Neurocognition and Treatment Outcomes in Schizophrenia

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Introduction

Schizophrenia is a debilitating neurodevelopmental disorder that affects many aspects of psychosocial and interpersonal life. Cognitive and motivational disturbances are conceivably the most debilitating and pervasive aspects of the schizophrenia syndrome, in the midst of the other better-recognized psychotic symptoms (i.e., delusions and multimodal hallucinations). Whereas psychotic symptoms often fluctuate with clinical state, cognitive symptoms are present early in the disease course and persist even in the absence of the more clinically apparent psychotic symptoms. Current pharmacologic therapies largely target the positive symptoms and have little effect on cognitive and motivational aspects of the disorder. Neurocognitive disturbances, particularly to executive function, contribute to substantial disability and loss of functioning in schizophrenia. Here, we will discuss that cognitive and executive functioning affect treatment outcomes and functional impact in schizophrenia, and we will also discuss current treatment strategies for cognitive and psychosocial intervention.

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Metrics of Functional Outcomes in Schizophrenia

A central problem in schizophrenia research has been the development of treatment modalities for functional impairments in our patients. Several lines of evidence have demonstrated that cognitive and behavioral aspects of the disorder are present in unaffected relatives. The concept of an endophenotype implies that certain phenotypes, be it cognitive, behavioral, or neurophysiologic, are present in patients with schizophrenia, but less so in unaffected relatives, and absent in healthy controls. Like many aspects of the disorder, daily functioning has been thought to be a heritable and measurable trait of the disorder [1–3]. Therefore, as a putative endophenotype, if it can be reliably quantified, it can be directly compared to other aspects of the disorder and can be investigated in genome-wide studies [2].

Various tools have been developed to assess social and occupational functioning, but there is a lack of a generally accepted tool for assessing functional capacity [4, 5]. Outcomes in schizophrenia are commonly measured in terms of level of independence, employment, interpersonal relationships, and quality of life. Currently, the University of California, San Diego Performance Skills Assessment (UPSA) is the most widely applied tool for clinical and research studies of schizophrenia and other mental disorders [6–8], as it has been shown to have stable psychometric

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properties and has been translated into several other languages [9]. A common caveat for most studies is that functionality is ascertained in terms of relative functioning at the time of assessment. That being said, functional capacity is seldom a static process; it can vary by clinical state and as our patient's age. Therefore, investigators have also attempted to ascertain measures of lifetime achievement and functionality, to better bridge this gap [10].

Neurocognition and Executive Dysfunction in the Schizophrenias

Global Cognitive Impairment

Clinicians have long appreciated the effects of cognitive dysfunction in the daily lives of patients with schizophrenia. Decades of research of cognitive functioning in schizophrenia have revealed consistent deficits across virtually all cognitive domains tested (i.e., IQ, working memory, executive function, episodic memory, sustained attention, processing speed, etc.); further, these observations have been relatively consistent, despite variation in neuropsychological instruments over time [11]. Global cognitive deficits have been reported early in the schizophrenia spectrum, although deficits to verbal memory, processing speed, and working memory are particularly salient as early as first-episode psychosis [12]. Global impairment has been related to poor global impairment in domains such as everyday care [13] and social and occupational functioning [14]. It is also of interest that neuropsychological impairments are not static, as the rate of cognitive decline rapidly accelerates at age 65, which is in stark contrast of normal aging [15], suggesting that schizophrenia portends a stage of accelerated brain aging.

Neurocognitive Effects on Clinical and Psychosocial Outcomes

Outcomes in schizophrenia are generally defined as either clinical or psychosocial outcomes. Clinical outcomes commonly refer to response to neuroleptic medications. Symptomatic remission is construed as a measurable reduction in positive and at times negative symptoms. Psychosocial outcomes attempt to quantify independent living, employment, interpersonal relationships, and overall success in the community.

Clinical Outcomes

Neuroleptic medications revolutionized the treatment of schizophrenia, whereby patients who were previously confined to lifelong institutionalization were able to participate in community living and had the opportunity to thrive. Broadly speaking, clinical outcomes refer to a patient's response to antipsychotic medications, i.e., symptomatic remission, and, by extension, the ability to keep community-dwelling patients living outside the confines of locked psychiatric units. Poorer performance on verbal memory and working memory predicted worse clinical outcomes in first-episode psychosis (FEP) 6 months after their first hospitalization, whereas processing speed and executive functions had little predictive value [16]. At 3-year follow-up, verbal memory appeared to predict symptomatic remission for FEP [17]. In chronic patients with schizophrenia, other neurocognitive measures such as verbal fluency [18] and gross metrics of executive function [19] predicted symptomatic remission. In contrast, in a relatively homogenous population cohort, a generalized pattern of cognitive deficits was shown to be associated with non-remission [20], which again is consistent with the notion of a global cognitive impairment. Of note, symptomatic remission has shown benefit to quality of life measures and other clinical outcomes, but generally has little significance on cognitive functioning [21].

Psychosocial Outcomes

Cognitive deficits are prominent at all stages of schizophrenia. Generally speaking, poor neuropsychological performance predicts worse psychosocial functioning [22–24]. Executive dysfunction and deficits to other cognitive domains negatively impact multiple aspects of psychosocial functioning, beginning from the most basic management of activities of daily

living (ADLs) [13, 25] to broader community functioning [26]. Other neurocognitive variables have been implicated in other measures of psychosocial functioning, such as verbal memory and working memory, which predicted employment status in chronic patients with schizophrenia [18].

A striking feature of the schizophrenia spectrum is that neurocognitive deficits are present early on in the illness course. Of these, executive function, verbal memory, and processing speed were significantly worse for patients with poor outcomes compared to those with relatively good outcome in ultrahigh-risk (UHR) populations [24]. Further, UHR populations who demonstrate worse deficits to attention and working memory are more likely to convert to manifest psychosis [27], with worse verbal memory predicting faster time-to-conversion [28]. Ultimately, clinically high-risk populations suffer worse clinical and psychosocial trajectories, such that individuals who do not convert to full-blown psychotic illness still experience attenuated positive symptoms and poorer social and role functioning than healthy age-matched controls [29].

In first-episode schizophrenia, baseline executive functioning also predicted global functioning at 1-year follow-up [30]. Further, verbal memory impairment predicted long-term remission of psychosis at 3-year follow-up, which also portended better social functioning [17]. Curiously, negative symptoms have been thought of as possible mediators of cognitive functions on psychosocial outcomes such that one study suggested that negative symptoms may contribute to the impact of verbal memory deficits in relation to social and occupational functioning during early psychosis [31]. The relationships between neurocognitive measures, negative symptomatology, and psychosocial function are complex, but similar patterns are seen in chronic schizophrenia [32, 33].

In chronic schizophrenia, there are similar patterns for cognitive metrics as UHR and FEP; however, graduated distributions of disability and cognitive deficits exist varying by stage of psychotic illness. A small but interesting longitudinal study assessed the long-term functional outcome 15 years' post cognitive testing. It suggested that verbal memory deficits strongly predicted community functioning and integration, whereas executive functions predict total duration of hospitalizations over the 15-year period [26]. This complex pattern of phenotypic variation suggests that cognitive metrics may co-segregate, but they may also have phenotypic exclusivity. Executive function as measured by performance on WCST predicted better social functioning during an eight-month rehabilitation program [34]. Further, executive functions would go on to predict general functioning, but specifically occupational and household functioning, in a group of 96 patients 1 year after discharge from an inpatient unit [14].

Generally, cognitive dysfunction predicts poorer psychosocial function. Interestingly, in a Swedish population cohort study of over 500 patients with schizophrenia, baseline executive function was an independent predictor of premature death on 20-year follow-up [35]. In the duration of the study, roughly 13% of patients passed by age 60.5, which is 20 years earlier than the national mean. Curiously, these deaths were not attributable to suicide, as the rate was less than 0.01%. This study is also important as it shows that symptomatic remission has little to no predictive value in determining the longitudinal status of survival in this patient population. It is also worth mentioning that in treatment-refractory populations, which generally have more pronounced deficits to executive function, cognitive flexibility, verbal fluency, and processing speed than other patients with schizophrenia, these effects also appear to be modulated by negative symptoms [36].

Interventions for Cognitive and Psychosocial Functioning

Cholinergic Systems

Central cholinergic tone is critical to learning and memory. Antipsychotic medications are plighted with affinity toward multiple receptor types, which lead to a multitude of side effects. Among these are anticholinergic effects which can negatively affect cognition and affect the

outcomes of intensive cognitive training [37]. Adjunctive acetylcholinesterase inhibitors, such as donezepil, have some evidence to support their use in improving executive function as well as other cognitive deficits [38]. Other forms of cholinergic modulations, particularly through alpha-7 nicotinic acetylcholine receptors, are being investigated. An alpha-7 receptor agonist, encenicline, was shown to enhance several domains of cognitive functioning, improved negative symptoms, and daily functioning in a phase 2 clinical trial [39]. Mechanistically, alpha-7 nicotinic receptors are thought to enhance cognition through modulation of NMDA receptors and dorsolateral prefrontal circuit engagement [40].

Glutamatergic Systems

The glutamatergic system has shown great promise for novel therapeutics for cognitive enhancement in schizophrenia [41]. Interestingly, minocycline via putative neuromodulatory and neuroinflammatory mechanisms has shown to be beneficial to negative symptoms and social and occupational functioning. It has led to improvements in executive functions after six-month follow-up early in the course of schizophrenia [42]. A small study suggested that L-carnosine improved executive functions, such as cognitive flexibility and set-shifting [43], although this was limited by tolerability. Other glutamatergic modulators, such as D-serine, have shown modest improvement in negative symptoms and executive functions [44] and composite MATRICS battery scores at higher doses [45]. However exciting these studies may be, they are limited by small sample sizes and lack of robust replication. That being said, the modulation of NMDA-mediated signaling has functional implications on learning and memory and therefore is a promising target for cognitive enhancement strategies in schizophrenia [46]. Medications targeting NMDA receptors, such as memantine, have shown promise in schizophrenia. Memantine initially showed no benefit to cognitive symptoms, but has shown some benefit in negative symptoms in clozapine-treated patients [47, 48]. Recent work suggests that memantine may be used to augment cognitive training strategies [49] and that it may be clinically useful in treatment-refractory subtypes of schizophrenia [50].

Cognitive Remediation

Although much emphasis has been placed on the potential of cognitive remediation for the cognitive symptoms of schizophrenia, much work needs to be done to refine pipeline and stratify patients based on neurophysiologic parameters. Wherein some studies do support a role for cognitive remediation, others studies suggests that the benefits of intensive cognitive training is only limited to the tasks at hand and do not generalize to other cognitive domains as they were intended. Overall, this places some doubt as to whether such intensive, and costly, trials produce clinically meaningful benefit [51–53]. Interestingly, patients who had significant improvement in verbal memory and executive functioning as a result of cognitive remediation had longer time-to-relapse, which provides evidence of cognitive remediation having sustained effects on clinical course [54]. Therefore, much work has been aimed at using biomarker-based strategies to identify individuals likely to benefit from the cognitive remediation [33].

Conclusions

Neurocognitive deficits have a profound impact on many facets of neurobehavioral and psychosocial outcomes in schizophrenia [55, 56]. With the concept of the schizophrenias—genetically and phenotypically distinct disease entities—resurfacing and that of a biologically informed nosology, we are at a time where cognitive and functional outcome measures can inform treatment strategies. Over the course of the years, several neuropsychological batteries and tests have been devised to assess for cognitive and psychosocial functioning. Currently, the most well-adopted batteries for cognitive studies are MATRICS consensus battery and CogState schizophrenia battery. These tools have been developed for sole purpose of ascertaining reliable cognitive metrics for pharmacologic and

cognitive interventions. Similarly, various measures of psychosocial functioning exist, the most widely applied being the UCSD Performance Skills Assessment. The benefit of standardized metrics would be to leverage direct comparisons on a population level. As both neurocognitive domains and overall global functioning have been reported as heritable traits, these can be theoretically studied through a genomic lens. Further, parsing and identifying subsets of patients who suffer from worse neurocognitive and psychosocial functioning profiles can lead to targeted therapies and interventions for those individuals most at need.

The cognitive deficits seen in the schizophrenias are present at all stages of the disorder and can be the defining clinical feature in certain cases. Investigators have vigorously studied the cognitive sequelae of the schizophrenias across the world and have found generalized deficits across all neurocognitive domains; hence, the concept of the global cognitive impairment [11] has been proposed.

Intuitively, one would presume that poorer neurocognitive performance portends worse prognosis and psychosocial functioning. However, this leaves much to desire in terms of mechanistic strategies for intervention and cognitive rehabilitation programs. Several studies have implicated various aspects of cognition with features of psychosocial and treatment outcomes; however, executive function, verbal memory, and processing speed appear to be individual measures with the most promise for targeted neurocognitive interventions, as they consistently relate to psychosocial and clinical outcomes across all stages of schizophrenia. It is important to note that cognitive dysfunction extrapolates to the most basic day-to-day functions, such as grooming and hygiene, to keeping up with their medications, to more complex tasks required for occupational and physical well-being. Further, the finding that baseline neurocognitive deficits were independent predictors of premature death in chronic psychosis only underscores the impact of neurocognitive functioning in the lives of our patients.

Currently, pharmacologic strategies for improving cognitive functioning in schizophrenia are limited, but there are many active areas of research, including augmenting glutamatergic and cholinergic signaling pathways, which are promising. The future holds promise for cognitive remediation, as new studies are showing novel ways of augmenting cognitive remediation with targeted pharmacology [49, 57], and recent advances in neurostimulation techniques are paving the way for neuroplasticity-mediated therapies. The ultimate goal of the research is to improve the way our patients think, feel, and live their lives.

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