

## Synopsis I

### **Cognitive impairment in long term schizophrenia**

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**Introduction** The term schizophrenia coined by Bleuler (1911) is used for a group mental illness characterised by reality distortions (hallucination and delusions), thought disorder, cognitive dysfunction, positive and negative symptoms. Bleuler derived the concept of the illness from Kraepelin's 'dementia praecox' (1896). The long term effects of schizophrenia such as negative symptoms and cognitive deficits appear to pose a major problem that hinders reintegration in schizophrenic patients.

Schizophrenia ranks in the top five causes of disability for young adult men and women in developed countries. Approximately 50% of schizophrenic patients are employed at any time in any capacity with only ten to 20% are involved in competitive environment and only ten per cent of patients are able to sustain full time competitive employment.

An earlier age of onset and poor overall functioning are risk factors for suicide in patients with schizophrenia. Suicide is the leading cause of death in people with schizophrenia. The lifetime risk of death by suicide in schizophrenic patients is close to ten per cent. Patients with prominent negative symptoms may have a somewhat reduced risk of suicide as compared to patients with mostly positive symptoms.

**Association of cognitive impairment and schizophrenia** Identified cognitive deficits with schizophrenia affect attention, memory and executive functions involving problem solving, planning and organisation.

**Attention:** One of the early experimental studies of attention found that patients with schizophrenia demonstrate slowed reaction time and moreover, could not improve their performance even when intervals between warning and stimulus were both predictable and long. Thus, patients appeared to be unable to sustain attention, compromising their readiness to respond across longer time intervals. Schizophrenic patients had deficits maintaining vigilance during a continuous performance test involving specific combinations of stimuli.

Attentional impairments may disrupt many other cognitive functions as poor attention would prevent many types of information from being processed fully.

**Attentional functions:** Attention is a multifactorial construct, including the ability to maintain an alert state, to orient to novel stimuli, to filter relevant information and to rapidly discriminate stimuli for some duration of time. Two aspects of attention that have received particular attention in schizophrenia research are sustained and selective attention.

**Sustained attention:** Sustained attention refers to the capacity to maintain a state of readiness to respond to small changes in the environment.

A widely used test to assess sustained attention is the Continuous Performance Test (CPT). In this test, stimuli, usually letters or digits, are presented briefly one at a time in a random

order. The subject has to respond when a certain target stimulus appears in some variants of the task only when preceded by a certain cue. Patients with schizophrenia usually display reduced sensitivity on CPT. This deficit is particularly pronounced on version with high processing loads; for example, tasks with rapid stimulus presentation, stimulus degradation or when precious stimulus must be remembered to make the current decision.

A single disturbance to the module responsible for representing and maintaining context in a computer simulation model of the CPT and other tasks yield performance impairments similar to those seen in schizophrenia.

**Selective attention:** Selective attention is the capacity to focus while ignoring irrelevant information. Selective attention is often assessed using the stroop colour word test (SCWT). Several studies have demonstrated impaired performance on the SCWT, particularly in the interference condition.

**Memory:** In the last several decades memory has been regarded as one of the major area of cognitive deficits in schizophrenia. Although the pioneers of schizophrenia research Krapelin and Bleuler considered memory functions to be relatively preserved in schizophrenia, numerous studies conducted in second half of this century have shown that patients with schizophrenia perform poorly on a wide range of memory task. Existence of a schizophrenic amnesia has been suggested.

**Verbal memory:** Verbal memory, including story recall and word list learning, seems to be more severely affected than nonverbal memory. Free recall is particularly affected, indicating a deficit of retrieval of information.

**Working memory:** Working memory is the type of memory that is active and relevant only for a short period of time and is defined in content and duration by the action it subserves. Working memory consists of a superordinate central executive system and two slave systems for the transient storage of visuospatial and verbal information. But working memory sometimes involve only slave system and sometimes the central executive system as well which is a source of confusion.

Transient storage and executive function working memory is distinguished by force (when only storage and retrieval of information are required) and backward digit span (when in addition to storage and retrieval, manipulation of the information is required) respectively.

In comparison of monozygotic twins discordant for schizophrenia, the effected twin performed worse than the healthy twin in the backward but not in the forward condition.

**Semantic memory:** The term semantic memory refers to stored information that is impersonal and includes knowledge of words and their meanings, knowledge about object and their categorisations, and general information about the world.

Core feature of thought disorders in schizophrenia was overinclusive thinking, a vagueness of boundaries between concepts, making them overexistensive and able to accommodate logical contradictions. Other studies have provided support for this notion.

**Executive functions:** The executive functions comprise capacities for volitional activity, forward planning and self-regulation.

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Schizophrenic patients have performance deficits on Wisconsin Card Sorting Test (WCST) of obstruction, set shifting and response to feedback. Chronic schizophrenic patients perform poorly on the WCST and capacity to maintain information 'on line' was reduced as they had difficulty of learning task even on instructions being provided.

Some others have directed attention to the unusual and strong relationship between performance on the WCST and general intellectual ability, aging and education, which suggest that nonspecific factors account for a substantial proportion of WCST performance in schizophrenia.

Tower of London test was derived from the Tower of Hanoi puzzle and an automated version of this was used which showed that schizophrenic patients were able to complete the task but required more moves and longer time to complete the task as compared to healthy controls.

Social cognition: For social cognition in schizophrenia the general focus is on the ability to infer another's intention or to represent the mental state of others (theory of mind skills) and social perception. Individuals with schizophrenia perform poorly on measures of theory of mind abilities.

Social perception can be assessed by facial affect recognition and social cue perception. Schizophrenic patients have stable deficits on test of facial affect perception compared with healthy control and psychiatric control subjects. Perception of negative emotions and fear may be particularly impaired.

There is strong relationship between cognitive function and social deficits in schizophrenia.

General intelligence: A general intellectual decline of ten points or more from premorbid levels was found in 51% in a sample of consecutively admitted patients. The remaining patients showed no significant decline relative to estimated premorbid intelligence quotient (IQ). half of these had impaired premorbid IQ and half displayed average premorbid intellectual levels. Those with average premorbid intellectual levels showed cognitive profiles similar to normal, except for deficits in executive function and possibly attention and encoding.

In addition to global impairment in IQ as a predictor of the development of schizophrenia, there was an additional risk conferred by cognitive deficits (i.e. mechanical knowledge and to a lesser extent, verbal IQ). One study found association of low educational test scores at ages eight, 11 and 15 and later development of schizophrenia while another study found that there was no deterioration in IQ scores while comparing prepsychotic children (mean age  $13.3 \pm 3.1$  years) with their postpsychotic IQ scores as adults with schizophrenia.

**Symptoms of schizophrenia** Cognitive dysfunction is significantly correlated with various types of negative symptoms. Deficient motor skills are represented in both the negative symptom and the cognitive dysfunction domain because symptoms such as blunted affect and motor retardation are observational measures of motor functioning.

Patients with the deficit syndrome appear to have a fairly specific sign of cognitive impairments with more substantial impairments in tests of parietal lobe and frontal lobe functions than nondeficit patients.

When correlations between negative symptom and cognitive symptoms are examined over time, there is evidence that these symptom dimensions are correlated but discriminable.

The correlations between negative symptoms and functional skills were reduced when the severity of cognitive impairment is considered. On the other hand, studies suggest that positive symptoms are clearly not the sole cause of the cognitive impairment found in patients with schizophrenia.

**Course and prognosis** Bleuler considered that course of schizophrenia was too irregular and variegated to allow the description of typical and atypical varieties, but he too accepted a tendency towards deterioration as a characteristic of schizophrenia. Kleist and Langfeldt had said that diagnosis must be revised if after ten years or more the patient was found to have recovered.

The impairments in social and vocational functions as the illness progresses are due to associated cognitive impairment and the severity of negative symptoms. The clinical progression of schizophrenia occurs during the initial decade of illness followed by relative clinical stability or improvement.

Two main strategies have been used to characterise outcome in various domains, including symptomatic, social and work function and activities of daily living standardised scales like Disability Assessment Scale (DAS) to evaluate social and vocational function and the Global Assessment Scale of Functioning (GAF) or Global Assessment Scale to evaluate both symptoms and functions have been in use, in most modern studies. A second strategy emphasises course patterns, trajectory (stable or deteriorating) and summary and evaluation of outcome.

Not all individuals who experience a psychotic illness meeting criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder develop chronic symptoms and functional impairments. In a 15 years course of schizophrenia, between nine per cent and 38% of the individuals meeting criteria for a schizophrenic psychotic disorder enjoy a sustained symptomatic and functional recovery. The sustained recovery may occur after multiple episodes and includes gradual improvement after a long period of illness. Five to 20% of the patients recover from a first episode without subsequent recurrence of symptoms. However one study did not find any patient who had only a single episode followed by recovery. In a multicountry 15 years follow-up study of first episode patients, social and vocational function measured by DAS was found as 33% - good to excellent, 23% - fair, 44% - poor. About one-third of patients will have a relatively good outcome with no more than mild symptoms and functional impairments, the remaining two-thirds will have moderate to severe symptoms and functional impairments.

Long term mortality is higher for individuals with schizophrenia than in general population, as much as five times higher than age matched general population in men and two times higher in women, with suicide accounting for about half of the excess mortality. About one of ten individuals diagnosed with schizophrenia will die by suicide, with the highest risk occurring during the recovery period after initial diagnosis.

Schizophrenic patients are at increased risk for death from cardiovascular disease, diabetes, lung disease and accidents which may be genetically based or may be due to life-style, social environmental factors.

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Bleuler found an interesting relationship between outcome and intelligence. Among his recovered cases were more of above average intelligence than could be expected by chance distribution, while among the severely deteriorated the opposite was true.

As the age of onset increases, the chance of remission slightly declines but tendencies towards rapid deterioration gradually replaced by preservation of the personality. A well integrated prepsychotic personality, adjusted in the social, several and occupational sphere has relatively good chance of return to normality.

Psychological conflicts and mental strain were found significantly more frequently in history of recovered patients than with others. Patients whose illnesses were psychologically precipitated were found to have better prognosis. Gradually emerging symptoms are associated with poor prognosis and an abrupt onset precipitated by stress is associated with a good prognosis. Cognitive deficits in schizophrenic patients are more static through the course of illness but may improve, be stable or decline over time. Declining neurocognitive function in particular may be a poor prognostic sign.

Substance use may influence prognosis, at least in part, by increasing likelihood of treatment nonadherence. Cannabis most likely increases risk of psychosis and may be associated with more frequent hospitalisations, poorer psychosocial functioning and more severe psychopathology.

The availability of family support is associated with better long term clinical and functional outcome in first episode patients. Stressful life events may be associated with increased relapse risk in individuals with schizophrenia.

There is good evidence that the shorter the duration of first episode of psychosis prior to initiating antipsychotics, the greater the level of symptomatic and functional recovery. The relation or duration of initial untreated psychosis and outcome is independent of premorbid function or mode of onset.

Some authors have associated genes with severity of the disease. A polymorphism of the gene that codes for an enzyme involved in the metabolism of dopamine, catechol O-methyltransferase (COMT), associated with more severe symptoms in some. A genetic alteration in the gene that codes for the N-methyl-D-aspartic acid (NMDA) receptor 2A subunit involved in glutamate neurotransmission has been associated with more severe symptoms.

**Outcome of management in long term** The outcome of schizophrenia may be variable but in many cases schizophrenia is long term illness with persistent illness and impairment of functioning. Treatment with different methods can have limitations as evidenced by high rates of relapse, poor functional outcome, poor treatment compliance and medical comorbidities in patients who experience reduction in their psychotic symptoms. Cognitive deficits are responsible for poor medication adherence, inadequate social functioning, reduction in health and wellness, and decrease in quality of life (Harvey *et al.* 2004).

Patients who received antipsychotics for their first episode were more likely to have a complete remission than were those who had their first episode before antipsychotics were available, and generally had less severe psychopathology at long term follow-up (mean = 22 years). Recurrent episodes early in the course of illness are associated with increased

likelihood of developing chronic residual positive and negative symptoms. In the 15 years follow-up of nine diverse sites from the World Health Organisation (WHO) International Pilot Study of Schizophrenia, the strongest predictor of long term outcome was the amount of time the patient was psychotic in the first two years after illness onset.

Psychosocial therapies like family therapy, training, cognitive remediation and other therapies directed at improving antipsychotic treatment adherence, may improve symptomatic and functional outcome. Family intervention studies have improved outcome in family stress, coping and knowledge. In the studies of relation between relapse and social function, no advantage in social functioning for the experimental family treatment group was found. Controlled studies of integrated psychological treatment in schizophrenia have reported modest gains in elementary cognitive functions but no clear benefit for complex cognitive task or social and vocational functioning.

The proportion of persons with chronic schizophrenia, with competitive employment is 20% or lower. One non controlled study indicated that patients who were paid in Department of Veterans Affairs work placement programmes more hours, showed more improvement in symptoms at follow-up and had a reduced rate of hospitalization compared with unpaid patients.