia (44). SCoRS has established validity in assessing cognitive performance relevant to real-life functioning, also known as ecological validity (42), among clinically stable patients (66). One of the key advantages of SCoRS is that it sensitively assesses cognitive performance relevant to real-world functioning despite being an interview-based measure (44). As an interview-based measure, it is easy to administer without the requirement of highly trained staff or special equipment (49).

The Schizophrenia Cognition Rating Scale obtains information from both patients and informants (persons who have the most experience of the patient in everyday situations) (44).

As such, this measure is one amongst a few which provide a means for incorporating the opinion of patients and their carers on the extent of cognitive impairment and functioning. (44). Although designed to assess the benefit of cognitive enhancers in clinical trials it was anticipated that this would be a useful test for clinicians to assess the level of cognitive impairment in patients for clinical purposes such as recommending cognitive enhancement therapies (44).

There has been recent interest in the use of virtual reality in the assessment of cognitive impairment in schizophrenia (67).

A systematic review of measures assessing cognition in severe mental illness, published in 2021 highlighted that there were no measures validated in populations in low-income countries, and only three validated in lower-middle-income countries (68).

Treating cognitive impairment in schizophrenia

Antipsychotic medication does not benefit cognitive impairments (27), and research into developing novel cognitive enhancers has been disappointing. Although cognitive impairment in Schizophrenia has long been identified as a prime target for novel drug treatments, none have succeeded in achieving licensing for use (46,69,70). However, alternative therapeutic methods such as cognitive remediation have demonstrated benefits in meta-analyses (27), with improvement demonstrable as long as ten years after intervention (7). Computerised cognitive training has shown promise and gained endorsement, however, (49) as have psychosocial treatments such as social skills training (71), and highly specialised interventions such as cognitive remediation, cognitive enhancement therapy and cognitive training (6,7,9,71-74).

Schizophrenia – outcomes and the concept of recovery

Although cognitive enhancers have not been identified, pharmacological interventions such as minimising the anticholinergic load (75,76) by means of selecting (newer) antipsychotics with less anticholinergic burden and using anti-muscarinic agents for extra-pyramidal side-effects sparingly, have been demonstrated to improve cognitive deficits in several studies (77-83).

The goal of schizophrenia management is 'recovery' which encompasses more than the clinical outcome of symptom remission, or functional outcome of vocational or educational role functioning. Recovery also incorporates quality of life as identified by satisfying interpersonal relationships, and low levels of stigma (84,85).

Although of obvious significance, the holistic outcome of recovery has proven difficult to quantify for the purposes of measurement and analysis, leading to difficulty in assessing the success of interventions promoting recovery (86).

A systematic review and meta-analysis in 2013 reports that only one in seven patients with schizophrenia fulfilled the criteria for recovery (87), and that this proportion had not increased since much older reports from the mid-1990s (87).

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