Neurocognition and Thought Disorder:

it's Association, Temporal Stability and Outcome Correlates

in

First-Episode Psychosis

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Declaration

I, the undersigned, hereby declare that the work contained in this dissertation is my own original work and that I have not previously in its entirety or in part submitted it at any university for a degree.

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Abstract

Neurocognitive deficits and thought disorder in schizophrenia have generally been accepted as core features of the illness, yet their underlying relationship, response to treatment, and correlations with outcome remain unclear. Most of the studies to date have used cross-sectional designs and focussed on stable patients already on treatment. The purpose of this study was to assess changes in neurocognition and thought disorder in antipsychotic naïve or minimally treated first episode psychosis (FEP) patients, over the course of 12 months of treatment according to a standard algorithm with flupenthixol decanoate (FD) long acting injectable antipsychotic.

This was a prospective, non-comparative, open-label, longitudinal study of 42 patients with FEP. There was an initial wash-out phase of up to 7 days after which treatment was initiated with oral flupenthixol, 1 to 4 mg/day for 1 week prior to when the first long-acting FD was given. The starting dose of FD was 10mg every second week, with dose increases allowed at 6-week intervals. The Matrics Consensus Cognitive Battery (MCCB) and Rorschach Percerptual Thinking Index (PTI) were used as the primary co-measures for the assessment of neurocognition, thought disorder and perceptual disturbances respectively, at baseline prior to treatment, at month 6 and month 12.

The main findings of this study were as follows: we confirmed the presence of significant neurocognitive impairment, thought disorder and perceptual disturbances prior to treatment, with improvement in neurocognitive performance and thought disorder from baseline to 6 months, with form perception improving later between month 6 and month 12. Improvements in symptoms were associated with improvements in neurocognitive performance, thought disorder and perceptual disturbances but a degree of residual impairment was evident at month 12. This study confirmed the association between neurocognition and form perception *per se* as well as their relative stability in FEP after initial improvement with treatment. We found support for the correlation between the amount of improvement in neurocognition, thought and perceptual disorder with outcome. We found the Social and Occupational Functioning Scale (SOFAS) to be a more robust measure of social and functional outcome with highest level of education (HLOE), substance abuse, reasoning-and-problem solving, form perception and Rorschach PTI emerging as predictors in a best subset regression analysis.

The findings of this study suggest that neurocognitive impairments, thought disorder and perceptual disturbances have both state and trait like features, that patients benefit from treatment with a low-dose FGA, and that residual neurocognitive and perceptual impairment after treatment may indicate persisting underlying cerebral pathology.

Abstrak

Neurokognitiewe inkortinge en gedagteproses versteuring in skisofrenie word algemeen aanvaar as kern eienskappe van die siekte, tog is die onderliggende verhouding, die respons op behandeling, en die verwantskap met uitkoms onduidelik. Die meeste studies het 'n oorkruis-deursnee navorsingontwerp gebruik en gefokus op stabiele pasiënte wat reeds op behandeling was. Die doel van hierdie studie was om die verandering in neurokognisie, gedagte vesteuring en perseptuele inkortinge te meet in eerste-episode psigose pasiënte wat behandeling naïef was, of wat minimale behandeling gekry het, oor die verloop van 12 maande, met die toediening van 'n langwerkende, lae dosis flupenthixol inspuiting.

Hierdie was 'n prospektiewe, nie-vergelykende, oop etiket, longitudinale studie van 42 eerste episode psigose pasiënte almal op behandeling volgens 'n vaste protokol. Daar was 'n inisiële uitwas periode van tot 7 dae waarna behandeling begin is op orale flupethixol, 1 tot 4 mg/dag vir 1 week voordat die eerste langwerkende flupenthixol inspuiting toegedien was. Die aanvangs-dosis was 10mg elke tweede week met verhogings in dosis elke sesde week daarna. Die "Matrics Consensus Cognitive Battery" (MCCB) en Rorschach "Perceptual Thinking Index" (PTI) is gebruik as die primêre instrumente vir die meting van neurokognisie, gedagte

versteuring en perseptuele inkorting in noue samehang voor aanvang van behandeling, op maand 6 en op maand 12.

Die hoof bevindinge van hierdie studie was as volg: Ons het die teenwoordigheid van beduidende neurokognitiewe, gedagte versteuring en perseptuele inkortinge bevestig voor behandeling, met verbetering in neurokognitiewe prestasie en gedagte versteuring tussen basislyn en maand 6, en verbetering in vorm persepsie wat later gevolg het tussen maand 6 en maand 12. Die verbetering in simptome was geassosieër met verbetering in neurokognitiewe prestasie, gedagte versteuring en perseptuele inkortinge maar teen maand 12 was 'n graad van residuele neurokognitiewe en perseptuele inkortinge aanwesig. Hierdie studie het die verwantskap tussen neurokognisie en vorm persepsie bevestig, asook die relatiewe stabiliteit daarvan in eerste episode psigose na aanvanklike verbetering op behandeling. Ons het bewyse gevind wat die korrelasie tussen neurokognisie, gedagte en perseptuele versteuring met uitkomste ondersteun. Ons het bevind dat die "Social and Occuapational Functioning Scale" (SOFAS) 'n meer robuuste meting van sosiale en funksionele uitkoms is, en dat hoogste opvoedkundige vlak, substans misbruik, redenering-en-probleem oplossing, vorm persepsie en die Rorschach PTI as voorspellers identifiseer was in 'n beste substel regressie analise.

Die bevindinge van hierdie studie suggereer dat neurokognitiewe, gedagte versteuringe en perseptuele inkortinge oor beide toestand en trek eienskappe beskik, en dat pasiënte verbeter het met behandeling op 'n lae dosis eerste generasie antipsigotikum, en dat residuele neurokognitiewe en perseptuele inkortinge na behandeling aanduidend kan wees van onderliggende serebrale patologie.

CONTENTS

CHAPTER 1:

INTRODUCTION

Schizophrenia is a heterogeneous disease characterised by its diverse symptom manifestations reflecting multiple etiological pathways (Tandon *et al.*, 2009; Baxter & Little, 1998). Its clinical features are distinguished by the clustering of positive, negative, disorganized, cognitive, mood and motor symptoms (Tandon *et al.*, 2009; Sadock & Sadock, 2007) with varying degrees of severity across patients and over the course of the illness.

The lifetime prevalence of schizophrenia is about 1% of the general population. The illness onset usually is evident during adolescence or early adulthood, and typically it follows a chronic course marked by frequent relapses, incomplete remissions, functional impairment, social and occupational disability, frequent co-morbid substance use, and high mortality rates (Tandon *et al.*, 2009; Sadock & Sadock, 2007). In South Africa the epidemiology and clinical features of schizophrenia are no different from the rest of the world with a prevalence of 0.81% and an unemployment rate of 50% amongst schizophrenia patients (US Census Bureau, 2004). The disease does not discriminate amongst gender, socio-economic status (SES) or

culture. However, Burns (2009) argues that the course and outcome of schizophrenia is poorer in developing countries. In South Africa, conditions of poverty, inequality, and violence are important socio-economic stressors that may impact on the treatment and outcome of patients living with schizophrenia.

Both thought disorder and neurocognitive deficits have been:

- considered core features of schizophrenia (Keshavan *et al*., 2008; Heinrichs, 2005; Metsànen *et al.*, 2005),
- shown to be relatively stable over time (Metsànen *et al.*, 2005; Kurtz, 2005),
- associated with poorer outcomes and prognoses (Van Winkel *et al.*, 2007; Bowie *et al.*, 2008).

Premorbid neurocognitive impairment and thought disorder have been found to be present prior to the onset of psychotic symptoms (Henry and Crawford, 2005; Metsànen *et al.*, 2004; Woodberry *et al.*, 2008). Neurcognitive deficits and thought disorder have also been evidenced in the first-degree relatives of schizophrenia patients, indicating a 'trait' vulnerability or endophenotype (Erlenmeyer-Kimling *et al.*, 2000; Saykin *et al.*, 1994; Metsànen *et al.*, 2005).

The correlation between thought disorder and neurocognitive deficits, the underlying mechanisms thereof and the association with positive, negative and disorganized symptoms in schizophrenia, remains unclear. Mild to moderate correlations have been found between neurocognitive impairments and negative and disorganized symptom clusters (O' Leary *et al.*, 2000; Davidson *et al.*, 2009). On the other hand positive symptoms have demonstrated no significant correlation with neurocognitive deficits in schizophrenia (Klingberg *et al.*, 2006). Thought disorder has been correlated with:

- basic attentional and information-processing deficits (Perry *et al.*, 1999; Minàssian *et al.*, 2005),
- executive and working memory impairments (Kerns and Berenbaum, 2002),
- semantic-memory-lexical processing problems (Kerns & Berenbaum, 2002; Goldberg & Weinberger, 2000),
- aberrant salience to environmental cues and internal representational states (Kapur, 2003).

Whether thought disorder is secondary to underlying neurocognitive deficits remains to be answered, but the close association and shared phenomenology between the two constructs seem to point to a common underlying neural pathway.

Although thought disorder has been regarded as a variant of generalized neurocognitive impairment commonly found in schizophrenia patients (Gold & Hurt, 1990), there seems to be a partial dissociation between the two constructs in terms of treatment response (Goldstein *et al.*, 2002; Remberk *et al.*, 2012). Modest and selective improvement in thought disorder and neurocognition have been documented after antipsychotic treatment in schizophrenia patients (Ruhrmann *et al.*, 2007; Remberk *et al.*, 2012; Goldstein *et al.*, 2002). Despite the association between neurocognition and thought disorder and its response to antipsychotic treatment, putative studies investigating the neurocognitive mechanisms underlying improvement in thought disorder and positive psychotic symptoms are lacking (Goldstein *et al.*, 2002). The current study offers the opportunity to assess improvement in neurocognition, thought disorder and symptomatology in response to antipsychotic treatment over time.

One of the impediments in schizophrenia research has been the lack of appropriate measurement tools investigating multi-dimensional constructs like neurocognition and thought disorder. Prior to 2004, the assessment of neurocognition was flawed by the compendium of different neuropsychological instruments purporting to measure the same cognitive domains (Keefe *et al.*, 2011; Goldberg *et al.*, 2010). The National Institute of Mental Health "Measurement and Treatment

Research to Improve Cognition in Schizophrenia" (MATRICS) initiative led to the development of the MATRICS Cognitive Consensus Battery (MCCB), which was endorsed by the National Institute of Mental Health (NIMH) as the standard measurement of cognition in all schizophrenia clinical trials (Green *et al.*, 2004; Nuechterlein *et al.*, 2008). The MCCB measures Speed of processing, Attention/Vigilance, Working memory, Verbal learning, Visual learning, Reasoning and problem solving, and Social cognition. It allows clinicians and researchers to administer various tests in a relatively short time (Holmen *et al.*, 2010). Despite the growing interest in using the MCCB as the standard measure of neurocognition in schizophrenia, very little research has been done to date using the MCCB in first-episode psychosis (FEP), immediately highlighting the importance of the current study. This study will also expand on the clinical utility and validity of the MCCB in the South African context.

The measurement of thought disorder has posed similar difficulties: in early research the assessment of thought disorder was based largely on the subjective judgements of clinicians in unstructured interview settings (Nuechterlein *et al.*, 1986). Subsequently, many different methods have been developed to assess thought disorder in schizophrenia using inter alia proverbs, verbal comprehension and vocabulary tests, speech and language rating scales, and the

Rorschach Inkblot Method (RIM) (Andreassen, 1986; Holzman, 1986; Exner, 2003).

The RIM offers a unique opportunity to measure thought disorder because it encourages the patient to discuss his thoughts in an open and honest fashion. It can detect the subtleties of thought disorder that structured questionnaires tend to overlook (Perry *et al.*, 2003). To date, the preferred Rorschach index for assessing thought disorder in schizophrenia and related disorders is the Perceptual Thinking Index (PTI) (Exner, 2000a). This study is novel insofar as the PTI and the MCCB has never before been correlated to assess the relationship and temporal association between neurocognitive deficits and thought disorder over time in a cohort of patients with schizophrenia.

Longitudinal studies in FEP are often limited due to the challenges associated with the attrition rate of patients. Statistical power is diminished due to the patient attrition rate and missing data at follow-up visits (Bozikas & Andreou, 2011). The timing of baseline assessments is another important factor to take into consideration: some studies conduct baseline assessments on patients who have received no antipsychotic treatment, while other studies do baseline assessments once patients are stable on antipsychotic medication.

There are very few studies comparing neurocognitive deficits before and after antipsychotic treatment (Hill *et al.*, 2008).

Assessing neurocognitive deficits and thought disorder in FEP offers several advantages. It provides a realistic baseline measure of these core factors in schizophrenia patients and it minimizes the effects of variables such as average illness duration (Keefe *et al.*, 2013), long-term antipsychotic treatment (Gold, 2004), institutionalization (Rajji *et al.*, 2013), and the effects of aging on the neurobiology of the disease (Goldberg *et al.*, 2010).

The current study provides a longitudinal assessment of a well-defined cohort of FEP schizophrenia spectrum patients (DSM-IV TR diagnosis of schizophreniform, schizoaffective and schizophrenia) , all treated with the same first generation agent (FGA) according to a fixed protocol. It will expand on the existing body of knowledge pertaining to neurocognitive deficits and thought disorder in schizophrenia patients by tracking the response to antipsychotic treatment serially over a period of 12 months. The intercorrelations between improvements in neurocognition, thought disorder and symptomatology on the one hand, and the prediction of treatment outcome from baseline neurocognitive and thought disorder assessments on the other, will further our understanding of the

complex interaction between the neurocognitive, clinical and functional dimensions of schizophrenia spectrum disorders during FEP.

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CHAPTER 2:

NEUROPATHOGENESIS OF SCHIZOPHRENIA

INTRODUCTION

Schizophrenia is a multi-faceted disease entity reflecting diverse and varying degrees of symptomatology over the course of the illness, with multiple possible neurobiological pathways and epigenetic interactions. To date there is no laboratory test to aid the diagnosis of schizophrenia and no single biomarker or gene variation has been isolated that could give a plausible explanation for the complete pathogenesis of the disease over the course of its lifetime (Titone, 2010).

With the technological advances made over the past few decades in the fields of Neuroscience and Genetics we have come closer to an understanding of how the brain works, and to what may go wrong in the brain that then leads to the development of schizophrenia. Understanding the neurobiological aspects of the disease is an important precursor to furthering our insight and to gaging our knowledge of the neuropsychological findings in schizophrenia research. Neurocognitive testing measures aspects of brain functioning and could therefore expand on existing data supporting

structural and functional neurobiological changes or disrupted neural networks often found in the brains of schizophrenia patients (Borofsky *et al*., 2010).

This chapter will deal with some of the major neuroscientific discoveries that shed more light on the neuropathogenesis of the disease and its neurobiomarkers.

BRAIN CHANGES IN SCHIZOPHRENIA

Both functional and structural brain changes have been found in schizophrenia, but the research data is not consistent, or evident, in all patients. Furthermore, many studies have contradictory findings making it difficult to map brain abnormalities that are specific to schizophrenia. To complicate matters further, the overlap between functional and structural brain imaging is inconclusive and the concordance between neurocognitive testing and brain imaging is similarly poor.

Imaging studies have consistently demonstrated global and regional structural brain abnormalities in people with schizophrenia (Haijma *et al.,* 2013*)*. While the presence of abnormalities at, and prior to the onset of first psychotic symptoms (Pantelis *et al*.,2003) is consistent with a neurodevelopmental origin, longitudinal studies have established that progressive changes also occur (Olabi *et al*.,2011). These changes are most pronounced in the early years of illness, and occur only in a subset of patients (Andreasen *et al*.,2013). There is debate as to the causes of the progressive changes - while they may reflect illness progression (Lieberman *et al.,* 2001), there is also evidence to suggest that they are related to antipsychotic treatment *per se* (Smieskova *et al*., 2009;Ho *et al*., 2011;Andreasen *et al.,* 2013), or they may be non-specific and secondary to factors such as substance abuse, poor adherence to treatment or the effects of co-morbid conditions (Zipursky *et al*., 2013).

Brain volume, ventricle size, and CSF spaces

Brain imaging studies have indicated that whole brain volume (WBV) in schizophrenia patients is smaller than in normal controls. In a meta-analysis Ward *et al.* (2000) found that WBV is smaller by 2%. Intracranial volume (ICV) is also smaller but shows a smaller reduction than WBV in schizophrenia patients. These differences have been more consistently evidenced in chronic schizophrenia.

Reduced brain volume is found differentially more in gray matter, but white matter abnormalities have also been reported (Liddle & Pantelis, 2003). Reduced brain volume has been noted with illness onset, noteworthy being similar findings in neuroleptic naive FEP (Ren *et al.*, 2013*;* Gur *et al.*, 1999). A recent study of 100 neuroleptic naive FEP schizophrenia patients matched against healthy controls showed significant volume reduction in the gray matter of the patient group involving the thalamo-cortical networks (Ren *et al.*, 2013). It is therefore probable that the brain volume changes observed in schizophrenia are related to the illness itself and are not an effect produced by antipsychotic medicine. On the other hand progressive loss of WBV has been found in longitudinal studies over a 4-year period in 50 FEP schizophrenia patients (Velakoulis *et al.*, 2000b). Wood *et al.* (2001) found similar results in comparing FEP and chronic schizophrenia, against controls, over a 4-year period. Further, recent work suggests a possible role for antipsychotic

treatment in these progressive changes (Smieskova *et a.,* 2009;Ho *et al*., 2011;Andreasen *et al.,* 2013).

One of the most consistent morphological findings of the brain in schizophrenia has been enlargement of the ventricles, in particular the lateral and third ventricle. These changes are not, however, specific to schizophrenia, but have been found in other psychiatric disorders such as depression (Elkis *et al.*, 1995). Enlarged ventricles in schizophrenia have been associated with obstetric complications, and genetic factors are also evident in contributing to this predisposition (McNell *et al.*, 2000; Sharma *et al.*,1998; Lawrie *et al.*, 2001). Ventricular and sulcal enlargement have been found to be progressive from illness onset and are associated with poorer outcome (Staal *et al.*,1999) and longer duration of untreated psychosis (DUP) (Madsen *et al.*, 1999).

In summary, significant brain volume reductions and ventricular enlargement have been found in patients with schizophrenia. These changes are noted at illness onset, appear to be progressive over time and have been associated with poorer outcome.

Frontal neocortex

While the reported brain changes in schizophrenia are widespread, one area frequently found to show changes is the frontal lobe. The prefrontal cortex is functionally diverse and includes executive, social cognitive, affective and motor functions. Abnormalities in this region would be consistent with the heterogeneity of the symptom expression of schizophrenia which include disruptions in these functions.

Several studies have indicated selective loss of gray matter in the dorsolateral prefrontal cortex (DLPFC) and in the orbitofrontal cortex (OFC) of schizophrenia patients (Ren *et al.*, *2013*; Goldstein *et al.*, 1999; Szezko *et al.*, 1999). These areas are associated with the executive and controlling / inhibitory functions of the brain.

Frontal abnormalities are evident before illness onset, which point to neurodevelopmental abnormalities in brain maturation early in life. Abnormal synaptic pruning during adolescence has been linked to the onset of the illness (Keshavan *et al.*, 2000; Vance *et al.*, 2000) as it coincides with prodromal changes which often precede the psychotic break in FEP. The notion of 'neurodevelopmental' schizophrenia has regained scientific popularity and will be discussed more extensively elsewhere.

Staging of the illness suggests that frontal lobe changes precede those in the temporal lobe and the more general gray matter decline in schizophrenia. Rapoport *et al.* (1999) have studied the decline in frontal and temporal regions in childhood-onset schizophrenia and their association with negative symptoms and symptom severity. Frontal abnormalities are apparent in FEP and further progression has been demonstrated over time (Ren *et al.*, 2013).

Temporal neocortex

Volumetric changes in the temporal lobes have been reported in schizophrenia, particularly reduced gray matter (Levitt *et al.*, 2010; Cronenwett *et al.*, 2010). An area of special interest is the posterior part of the superior temporal gyrus, including the planum temporale. The planum temporale is responsible for the processing of language (Shapleske *et al.*, 1999) and volume reductions in this area as well as the parahippocampal gyrus and fusiform gyrus (Wright *et al.*, 2000; Paillere-Martinot *et al.*, 2001) have been implicated in schizophrenia.

Progressive tissue loss in the temporal lobes has been found in childhood-onset schizophrenia, although longitudinal studies in general do not support ongoing progressive deterioration (DeLisi *et al.*, 1995). Significant volume reductions of the temporal cortex have been associated with neuroleptic naive FEP schizophrenia patients

(Lui *et al.*, 2009; Meisenzahl *et al.*, 2008), which confirms the involvement of the temporal lobes during illness onset. Furthermore, abnormalities in the sulcal and gyral patterns of the temporal lobes may indicate neurodevelopmental pathology (Kikinis *et al.*, 1994).

The superior temporal gyrus, a region in the temporal lobes that includes the planum temporale, has consistently been implicated in schizophrenia. In a review by Shenton *et al.* (2001) of FEP studies, 100% gray matter reduction of the superior temporal gyrus is observed in schizophrenia. The superior temporal gyrus and planum temporale plays a role in auditory processing and source monitoring of internal mental activity.

Parietal cortex

Although the parietal lobes have not been a major focus of attention in schizophrenia, volumetric reductions and functional deficits have been reported in these areas (Goldstein *et al.*, 1999; Gur & Gur, 2010). Left-right asymmetry involving the angular gyrus has been found. The angular gyrus of the inferior parietal lobule has been implicated in the semantic-lexical network (Schlaepfer *et al.*, 1994; Goldstein *et al.*, 1999). Under-activity of the parietal lobe has been associated with psychomotor poverty symptoms and the severity of disorganization symptoms (Liddle *et al.*, 1992; Kaplan *et al.*, 1993).

Cingulate cortex

Studies have indicated cingulate abnormalities (Ren *et al.*, 2013) in chronic schizophrenia and childhood-onset schizophrenia using voxel-based morphometry (VBM), and lower N-acetylaspartate (NAA) bilaterally has been found in the anterior cingulate regions (Sigmundsson *et al.*, 2001; Sowell *et al.*, 2000). Yucel *et al.* (2002b) demonstrated abnormal cingulate gyrification in the left hemisphere, with reduced fissurization in patients with schizophrenia.

Anterior cingulate activation has been found to be inappropriate to stimulus demands in patients with schizophrenia, with either excessive or underactive responsiveness involving selective attention and response selection Bertolino *et al.*(2000).

Hippocampus and amygdala

Significant reductions in hippocampal and amygdala volumes have been found in schizophrenia, which are apparent during FEP (Nelson *et al.*, 1998; Hirayaso *et al.*, 1998; Velakoulis *et al.*, 1999). Nelson *et al.* (1998) reported more left-sided volume reductions, whilst Velakoulis *et al.* (1999) found bilateral hippocampal changes.

Reduced hippocampal volume may be a trait marker as suggested from twin studies, and bilateral reductions are found in first-degree

relatives of patients with schizophrenia (Seidman *et al.*, 1999). Other than the involvement of genetic factors in hippocampal volume, the role of environmental factors may also contribute to hippocampal decrease. Neurochemical (e.g., glutamate) or hormonal (e.g., cortisol) effects of environmental stress on hippocampal volume are well documented and might interact with genetic susceptibility in some cases. For example, Stefanis *et al.* (1999) and McNeil *et al.* (2000) have studied how perinatal birth complications may have caused patients with schizophrenia to have smaller hippocampi.

The amygdala forms part of the limbic system, which plays a primary role in the processing of emotions. Reduced activation of the amygdala was found in patients with schizophrenia during induction of sad mood (Schneider *et al.*, 1998), whilst Phillips *et al.* (1999) found overactivation of the amygdala during the patients' processing of facial expressions of disgust. The latter was associated with misappropriation of disgust with fear, which is consistent with the clinical notion that schizophrenia patients find it difficult to interpret emotions accurately and respond appropriately to emotional cues.

Subcortical structures

Overactivation in the cortico-striatal-thalamic circuits, with connections to the midbrain, striatum, and basal ganglia, has been

reported in patients with schizophrenia (Liddle *et al.*, 1992). Thalamic hyperactivity is observed during periods in which the patient displays positive symptoms of the disease (Silbersweig *et al.*, 1995). It follows that psychotic symptoms entail excessive feedback via the cortico-striatal-thalamic circuits. This is consistent with the putative mechanism of antipsychotic medication which is blockade of D2 receptors in the striatum (Lawrie *et al.*, 1999). The cerebellum is reciprocally connected to the association cortex via the midbrain and the thalamus. In schizophrenia reduced cerebellar activation is seen during performance of tasks that engage the association cortex, which is consistent with disruption of cortico-striatal-thalamic connections (Andreasen *et al.*, 1996; Kiehl & Liddle 2001).

AETIOLOGICAL MODELS OF SCHIZOPHRENIA

Aetiological models of schizophrenia have heuristic value in understanding the pathogenesis, development, and progression of the disease, but clear linear cause-effect interactions have eluded science so far. A few of the mainstream schizophrenia 'hypotheses', which are not mutually exclusive, are briefly outlined below

Hypofrontality

Prefrontal abnormalities are well described in schizophrenia with numerous studies indicating a decrease in prefrontal gray matter, hypometabolism / hypodopaminergia and impaired performance on cognitive tasks (Howes & Kapur, 2009). Aberrant prefrontal functioning in patients with schizophrenia is present at illness onset and is temporally associated with adolescence, the developmental period during which maturation of the frontal cortices are critical (Weinberger *et al.,*1988).

The DLPFC region has been of particular interest in schizophrenia. Post-mortem studies have indicated a decrease of cortical thickness in the DLPFC of 3-12% of schizophrenia patients (Pakkenberg, 1993; Daviss & Lewis, 1995). The presence of structural abnormalities in schizophrenia has also been supported by MRI studies, which

revealed subtle reductions in gray matter volume of the DLPFC. The reduction in gray matter is not necessarily due to a loss in neuronal numbers. Studies have indicated that the DLPFC neuropil, the axon terminals and dendritic spines of the synapses, are reduced in patients with schizophrenia (Selemon & Goldman-Rakie, 1999). Furthermore, the observation by Keshavan *et al.* (2000) of decreased DLPFC phosphomonoesters and increased phosphodiesters in neuroleptic naive FEP, is indicative of a decrease in synaptic numbers. Reductions in DLPFC N-acetylaspartate (NAA) have been reported (Bertolino *et al.*, 1996; Deicken *et al.*, 1997) and these are markers of disturbed neuronal and / or axonal integrity.

Thus, the reduction of DLPFC gray matter in schizophrenia appears to be explained by smaller neurones, aberrant axonal terminals and dendritic spines, and reduced synaptic numbers. These lines of evidence point to a disturbance in synaptic connectivity of the DLPFC, which correlates with impaired activation on working memory (WM) tasks in other brain regions (Bertolino *et al.*, 2000).

The notion of a hypodopaminergic DLPFC is held to be central in the core pathology of schizophrenia and has been supported by many studies. Hypofrontality is, however, unable to account for the diverse changes observed in other brain regions associated with the illness.

The role of the subcortical dopamine projections from the mesencephalon and thalamic nuclei is also deemed important. Reductions in D1 receptor density have been found in the DLPFC of neuroleptic naive schizophrenia patients (Okubo *et al.*, 1997) and reduced mediodorsal thalamic nucleus (MDN) volume has been found in post-mortem studies (Pakkenberg, 1990; Popken *et al.*, 2000; Young *et al.*, 2000). Furthermore, Danos *et al.* (1998) found supportive evidence of thalamic neurone density reduction in schizophrenia patients. Reduced MDN projection neurones are also associated with reduced DLPFC dendritic spine density, which supports the role of the MDN-DLPFC connectedness in the causation of schizophrenia.

Executive function deficits are regarded as core deficits in schizophrenia patients when assessed on WM, problem solving, set-shifting, and delayed-response performances. These cognitive functions require an intact DLPFC circuitry with its connections to the MDN and thalamic inputs. With normal development, delayed-response behaviour is increasingly mediated by the DLPFC with less reliance on the MDN to serve these functions (Alexander & Goldman, 1978). Schizophrenia patients have reduced activation of the DLPFC on WM tasks (the ability to hold information "on line" to guide behaviour) (Weinberger *et al.*, 1986; Goldman-Rakic, 1994*)* and on delayed response tasks (Park & Holzman, 1992). Weinberger *et al.*

(1988) found that schizophrenia patients show less activation of the DLPFC on the Wisconsin Card Sorting Task (WCST), a task that taps into cognitive set-shifting or flexibility. Executive function deficits are not the primary cause of schizophrenia, but they are regarded as risk factors that interact with social and environmental demands (Hollis & Taylor, 1997).

Dysconnectivity

The symptom expression of schizophrenia is diverse, including for example disorders of affect, movement, and cognition (Nuechterlein *et al.,* 2004). This likely reflects involvement of multiple neural pathways and diverse brain regions. Studies of fronto-temporal and fronto-thalamo-striatal dysconnectivity have supported the notion of disordered synaptic communication between remote brain regions rather than neuronal cell loss.

Several post-mortem studies have indicated structural abnormalities in sites connected to the DLPFC, i.e., the parahippocampal gyrus (Brown *et al.*, 1986), anterior cingulate, and superior temporal sulcus (Benes & Bird, 1987). Similarities between patients with schizophrenia and those with subcortical brain lesions have suggested that there may be a primary dysfunction of the fronto-thalamo-striatal pathways in the presentation of schizophrenia. Some

have argued that frontal lobe deficits, typically seen in schizophrenia patients, are linked to the disruption of the subcortical circuits and their projections to the DLPFC (Barnes, 1988; Pantelis *et al.*, 1989). Patients with subcortical lesions involving the basal ganglia and thalamus have symptoms resembling the negative symptoms, bradyphrenia, abnormal movements and cognitive deficits found in patients with schizophrenia (Barnes, 1988; Pantelis *et al.*, 1989; Cummings, 1986). The involvement of the basal ganglia in patients with schizophrenia is evidenced by abnormal eye movements and movement disorders, which are connected to the DLPFC and OFC (Barnes, 1988; Holtzman, 1987). Furthermore, Groenewegen *et al.* (1991) argue that emotional and behavioural abnormalities in schizophrenia implicate the limbic system and anterior cingulate projections.

Functional imaging studies predicting prefrontal rCBF using measures of hippocampal volume found that prefrontal activation on the WCST was related to hippocampal volume in schizophrenia patients (Weinberger *et al.,*1992). These results support the notion that prefrontal malfunction observed in schizophrenia is secondary to structural hippocampal abnormalities, with the latter typically occurring earlier in life (Benes, 1989). Changes in DLPFC volumetric measures and corresponding changes in thalamic structures have

been observed, which support the involvement of the DLPFC-MDN circuitry in schizophrenia (Benes, 2004).

Bertolino *et al.* (1996) have found an association between prefrontal cellular abnormalities and excessive dopamine levels in the striatum of patients with schizophrenia. The modulatory role of dopamine is hypothesised to be dissociated in schizophrenia with subcortical striatal D2/3 hyperdopaminergia and conversely D1 prefrontal hypodopaminergia (Howes & Kapur, 2009). Striatal hyperdopaminergia is associated with an aberrant attribution of salience to stimuli, which could explain the hallucinatory and delusional interpretation of stimuli (Kapur, 2003; Kapur *et al.*, 2005). On the other hand, prefrontal hypodopaminergia is often associated with the negative symptoms and cognitive impairment seen in schizophrenia (Goldman-Rakic *et al.*, 2004; Tamminga, 2006).

Abnormalities in frontotemporal white matter tracts, which translate into regional brain connectivity and fibre pathways, have been observed by using advanced imaging techniques (diffusion tensor and magnetization transfer imaging) to observe the brain activity of patients with schizophrenia (Lim *et al.*, 1999; Foong *et al.*, 2001).

Measures of cognitive function have indicated a dissociation between regional brain networks in schizophrenia. Word generation tasks are associated with prefrontal activation and simultaneous suppression of activity in the STG of normal subjects. In schizophrenia prefrontal activation is normal on word generation, but increased activity is observed in the STG (Frith *et al.*, 1995; Fletcher, *et al.*, 1996). WM tasks are usually associated with the activation of the DLPFC, but this is conversely observed to be decreased in subjects presenting with schizophenia. However, observation of subjects undertaking WM tasks, shows that endogenous NAA levels correlated with activation of a widely distributed WM network involving the DLPFC, temporal, and inferior-parietal cortices (Bertolino *et al.*, 2000). Josin & Liddle (2001) have been able to distinguish schizophrenia patients from normal subjects with 100% reliability using data gathered from observing the functional connectivity between the prefrontal cortex and other cerebral sites. Furthermore, frontotemporal dysconnectivity has been defined as a state marker of schizophrenia with remitted patients and high-risk relatives showing no abnormalities in frontotemporal connectivity (Bertolino *et al.,* 2000). Thus, measures of cognitive function support the findings of structural and functional brain imaging that point towards the involvement of prefrontal-temporal cortical dysconnectivity in patients with schizophrenia.

Further support for the model of dysconnectivity as a primary cause underlying the wide spectrum of symptomatology in schizophrenia, comes from studies of neurological conditions involving intracortical connections associated with psychosis. Of these neurological conditions the velocardiofacial syndrome (VCFS) and metachromatic leucodystrophy (MLD) have drawn interest. VCFS and MLD (a pure connectivity disorder), are both associated with late age illness onset similar to schizophrenia. MLD is a rare disorder of aryl sulphatase deficiency leading to the functional dysconnection of the cortical regions (Hyde *et al.*, 1992), with illness onset between 13-30 years of age and symptoms closely resembling that of schizophrenia. Neuropathological abnormalities are observed in the white matter of MLD subjects, with prominent changes in prefrontal white matter evident at the time of illness onset (Hyde *et al.*, 1992). This suggests that functional dysconnectivity of the prefrontal cortex is responsible for psychosis, analogues to what has been observed in schizophrenia.

In summary, the late expression of psychosis in schizophrenia might reflect early developmental abnormalities, which alter intracortical connectivity during the critical period for prefrontal maturation. Prefrontal connectivity involves the temporal, subcortical, and limbic regions.

Neurodevelopment

Since the inception of Kraepelin's concept of "dementia praecox", early models of schizophrenia regarded the illness as following a slow and progressive course with degenerative brain changes leading to an end state of dementia. Kraepelin and Bleuler noted abnormal neurological and behavioural signs in the childhood histories of patients with schizophrenia. Bender (1947) described schizophrenia as a developmental encephalopathy and others have noted developmental abnormalities (Fish & Hagin, 1972). The notion of schizophrenia as a degenerative disease has been disputed by longitudinal studies indicating recovery, static neuropsychological impairment, absence of astrogliosis, and absence of neurodegeneration (Harding *et al.*, 1992; Aylward *et al.*, 1984; Weinberger, 1986). By the end of the 1980s research attention shifted and the notion of abnormal brain development in the pathogenesis of schizophrenia gained momentum. The evidence suggests subtle abnormalities of cortical development, particularly in the prefrontal cortex with its connectedness to other brain regions.

Several lines of evidence point to a neurodevelopmental process, rather than neurodegeneration, in the progression of schizophrenia. Brain morphology in schizophrenia is characterised by increased neuronal density (smaller neurons), regional decrease in dendritic spine density, especially in subcortical white matter, temporal regions

and DLPFC, decreased intra-neuronal space and reduced brain volume (Piper *et al.*, 2012; Glantz & Lewis, 2000). Furthermore, the absence of gliosis and of neuronal cell death, count against adult-onset neuropathology (Piper *et al.*, 2012).

Differences of opinion exist in what the mechanism of neurodevelopmental process is for schizophrenia. Early formulations led to the notion of an early prenatal or perinatal developmental insult, which could be neurogenetic or environmental in origin. This "lesion" remains dormant until brain maturational interactions (environmental stressors and/or cortical maturation) during puberty alter the cytoarchitecture of the regional brain networks prior to illness onset (Piper *et al.*, 2012).

Early developmental risk factors are obstetric complications (infection, micro-nutrient deficiency, birth complication, famine), minor neuromotor abnormalities, delayed attainment of developmental milestones, behavioural, personality, and intellectual abnormalities (Piper *et al.*, 2012; Petronis, 2004). Musculoskeletal anomalies, postural abnormalities and associated reactions, and weakness in the left hand, have been observed in pre-schizophrenic children under the age of 2 (Walker, 1994). Cannon *et al.* (2002) also found language impairments among children who later were

diagnosed with schizophrenia. Lower IQ scores have been reported in children who later develop schizophrenia, with at least 1 SD below the mean in most cases (IQ 80-85 range) and a third having IQ scores below 70 (Jacobsen & Rapoport, 1998). Of interest is that these premorbid IQ deficits have been more marked in males (Aylward, Walker & Bettes, 1984).

The role of DNA sequence variation in gene expression is considered to be an epigenetic mediator in the neurodevelopment of schizophrenia. Anecdotal evidence from cases of VCFS, an inheritable genetic disorder that closely resembles the clinical features of adult schizophrenia, is worth mentioning (Eliez & Feinstein, 2004). As many as 30% of children who have this microdeletion of chromosome 22 syndrome, develop schizophrenia as young adults. VCFS is marked by cardiac anomalies, clefting of the secondary palate, small stature, distinctive facial appearance, slender hands, and learning difficulties or mental retardation (Shprintzen *et al.*, 1978).

The existence of early neuromotor, muscoskeletal, physical, behavioural and neuropsychological anomalies in a proportion of pre-schizophrenic children, support the notion of abnormal brain development during foetal or neonatal life. Epigenetic expression and

aberrant genetic control of brain development seem to be linked to birth complications and other environmental stressors (Bayer *et al.,* (1999).

The "late" neurodevelopmental model of schizophrenia was first described by Feinberg (1983, 1997). According to this model excessive synaptic / dendritic pruning during adolescence leads to neural dysconnectivity and psychotic symptoms. This process of abnormal neural maturation explains the long delay between perinatal neurological abnormalities and disease expression around the time of adolescence. This implies an additional pathological process and further structural brain changes and cognitive decline around the time of FEP, which characterizes schizophrenia as a progressive late onset neurodevelopmental disorder (Woods, 1998; McGlashen & Hoffman, 2000). Other possible mechanisms for schizophrenia include abnormal myelination (Benes, 1989), neuronal sprouting (Stevens, 1992), or the adverse effects of stress (Piper *et al.*, 2012; Bogerts, 1989) in producing neural disarray.

A similar approach to protracted disease expression in neurodevelopmental schizophrenia indicates compensatory limbic reorganization in response to developmental insult (Grace & Moore, 1998). The limbic system subsequently fails to subserve the

executive functions, with increasing environmental demands and stress placed on the prefrontal cortex, around the time of adolescence. Executive functions such as WM are dependent on DA innervation within the prefrontal cortex, which is reduced by as much as 33% in schizophrenia (Howes & Kapur, 2009; Akil *et al*., 1999).

Moreover the hippocampus has been found to play a modulating role in the working of the hypothalamic-pituitary-adrenal axis (HPA) in response to stress-released glucocorticoids (Sapolsky *et al.*, 1990). The importance of the hippocampus in neurodevelopmental schizophrenia has been underscored by studies indicating that prefrontal disruption may overload the hippocampus, which subsumes some of the WM functions while the prefrontal cortex is developing (Cullinan *et al.*, 1995; Diamond, 1990). Available imaging data have supported this idea that some of the WM functions are mediated by the hippocampus in schizophrenia patients (Meyer-Lindenberg *et al.*, 2001; Weinberger *et al.*, 1993) and increased hippocampal volume has been found prior to FEP (Pantelis *et al.*, 2003; Phillips *et al.*, 2002).

A second perspective, in the late neurodevelopmental model, postulates that cortical mal-development in utero interacts with normal developmental processes that occur much later in life

(Weinberger, 1986, 1987). In addition to synaptic maturation of the prefrontal cortex, inputs from subcortical projections also undergo dramatic changes during early adulthood. Studies have indicated that elaboration of postnatal dopamine input reaches its highest density in early adulthood (Lambe *et al.*, 2000).

The frontal lobes and their connectedness to temporal and subcortical regions are pivotal to highly evolved behaviours emanating from the demands of adulthood. Early developmental abnormalities may subtly alter intra-cortical connectivity, which may lead to further neural maturational abnormalities in the prefrontal cortex and its subcortical projections. This view is similar to the "risk" model, which proposes that early or late neurodevelopmental abnormalities act as risk factors that interact with exposure to other environmental risk or protective factors (Hollis & Taylor, 1997).

Psychoactive substances also increase the risk of schizophrenia because of their effects on dopaminergic function (Yui *et al.*, 2000). In this regard, it is worth mentioning the link between cannabis use and the onset of schizophrenia. Cannabis acts primarily on cannabinoid receptors that lead to an increase in striatal dopamine release (Cheer *et al.*, 2004; Tanda & Pontieri, 1997). Thus, in essence the neurodevelopmental theory of schizophrenia postulates

that early disruption of brain development can alter the trajectory of brain maturation and changes the cytoarchitecture of different brain regions. Environmental risk factors interact with the epigenetic expression of the clinical features of the disease.

Neurodegeneration

The debate over whether the neurodevelopmental hypothesis represents a static encephalopathy or progressive neurodegeneration remains unresolved (Thompson & Levitt, 2010; Velakoulis *et al.*, 2000). Limited neurodegeneration before, during, and after schizophrenia onset has been suggested in the temporal and frontal lobes, by available imaging data from studies indicating progressive volume reductions in the first 2-3 years following illness onset (Gur *et al.*, 1998). Sequential volume reductions of the temporal lobes generally occur later on during the course of the illness with the frontal lobe and thalamic structures preceding temporal changes around the time of illness onset (Jacobson *et al.*, 1998).

Post-mortem findings indicate an absence of gliosis or signs of neural apoptosis. These findings have been used as counter arguments against the notion of neurodegeneration in schizophrenia. However, a few studies have found increased periventricular and

subependymal gliosis, pyramidal and non-pyramidal neuronal loss in the anterior cingulate, nucleus accumbens, and mediodorsal thalamus (Benes *et al.*, 1991; Young *et al.*, 2000; Pakkenberg, 1990). Thus, although large-scale cortical neuronal loss is absent in schizophrenia, available research data reveal limited neuronal and / or glial reductions, especially in the subcortical areas.

The role of apoptosis has been adapted in schizophrenia to include a process of excessive synaptic pruning or "synaptic apoptosis" during puberty (Mattson *et al.*, 1998). Abnormalities in pro- and anti-apoptotic proteins, as well as DNA fragmentation profiles, have been found in post-mortem studies of schizophrenia brains suggesting neuropathological pathways similar to apoptosis evidenced in neurodegenerative disorders (Jarskog *et al.*, 2000; Benes *et al.*, 2003).

Consistent findings of brain abnormalities in schizophrenia have been enlargement of the lateral and third ventricles, and reductions in cortical gray matter volume. Recent studies indicate progressive lateral ventricular volume increase years after illness onset, which challenges a purely neurodevelopmental model of schizophrenia (Kempton *et al.*, 2010; Pantelis *et al.*, 2005). Furthermore, progressive volume reductions in fronto-temporal gray matter that

consists primarily of reductions in neuropil have been found in the brains of patients with childhood-onset schizophrenia, FEP, as well as in certain chronic and prodromal patients (Mathalon *et al.*, 2001; Gur *et al.*, 1998; Schlaepfer *et al.*, 1994).

Another important consideration in the 'static vs. progressive' debate is the duration of untreated psychosis (DUP). Longer DUP has been correlated with an increase in symptom severity, poorer treatment response, and less favourable outcome (Lieberman *et al.*, 2001b). These findings have led to the idea that untreated psychosis is inherently neurotoxic, causing further progression of underlying neuropathologies (Loebel *et al.*, 1992; Wyatt, 1991).

Longitudinal studies have shown that neurocognitive impairments remain relatively stable after illness onset but that deterioration may occur before, during, and after, illness onset (Rund, 1998; Hoff *et al.*, 1999; Cannon *et al.*, 2002). A subset of patients, with primarily negative symptoms or 'deficit syndrome', has been found to show progressive cognitive deterioration and diffuse cognitive impairment throughout the course of the illness (Mittleman & Buchsbaum, 2007). These presentations are often found in chronically institutionalized, geriatric patients (Friedman *et al.*, 2002). It is, therefore, unclear whether this subset of patients has "true" neuropathic atrophy or

whether it is a culmination of the effects of institutionalism, anti-psychotic treatment, and/or interaction with other comorbid neuropathologies. Indeed, it has been argued that all of the so-called progressive changes in schizophrenia could be explained on the basis of secondary factors such as substance abuse and medication effects (Zipursky., Reilly & Murray2012).

Therefore, it seems that more recent brain imaging studies indicate longer-term brain changes after illness onset. However, the findings are not conclusive.

Asymmetry

The notion of hemispherical imbalances in schizophrenia patients has been controversial and the available literature is marked by divergent and often contradictory results. However, studies indicating asymmetries in brain structure and functioning in schizophrenia are worth mentioning in the context of intra-cortical connectedness and integration of regional neural networks.

Flor-Henry (1969) was the first to implicate left hemisphere imbalances in schizophrenia patients and thereafter numerous studies have followed a similar trend (Gur, 1978; Posner *et al.*,

1988). The role of weak right hemispheric pathways in the neuropathology of schizophrenia has also received widespread attention, with studies looking at the integration of the right prefrontal cortex, temporal cortex, and primary sensory cortex (Nuechterlein, 1985; Grove *et al.*, 1991).

Early neuromotor delays and anomalies implicating left-sided weakness of the body and associated reactions of the left hand (such as posturing and neglect) have been suggested by retrospective studies of early childhood histories of schizophrenia patients (Meehl, 1989; Meehl, 1990; Mirsky & Duncan, 1986; Johnstone *et al.*, 1990). These signs of neuromotor delays during early development might be closer to the neurobiological substrate of the illness by implicating contra-lateral right-sided impairment. Harrison (1997) has even found that reduction in normal brain asymmetry is evident prenatally.

Functional imaging data from Positron Emission Tomography (PET) studies have indicated that normal subjects produce prefrontal activation and differential right hemisphere activation on Continuous Performance Tests (CPT) (Nuechterlein *et al.*, 2004). Schizophrenia patients, however, show less prefrontal activation and less activation of the right temporo-parietal areas compared to normal subjects. Cohen *et al.* (1987) stated that the role of the right temporal cortex in

the processing of visual vigilance on the CPT, could provide an explanation for the differential right hemisphere metabolic inactivation found in schizophrenia patients. Shallice (1988), on the other hand, has offered an alternative explanation for the role of right hemisphere abnormalities on vigilance tasks, by stating that the prefrontal cortex fails to organise strategies and activate brain regions for the processing of specific types of information.

Older studies have indicated left-sided lesions with multifaceted hemi-neglect signs in schizophrenia: motor neglect as indicated by a tendency to turn to the left (Bracha *et al.,* 1987; Pycock & Marsden, 1978); right-sided sensory neglect (Manshreck & Ames, 1984); and impaired ability to shift attention to the right (Posner *et al.,* 1988). Potkin *et al.* (1989) found that patients with schizophrenia have fewer eye fixations in right hemi-space. Manshreck & Ames (1984) demonstrated right hand impairments on tests of graphesthesia / stereognosis and increased leftward turning on a swivel chair (Lyon & Satz, 1991).

Cutting (1985, 1990) made comparisons between patients with right-sided brain lesions after cerebrovascular accidents / temporal lobe epilepsy and found analogous neuropsychological impairment and clinical features similar to schizophrenia. In another study by Parnas

et al. (1982) non-affective psychosis was found with right and left-sided lesions in temporal lobe epilepsy patients, but classical "Bleulerian schizophrenia" was predominately associated with right-sided lesions. Another interesting finding stems from delusional misidentification or "Capgras syndrome" that is common in schizophrenia (Kimura, 1986) and that is associated with right hemisphere brain dysfunction (Feinberg & Shapiro, 1989). Capgras syndrome prevalence rates of 40% have been reported in schizophrenia (Kimura, 1986).

The neurodevelopmental and dopamine hypotheses have received more emphasis in recent literature. This provides an inclusive framework incorporating genetic, environmental, epidemiologic, and neurocognitive research data (Piper *et al.*, 2012; Howes & Kapur, 2009; Kapur, 2003). Loss of normal brain asymmetry has also been linked to neurodevelopmental pathology in schizophrenia (Piper *et al.*, 2012).

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CHAPTER 3:

NEUROCOGNITIVE DEFICITS IN SCHIZOPHRENIA

HISTORICAL DEVELOPMENTS OF NEUROCOGNITION IN SCHIZOPHRENIA

Before the advent of standardised neuropsychological testing and modern brain scanning technology, early conceptualizations of neurocognition in schizophrenia included attentional, reasoning, memory, and information processing deficits (Weiner, 1966). Original descriptions by Kraepelin (1919/1971) and Bleuler (1950) made reference to abnormalities in attention, associative and volitional processes.

Traditional psychodynamic conceptualizations of cognitive functions in schizophrenia show remarkable empirical consistency with current neurocognitive findings in schizophrenia. Weiner (1966), building on the work of Rappaport *et al.* (1945/46), described abnormalities in schizophrenic thinking processes that included defective reasoning, concept formation, attention and general intelligence.

Early notions of a "generalized deficit" indicated a pattern of diffuse neurocognitive decline in schizophrenia. Chapman and Chapman

(1973) found that patients with schizophrenia tend to do more poorly on a wide variety of cognitive tasks when compared to controls. Results of neurocognitve testing using the Halstead-Reitan battery on large normative samples have pointed towards a generalized deficit in schizophrenia (Blanchard & Neale, 1994; Braff *et al.,* 1991).

In contrast to the idea of diffuse neurocognitive deficits, other studies have indicated differential impairments, which may be associated with regionally specific neurocognitive deficits in schizophrenia. Circumscribed deficits in executive function (cognitive set-shifting and WM), attentional and memory impairment have been regionally connected to frontomedial-temporal lobe abnormalities in schizophrenia (Kolb & Whishaw, 1983; Shallice *et al.,* 1991; Weickert *et al.*, 2000). In comparison to other mental disorders, Goldberg *et al.,* (1993a) found that patients with schizophrenia scored significantly lower than affective disorder groups on tests of attention, psychomotor speed, memory, abstraction and problem solving ability. Importantly, after controlling for general IQ between groups, the schizophrenia group performed significantly poorer on the WCST and tests of visual memory (Goldberg *et al.*,1993a). These findings are consistent with the hypothesis of executive, memory, and attentional deficits as key neurocognitive deficits in schizophrenia.

NEUROCOGNITIVE DEFICITS

Different neuropsychological measurements, methodological differences, and the inherent symptom diversity found in the "group of schizophrenias" make direct comparison of neurocognitive testing very difficult across patient samples. Despite these methodological difficulties, available test results often converge on severe and differentially prominent neurocognitive deficits across the schizophrenia spectrum (Goldberg *et al.*, 2003).

Recent studies have indicated generalized neurocognitive deficits in schizophrenia (Lencz *et al*., 2006; Dickinson *et al*., 2008). Impairments are described in the domains of processing speed (Dickinson *et al.*, 2007), verbal fluency (Henry & Crawford, 2005), attention (Fioravanti *et al*., 2005), verbal memory, learning (Saykin *et al.,* 1994), visual-motor processing (Saykin *et al*., 1994), executive functions, and working memory (Lee & Park, 2005; Reichenberg & Harvey, 2007; Barch & Smith, 2008). However, attentional, memory, and executive functions have traditionally received more emphasis in schizophrenia research. This was in an attempt to circumscribe the core neurocognitive deficits underlying regionally disrupted neural systems in schizophrenia (Saykin *et al*., 1994; Lysaker *et al*., 2009).

These neurocognitive functions are briefly discussed with reference to their significance in schizophrenia research.

Attentional deficits

Attention is not a unitary construct and involves the ability to focus, to keep focus, to selectively attend, vigilance, and reaction time (Lezak, 2004). The inability to ignore information irrelevant to the task, and the inability to shift attention according to environmental cues, characterized early conceptualizations of attentional deficits in schizophrenia (Shakow, 1950; Lang & Buss, 1965). Shallice (1988) referred to the "supervisory" attentional system, which is the executive function of attention: the ability to direct attention and to shift attention in a coordinated manner according to changing internal and external stimuli.

The concepts of inappropriate attending or defective filtering of stimuli have received prominence again in recent literature indicating the role of dopamine to mediate the salience to environmental stimuli and internal representational states (Kapur, 2003; Howes & Kapur, 2009). According to this model the hyperdopaminergic dysregulation of brain function leads to aberrant salience of experience: delusions and hallucinations are secondary reactions in the patient's attempt to make sense of the intrusive rush of ideas and perceptions (Kapur, 2003).

Brain structures that have been implicated in attentional paradigms involving selective attention and conflicting responses are the dorsal part of the anterior cingulate cortex and adjacent medial frontal cortex (MacDonald *et al.*, 2000). Reduced activation of the anterior cingulate cortex has been shown in schizophrenia patients on the Stroop task, which entails shifting attention between conflicting responses and the ability to inhibit a proponent response at the expense of a less salient response (Carter *et al.*, 1997).

Research using neurocognitive testing also indicated deficits in vigilance, slowed reaction time, selective attention, and distractibility (Perlstein *et al.*, 1998; Elvevag *et al.*, 2000a; Fioravanti *et al*., 2005). Patients with schizophrenia also display deficits in maintaining vigilance on the Continuous Performance Test (CPT); the ability to ignore inappropriate cues and to respond to target stimuli (Mirsky, 1988). Impairments in vigilance or sustained attention have been viewed as core vulnerability factors in schizophrenia, are not limited to periods of active psychosis, and are prominent in the first degree relatives of schizophrenia patients (Nuechterlein *et al.*, 1994).

Individuals with childhood-onset schizophrenia show similar attentional deficits to those with later onset schizophrenia (Asarnow *et al.*, 1995). Children with schizophrenia do poorly on the span of apprehension task (Asarnow *et al.*, 1991, 1995) and have reduced

performance on the CPT (Strandburg *et al.*, 1994). "High-risk" children, who are genetically susceptible to developing schizophrenia, have shown similar deficits in attention and information processing speed (Erlenmeyer-Kimling *et al.*, 2000). This indicates that basic attentional deficits are potentially predisposing factors in schizophrenia spectrum disorders.

Memory

Impairment of episodic memory was one of the first neurocognitive deficits noted in schizophrenia studies (Hull, 1917). Early research findings indicated significantly poorer learning abilities when compared to healthy controls and neurotic groups. What has been found is an association between learning capacity and motivational / attentional factors, better performance by patients with paranoid schizophrenia when compared to other types, and a positive correlation between learning impairment with symptom severity and chronicity in schizophrenia (Shakow, 1950; Shakow, 1963). Early studies involving neurocognitive performance in schizophrenia should be interpreted with cautious scrutiny because of the different diagnostic classification systems and the lack of refined diagnostic tools and brain imaging technology before the 1980's.

Other studies have indicated that patients with schizophrenia do worse on story recall, paired associates, word lists, and visual designs when compared to healthy controls (Saykin *et al.*, 1991). Furthermore, memory in schizophrenia has been associated with negative learning slopes (Paulsen *et al.,* 1995), and impaired recognition on cueing (Gold *et al.*, 1992). Saykin *et al.* (1994) discriminated between FEP and healthy controls using verbal memory as primary variable and found it to be independent from anticholinergic medication or neurocognitive deficits involving attentional or executive domains. Memory impairment is not restricted to chronic or institutionalized patients with schizophrenia (McKenna *et al*., 1990). It has been found to be pronounced in comparison to other neurocognitive deficits found in schizophrenia (Braff *et al.*, 1991; Saykin *et al*., 1991).

Episodic memory deficits have been associated with an amnestic clinical presentation, which include impairments of recall, learning, recognition, and aspects of longer-term memory. Short-term and implicit memories were relatively spared (Achim & LePage, 2005; Ranganath *et al.*, 2008).

Executive functions

Neurocognitive deficits in planning, cognitive set-shifting, working memory, and response inhibition have been consistent findings in schizophrenia research and are central to the development and clinical manifestation of the illness. These findings correlate with numerous studies of brain morphology and function, indicating reduction in DLPFC gray matter and NAA concentrations in schizophrenia (Daviss & Lewis, 1995; Bertolino *et al.*, 1996; Deicken *et al.*, 1997) with corresponding prefrontal dopaminergic hypoactivation (Akil *et al*., 1999).

In schizophrenia, an overall executive function deficit is implicated that is more severe than in patients with frontal lesions (Lee & Park, 2005; Barch & Smith, 2008). Deficits have been demonstrated on the WCST with poor abstraction, set-shifting, and perseveration (Berman *et al.*, 1986; Morice, 1990) even when controlling for IQ, in comparison to healthy controls (Weickert *et al.*, 2000). Asarnow *et al.,* (1994) have found similar executive function impairments in children with schizophrenia. Furthermore, executive deficits have been found on:

- intradimensional / extradimensional set-shifting tasks (Pantelis *et al.*, 1999),
- planning ability as measured by the Tower of London (TOL) test (Pantelis *et al.*, 1997),

- WM deficits or the ability to hold information "on-line" as seen on the letter-number-span (LNS) test (Lee and Park, 2005; Reichberg & Harvey, 2007),
- digit span (Flemming *et al.*, 1997; Aleman *et al.*, 1999),
- spatial memory span (Pantelis *et al.*, 1997) and on
- the delayed response alternation task (Gold *et al.*, 1991).

The hypofrontality hypothesis has been difficult to reconcile with the findings of several studies that have reported greater activation of the frontal cortex during WM tasks in schizophrenia when compared to healthy controls (Callicott *et al*., 2000; Manoach *et al*., 2000). Perlstein *et al.,* (2001) postulated that the unexpected increase in activation on WM tasks could be attributed to the role of the DLPFC in the processing load. Decreased frontal activation has been found only when the processing load / task complexity was high and, therefore, excessive activation was associated with low-load baseline tasks. The role of the DLPFC is to resolve competing responses (MacDonald *et al*., 2000), but it is unable to meet the demands in high processing tasks that compete with the self-generated mental activity associated with positive symptoms.

The prefrontal cortex is implicated in the initiation of motor acts and verbal responses and the suppression or inhibition of unwanted responses or impulses (Lezak, 2004). In patients with schizophrenia

who have difficulty initiating activity the DLPFC is under-activated (Liddle, 1987). This results in the loss of inhibitory function or sensori-motor gating, as tested via prepulse inhibition (Perry *et al.*, 1999), and difficulty in suppressing inappropriate mental activity on the Stroop test (Baxter & Liddle, 1998).

General intelligence

The question of general intellectual decline over the course of schizophrenic disturbance versus premorbid intellectual performance has been debated by early research using standard intelligence scales like the Stanford-Binet and Wechsler-Bellevue tests. Trapp and James (1937) were the first to document findings from a longitudinal study administering the Stanford-Binet to 41 hospitalized patients, indicating a mean drop of 7.6 IQ points over time (4 months to 13 years). Other studies followed that supported the concept of progressive intellectual deterioration after illness onset (Rappaport & Webb, 1950; Schwartzman & Douglas, 1962). On the other hand however, there are also early studies opposing these findings and indicating improvement in IQ scores in a large percentage of hospitalized patients with schizophrenia and a positive correlation between clinical improvement and raised IQ scores during hospitalization (Rabin, 1944; Haywood & Moelis, 1963). Early research findings were thus inconclusive with regards to general intellectual decline or improvement over the course of the illness.

More recent studies have indicated a decline in the mean IQ of children and adolescents before illness onset (Fuller *et al.*, 2002; Reichenberg *et al.*, 2005), and lower premorbid IQ has been associated with increased risk to develop schizophrenia later in life (Zammit *et al.*, 2004; Reichenberg *et al.*, 2006).

Furthermore, results from a National Institute of Mental Health (NIMH) study on child and adolescent schizophrenia, have indicated a decline in IQ from a mean of 87,7 (pre-psychotic) to a mean of 83,7 points (post-psychotic) (Alaghband-Rad *et al*., 1995). Intellectual deterioration and decline in scholastic performance preceding a FEP have been described in patients with childhood onset schizophrenia (Fuller *et al*., 2002). Lower IQ has been related to the severity of the illness (Daneluzzo *et al*., 2002). Later onset schizophrenia has shown a similar decline in IQ in pre-psychotic individuals when compared to healthy controls (Aylward *et al*., 1984).

Longitudinal studies of IQ after illness onset indicate that general intellectual deterioration in schizophrenia is not greater than the decline associated with normal aging (Kurtz, 2005). In a systematic review of studies with repeated IQ testing in patients with schizophrenia and healthy controls, a larger practice effect was found in the control group (mean IQ change of +2.08), which indicate that patients with schizophrenia benefit less from repeated IQ testing (Hedman *et al.*, 2013). This finding may imply that, in schizophrenia,

learning is compromised due to a neurodevelopmental neurocognitive deficit.

In summary, little supportive evidence exist for general intellectual deterioration over the life course of schizophrenia. However, several studies have demonstrated a notable decline in IQ during the pre-psychotic / prodromal phase, with further decline in the early phase after illness onset (Heaton *et al*., 1994; Hyde *et al*., 1994; Mockler *et al*., 1997).

RELATION BETWEEN NEUROCOGNITIVE DEFICITS AND SYMPTOMS

Early theories of schizophrenia attempted to explain the heterogeneity of schizophrenia symptoms as reflecting a single underlying neurocognitive deficit. These involved conceptualisations of 'cognitive dysmetria' (Andreasen *et al.*, 1999), 'theory of mind' (Frith, 1992), WM deficits (Goldman-Rakic, 1994), information processing deficits (Braff, 1993) and semantic memory deficits (Cutting & Murphy, 1988).

Cognitive dysmetria refers to a disruption of the patient's ability to co-ordinate mental activity. It results from functional and anatomical disconnectivity in brain regions, which are often expressed as flattened affect, disorganized thought, avolition, hallucinations, and delusions (Andreasen *et al.*, 1996, 1998, 1999).

Theory of mind postulates that patients with schizophrenia lack awareness of their own mental states as well as the mental states (emotions, goals, intentions) of other people (Frith, 1992). This lack on self-awareness often leads to the inability to generate willed actions (avolition, inappropriate behaviour), disordered self-monitoring (delusions, hallucinations), and disordered monitoring of the intentions of others (ideas of reference, paranoid delusions) (Frith

1992). Schizophrenia patients also fail to follow conventional norms in guiding their speech (incoherence), which is seemingly due to their inability to be aware of the other person's inner experience and knowledge base (Rochester & Martin, 1979).

Goldman-Rakie (1994) used WM deficits, with the associated disrupted prefrontal cortical function in schizophrenia, to explain a range of positive and negative symptoms. Thought disorder may be related to the inability to hold a concept in mind and positive symptoms may reflect the inability to keep track of internal or external stimuli against established memories (Fuller *et al*., 2003).

Information processing and attentional deficits have been considered central to a wide spectrum of symptoms in schizophrenia (Braff, 1993). The "filtering" of relevant from irrelevant stimuli, while inhibiting attention toward certain tasks, have been tested experimentally on a wide range of attentional and information processing paradigms (such as CPT, PPI, backward masking) indicating that patients with schizophrenia process information more slowly and less efficiently, especially when under high processing demands with multiple tasks and distractions (Fuller *et al.*, 2003).

Semantic memory or "real world knowledge" abnormalities (Cutting & Murphy, 1988) with its overlap with executive and temporal / episodic memory, has been regarded as central to the phenomenology of schizophrenia (Frith & Frith, 1992). The concept of 'over-inclusive thinking' (Cameron, 1947; Payne, 1973) involves a disorder of concept formation. This means disrupted knowledge about the world and its representation in semantic memory, which has been central in explaining disordered thinking in schizophrenia patients. Several other authors have focussed on failures in cognitive systems, which represent 'knowledge' in schizophrenia patients (Frith & Frith, 1992; McKenna, 1991; Hoffman, 1987). This is synonymous with the concept of semantic memory and has been implicated in the development of thought disorder, hallucinations, and delusions.

Positive, negative, and disorganised symptoms

Crow (1980) originally proposed that positive symptoms are caused by dopaminergic imbalances, and that structural cerebral abnormalities are responsible for the negative symptoms in schizophrenia patients. Liddle (1984, 1987a) separated symptoms into three syndromes based on correlations of characteristic symptoms in chronic schizophrenia: reality distortion (positive symptoms), psychomotor poverty (negative symptoms), and disorganization (Baxter & Liddle, 1998). Other factor analytic studies have supported the three syndromes proposed by Liddle (Liddle &

Barnes, 1990; Brown & White, 1992; Thompson & Meltzer, 1993). Each of the syndromes has been associated with a pattern of neurocognitive correlates and regional brain functioning.

Negative symptoms (psychomotor poverty) involve an absence or decrease of brain functions and include blunted or restricted affect, abulia (loss of motivation), alogia (poverty of speech), avolition (lack of initiative), apathy (lack of interest), and reduced social drive (Crow, 1980; Andreasen, 1982; Carpenter *et al.*, 1988). More recently, authors have found it useful to make a distinction between primary negative symptoms or 'deficit' schizophrenia and secondary negative symptoms, which might be attributed to the effect of chronic hospitalization, neuroleptic treatment, and depression (Kirkpatrick *et al.*, 2006).

The pathogenesis of negative symptoms remains unclear. They are relatively treatment refractory over the course of the illness (Keshavan *et al.*, 2008; Erhart *et al.*, 2006; Stahl & Buckley, 2007). A few studies have linked negative symptoms to left DLPFC under-activity (Howes & Kapur, 2009; Ebmeier *et al.*, 1993).

Positive symptoms (reality distortion) in schizophrenia imply a breakdown in reality testing and include delusions, hallucinations,

and other forms of reality distortion (Tandon *et al.*, 2009). Keshavan *et al.* (2008) have linked positive symptoms to hyperactivity of the dopaminergic mesolimbic circuit, which often characterizes the formal onset of psychosis or FEP (Kapur, 2003). Furthermore positive symptoms have been associated with over-activity of the left medial temporal lobe and under-activity of the left lateral temporal lobe (Liddle *et al.*, 1992a; Ebmeier *et al.*, 1993).

Symptoms of disorganization in schizophrenia include thought disorder, disorganized behaviour / speech and neologisms. It entails derailment or looseness of association and poverty of thought content (negative thought disorder) (Tandon *et al.*, 2009). In this regard, Andreasen (1979) has developed a comprehensive scale for the assessment of thought, language and communication disorders, which includes poverty of content, pressure of speech, distractible speech, tangentiality, derailment, stilted speech, echolalia, self-reference, circumstantiality, loss of goal, perseveration, and thought blocking. Disorganization has been associated with decreased perfusion of the right ventral prefrontal cortex and insula, and increased perfusion in the right anterior cingulate (Liddle *et al.*, 1992a; Ebmeier *et al.*, 1993).

Neurocognitive correlates of positive symptoms (reality distortion)

Positive symptoms in schizophrenia have been regarded as excess, or neurological release, signs (Fuller *et al.*, 2003; Strauss *et al.*, 1974), which occur when higher cortical functions are impaired, thereby resulting in disinhibition. Several studies have found no, or weak, correlations between positive symptoms and neurocognitive measures (Klingberg *et al.*, 2006; Weickert & Goldberg, 2000; Bilder *et al.*, 1985).

The notion of positive symptoms being viewed as accessory release phenomena, or attempts to make sense of aberrant salience in schizophrenia, offers a viable explanation for the weak correlation between positive symptoms and underlying neurocognitive deficits (Keshavan *et al.*, 2008; Kapur, 2003).

However, the association between positive symptoms and neurocognitive deficits has been inconsistent. Some studies indicate fewer neurocognitive deficits (Bilder *et al.*, 1985), poor figure ground perception (Goldberg *et al.*, 2003), and a positive association with the WCST, Trail-making Test A (TMTA) and right hand graphesthesia errors (Cuesta & Peralta, 1995a; Bornstein *et al.*, 1990).

A few attempts at explaining the phenomenology of hallucinations and delusions in schizophrenia are also worth mentioning. Experimental and anecdotal findings indicate that inner speech can co-exist with auditory hallucinations (David & Lucas, 1993; Haddock *et al.*, 1995). Patients with hallucinations and delusions are prone to failures in source monitoring (Vinograov *et al.*, 1997; Johns & McGuire, 1999). An association exists between auditory hallucinations and attenuation of left hemisphere / right ear involvement in schizophrenia (Green *et al.*, 1994; Bruder *et al.*, 1995; Levitan *et al.*, 1999). Positive symptoms have been linked to less salient visual scanning strategies compared to patients with schizophrenia with primarily negative symptoms (Phillips & Davids, 1994; Streit *et al.*, 1997).

Neurocognitive correlates of negative symptoms (Psychomotor poverty)

Several studies have found significant correlations between negative symptoms and a range of neurocognitive impairments in schizophrenia. Deficits involving general intelligence, memory, attention, object naming, cognitive slowing, executive and sensory-motor function have been found (Basso *et al.*, 1998; Himelhoch *et al.*, 1996; O'Leary *et al.*, 2000). These deficits correspond to fronto-temporal abnormalities, which are associated with higher cognitive functions (Kaplan *et al.*, 1993; Schroder *et al.*, 1995) and are

generalized in nature (Addington *et al.*, 1991; Schroder *et al.*, 1995; O' Leary *et al.*, 2000).

Negative symptoms in schizophrenia represent, essentially, a disorder of volition (Foussias & Remington, 2008), which implies difficulty with initiating activity and goal directed behaviour. This is consistent with our understanding of frontal lobe function (Liddle & Morris, 1991). Neurocognitive findings support the hypofrontality hypothesis, with evidence of slowed mental processing and impairment on a word generation task (Baxter & Liddle, 1998; Liddle, 1994). Negative symptoms have shown significant correlations with the WCST and Booklet Category Test (Goldberg & Weinberger, 1995; Cuesta & Peralta, 1995b), which are measures of executive function that more specifically tap into cognitive flexibility or set-shifting ability. However, research findings have not always been consistent. A few studies report no correlation between negative symptoms and executive impairments (Morrison-Stewart *et al.*, 1992; Van der Does *et al.*, 1993).

Attentional impairments have frequently been associated with negative symptoms and schizophrenia in general (Nieuwenstein *et al.*, 2001; Nuechterlein, 1991). They are regarded as genetic vulnerability markers (Foussias & Remington, 2008; Salvatore *et al.*, 2007). Modest correlations have been found between negative

symptoms and measures of attention (Bozikas *et al.*, 2004; Cohen & Docherty, 2004) when tested on measures such as the CPT (Nieuwenstein *et al.*, 2001; Strauss *et al.*, 1993) and the span of apprehension test (Nuechterlein *et al.*, 1986).

On the other hand, there are studies that found no association between negative symptoms and attention (Cornblatt *et al.*, 1997), or differences between auditory and visual CPT (Cohen & Docherty, 2004). Lysaker *et al.* (2009) offered an explanation by indicating two distinct groups of patients with negative symptoms: those with attentional impairment on the CPT and those without. Additionally, they also found that the group with attentional impairment had more severe levels of avolition (Cohen & Docherty, 2004).

Cognitive slowing or bradyphrenia is a clinically distinctive feature of the negative symptoms of schizophrenia, and of subcortical dementia (Cummings, 1986), but neurocognitive testing has failed to demonstrate a typical 'subcortical dysfunction' in schizophrenia (Nelson *et al.*, 1990). The same applies for memory retrieval deficits, which were not found in schizophrenia patients with predominantly negative symptoms (Pantelis & Nelson, 1994).

In summary, negative symptoms invariably relate to poor neurocognitive performance. This accounts for 18 % of the total neurocognitive impairment (Goldberg & Weinberger, 1995; Basso *et al.*, 1998), reflecting generalized deficits (O'Leary *et al.*, 2000). Negative symptoms are associated with frontal and soft neurological signs (Wong *et al.*, 1997) and additional structural brain changes involving the fronto-temporal cortex (Schroder *et al.*, 1995; Kaplan *et al.*, 1993).

Negative symptoms in schizophrenia appear to reflect an underlying cerebral dysfunction involving especially the frontal cortex with its concordant executive neurocognitive deficits. The debate as to whether negative symptoms reflect a generalized neurocognitive deficit and its trajectory over the course of the illness and response to treatment remains unresolved.

Neurocognitive correlates of disorganized symptoms (disorganization)

Disorganized symptoms have been correlated with poor neurocognitive performance involving decreased intelligence, attention-span, sensory-motor performance, memory, verbal processing abnormalities, inability to inhibit inappropriate responses, and poor concept formation in schizophrenia patients (Basso *et al.*,

1998; O'Leary *et al.*, 2000; Kerns & Berenbaum, 2002). Indeed, some studies indicate that the factor-analysis derived disorganised domain from PANSS correlates more strongly than the other domains with cognitive performance. This has prompted the suggestion that the disorganised factor be referred to as the cognitive factor (Good *et al.*, 2004). However, several studies could not confirm a significant correlation between disorganization symptoms and neurocognitive impairments using the Positive and Negative Syndrome Scale (PANSS) (Klingberg *et al.*, 2006). The PANSS does not include disorganization as a standard factor, although a correlation of .29 has been reported between PANSS disorganization and the CPT (Mass *et al.*, 2000). Similar weak correlations were found between disorganization and neurocognitive testing. This ranged from .04 to .43 in neuroleptic-naive FEP patients (Good *et al.*, 2004).

Neurocognitive impairments have been found in patients with negative and disorganization symptoms. However, research data indicated that their cerebral correlates were different. Disorganization primarily involved the parietal association cortex, primary frontal motor strips, anterior cingulate, and subcortical white matter (Liddle *et al.*, 1992a; Kaplan *et al.*, 1993; Schroder *et al.*, 1995), whereas negative symptoms were mainly associated with frontotemporal abnormalities (Wong *et al.* 1997; Schroder *et al* 1995).

Although the reported correlation between neurocognitive deficits and disorganization have lately received more support in schizophrenia research, their underlying mechanism and association remains unclear.

COURSE OF NEUROCOGNITIVE DEFICITS IN SCHIZOPHRENIA

Neurocognitive deficits are evident in the premorbid / prodromal phase of the illness (Henry & Crawford, 2005; Woodberry *et al.*, 2008). Progression is notable prior to, during, and shortly after illness onset (Tandon *et al.*, 2009; Bilder *et al.*, 2006; Hambrecht *et al.*, 2002).

The relative persistence of neurocognitive impairments over the long-term course of schizophrenia has been well documented across studies (Hoff *et al.*, 2005b; Delisi *et al.*, 1998; Jarskog *et al.*, 2004). There is no significant age-related decline, except for a small group of chronic, elderly, institutionalised schizophrenia patients who continue to show progressive cognitive deterioration of the "dementia praecox" type (Hedman *et al.*, 2013; Kurtz, 2005; Rajji *et al.*, *2013*). A literature review by Kurtz (2005) revealed two neurocognitive trajectories during the life course of patients with schizophrenia: those with relative stability of neurocognitive impairments are seen mainly in community outpatients, and those, observed mainly in elderly institutionalised patients over the age of 65, showing marked neurocognitive decline.

A recent systematic review by Bozikas & Andreou (2010) indicated relative stability of neurocognitive deficits in schizophrenia patients

for periods of up to ten years following a FEP. However, other FEP studies have indicated improvement across different neurocognitive domains tested at index hospitalization after being stabilized on medication, and then again with follow-up after 5 years (Gold *et al.*, 1999). Yet other studies have documented a longitudinal decline on several neurocognitive measures in support of the neurodegeneration model of schizophrenia (Harvey *et al.*, 1999a; Fucetola *et al.*, 2000). However, despite recent studies indicating progressive brain changes after illness-onset (Kempton *et al.*, 2010; Velakoulis *et al.*, 2000b), these changes have not been consistently correlated with neurocognitive decline. The exception is verbal memory, which shows some evidence of further decline (Bozikas & Andreou, 2010; DeLisi *et al.*, 1998).

Thus, the course of neurocognitive deficits in schizophrenia seems to be in favour of a 'static encephalopathy' model. However, a host of possible confounding variables, heterogeneous patient samples, possible practice effects, and the use of different neurocognitive measurements, might lead to inconsistent research findings.

TREATMENT AND OUTCOME CORRELATES OF NEUROCOGNITIVE DEFICITS

Modest improvements in neurocognitive function have been documented in response to antipsychotic treatment (Klingberg *et al.*, 2008; Szoke *et al.*, 2008; Keefe & Harvey, 2001) with few differences between first generation agents (FGA) and newer second-generation antipsychotic agents (SGA) (Keefe *et al.*, 2007; Tandon *et al.*, 2008; Keefe & Harvey, 2001). The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and the European First Episode Schizophrenia Trial (EUFEST) similarly indicated modest improvement in cognition across groups, with little differentiation between FGAs and SGAs (Richard *et al.*, 2007; Davidson *et al.*, 2009).

The notion of SGAs as so-called 'cognitive enhancers' has been underscored by a few studies indicating the significant cognitive benefit of olanzapine when compared to risperidone and haloperidol (Purdon *et al.*, 2000; Leucht *et al.*, 1999). A lesser benefit was found when comparing risperidone to haloperidol (Green *et al.*, 1997; Kern *et al.*, 1999). The improving of negative symptoms has been considered another advantage of SGAs over typical antipsychotics (Lublin *et al.*, 2005), but several studies have found that FGAs (haloperidol, flupentixol) were not inferior to SGAs in improving negative symptoms. Ruhrmann *et al.* (2007) found comparable

improvements between flupentixol and risperidone in patients with chronic schizophrenia regarding negative symptoms, depressed mood, and the cognitive factor of the PANSS.

Only a small number of studies have compared FGAs other than haloperidol to SGAs (Gattaz *et al.*, 2004; Jones *et al.*, 2006; Lieberman *et al.*, 2005). This leaves the relative effectiveness of SGAs compared to FGAs still open-ended.

Neurocognitive impairment, amongst other factors, is a strong predictor of functional and vocational outcome in schizophrenia patients (van Winkel *et al.*, 2007; Bowie *et al.*, 2008), with the severity of cognitive deficits related to psychosocial rehabilitation, community reintegration, and work capacity (Green, 1996; Green & Nuechterlein, 2004; Jablensky, 2000). Correlations between global level of functioning and specific neurocognitive deficits have been documented (Goldberg *et al.*, 1993): with executive and attentional impairments accounting for 20%, and memory accounting for 30% to 40% of variance in functional outcome (Green, 1996).

Premorbid social / neurocognitive impairments and negative symptoms have been associated with poor outcome, and are considered as 'trait' vulnerability factors in the development of

schizophrenia (Hollis, 1999; Schmidt *et al.*, 1995). Positive symptoms on the other hand show little covariance with functional outcome measures (Green *et al.*, 2000).

More recently, the inclusion of social cognition in the measurement of neurocognitive domains has been considered a core feature and a strong predictor of outcome (Van Hooren *et al.*, 2008; Penn *et al.*, 2008; Sprong *et al.*, 2007). More importantly, neurocognitive deficits have also been associated with treatment adherence (Keefe *et al.*, 2013) and increased risk for relapse in FEP (Chen *et al.*, 2005).

MEASUREMENT OF NEUROCOGNITION IN SCHIZOPHRENIA WITH THE MATRICS COGNITIVE CONSENSUS BATTERY

The measurement of neurocognitive deficit has gained significant prominence over the last few decades in schizophrenia research due to its consideration as a core feature of the illness, its association with functional outcome, and its status as a key determinant of treatment response.

Prior to 2004 the assessment of neurocognitive deficits in schizophrenia was impeded by the host of different neurocognitive measurements purporting to measure the same neurocognitive constructs, and the possible practice effects that are common with repeated measurements in longitudinal studies. This made comparison of neurocognitive results across patient samples very difficult. For this reason, as well as the possible potentiating effect of neuroleptic medication on neurocognition, the National Institute of Mental Health (NIMH) "Measurement and Treatment Research to Improve Cognition in Schizophrenia" (MATRICS) initiative led to the development of the MATRICS Cognitive Consensus Battery (MCCB). The MCCB was subsequently endorsed by the NIMH as the standard measurement of cognition in all schizophrenia trails (Green *et al.*, 2004; Nuechterlein *et al.*, 2008).

The MCCB was developed based on consensus ratings by experienced neuroscientists and neuropsychologists of traditional "gold standard" neurocognitive tests selected for their proven test-retest reliability, sensitivity for cognition specific to schizophrenia, limited practice effect and practicality / tolerability for use in clinical trials (Nuechterlein *et al.*, 2008). The MCCB consists of 10 subtests grouped into 7 domain scores (Speed of Processing, Attention / Vigilance, Working Memory, Verbal Learning, Visual Learning, Reasoning and Problem Solving, and Social Cognition). A global composite score is worked out by the MCCB computer scoring program and transformed into a global neurocognitive T-score (Nuechterlein *et al.*, 2008).

Since its inception the MCCB has increasingly been used in schizophrenia research. A meta-analysis conducted on 118 clinical trials until 20 April 2011 indicated that 53.8% used the MCCB alone or in combination with other neurocognitive tests (Keefe *et al.*, 2011). Baseline MCCB composite T-scores for patient groups have been found to range between 20.8(8.5) and 27.8(8.6) indicating a general neurocognitive deficit (Keefe *et al.*, 2011). The MCCB standardization study found slightly higher T-scores in stabilized patients with schizophrenia, ranging from 33.4 to 39.4, with Speed of processing and Social Cognition discriminating the best between patient and healthy control groups (Kern *et al.*, 2011). Holmen *et al.* (2010) found a generalized neurocognitive deficit in early-onset

schizophrenia, with the patient group scoring 0.8 to 1.8 Standard Deviations (SDs) below the healthy control group on the MCCB. They found no significant differences between medicated and non-medicated patients at index, and the Social Cognition subtest was questioned due to its lack of discriminant validity (Holmen *et al.*, 2010).

In another multi-site study, comparing risperidone to lurasidone in stabilized schizophrenia outpatients, screening and baseline measurements indicated MCCB composite T-scores of 24.7(12.1) and 26.7(12.4) respectively, which were 2.5 SDs below healthy controls (Keefe *et al.*, 2011). A small practice effect (z=0.18) was documented for the composite T-score in this study.

Despite the growing interest in using the MCCB as the standard neurocognitive measurement in schizophrenia research, to date very few studies have been conducted using the MCCB in FEP before and after commencing treatment (Hill *et al.*, 2008). The present study will expand on existing knowledge using the MCCB in FEP by documenting neurocognitive deficits at baseline, month 6, and month 12 in response to antipsychotic treatment.

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CHAPTER 4:

THOUGHT DISORDER IN SCHIZOPHRENIA

INTRODUCTION

Thought disorder has traditionally been considered the signature or hallmark feature of schizophrenia, which is essentially characterized by illogical thinking, incoherence, loss of goal directed speech, deviant verbalizations and looseness of associative thinking (Andreasen, 1979). It includes both 'positive thought disorder' marked by derailment (looseness of association), over inclusiveness and neologisms, and 'negative thought disorder' that is marked by poverty of content and impoverished speech (Andreasen, 1986).

Early concepts of thought disorder considered looseness of association to be a fundamental characteristic of schizophrenia (Bleuler, 1950; Kraepelin, 1919). Others emphasized the role of over inclusiveness (Cameron, 1944), drive-dominated primary process thinking (Fenichel, 1945), and key cognitive features involving faulty reasoning, concept formation, and reality testing (Chapman & Chapman, 1973). There is now a growing consensus that thought disorder is a multi-dimensional concept with varying degrees of severity that occurs in schizophrenic and non-schizophrenic psychotic conditions (Levy *et al.*, 2010).

Thought disorder can be classified according to disorders of thought content (abnormal ideas, for example, delusions) and disorders of form of thought (observed from expressive language that reflects disordered thinking, for example, derailment, tangentiality and circumstantiality) (Sadock & Sadock, 2007). The term ‘’thought disorder’’ in this study refer to a disturbance in thinking that affects language and communication (thought processes). Thought disorder is not pathognomonic to schizophrenia; it occurs in other psychiatric conditions such as mania and in the autism spectrum disorders (Andreasen & Grove, 1986; Solomon *et al.*, 2008), in healthy people during transient states of anxiety and stress (Johnston & Holzman, 1979), and in patients with neurological impairments (Jefferson & Scott, 2004). It is common amongst the first-degree relatives of patients with schizophrenia (Bearden *et al.*, 2011; Levy *et al.*, 2010) and in individuals with schizotypal personality traits (Kiang, 2010). These findings indicate that the milder forms of thought disorder present in relatives of patients with schizophrenia have a genetic basis, with thought disorder being the manifestation of a genetic vulnerability trait factor.

The persistence of thought disorder in schizophrenia has been shown to be relatively stable over time (Docherty *et al.*, 2003; Marengo & Harrow, 1997). Antipsychotic treatment is associated with moderate improvement in thought disorder (Remberk *et al.*, 2012; Goldstein *et al.*, 2002) leaving only residual signs evident after

treatment (Spohn & Strauss, 1989). The degree of thought disorder has been correlated to the severity of psychotic symptoms (Docherty *et al.*, 2003), illness duration (Maeda *et al.*, 2007), and functional and social outcome (Bowie & Harvey, 2008; Keefe *et al.*, 1987). Thought disorder is considered to be both state and trait related, which covaries with improvement in symptoms. (Docherty *et al.*, 2003).

The relationship between thought disorder and neurocognitive deficits in schizophrenia remains unclear. There is growing evidence that thought disorder is not merely a function of psychosis (Marengo & Harrow, 1997) and that a partial dissociation exists between thought disorder and neurocognitive deficits (Gold & Hurt, 1990). Research on the association between thought disorder and neurocognition in schizophrenia has emphasized the salience of executive and semantic-lexical processing (Kerns & Berenbaum, 2002). Research to date has yielded inconclusive results on the relative contribution of these functions to the development of thought disorder in schizophrenia.

In this chapter the association between neurocognitive deficits and thought disorder in schizophrenia is explored, and its corresponding neural correlates examined. The use of the Rorschach test will also be discussed in terms of its utility and sensitivity to measure thought disorder in schizophrenia.

SIGNS OF THOUGHT DISORDER

Thought disorder can be broadly defined as a disturbance in thinking that affects language, communication, and thought content (Sadock & Sadock, 2007), however thought disorder in this study refers to a disturbance in thought process as manifested in language and speech abnormalities.

The implicit view that language disturbances in schizophrenia are secondary to thought disturbance have been challenged in recent studies indicating that it is the language-semantical-lexical network *per se* that is impaired in schizophrenia (Radanovic *et al.*, 2013). The association between thought and language exists but is not perfectly related empirically (Radanovic *et al.*, 2013). However, most of the signs of thought disorder can be classified as communication disorders. This said, studies have indicated that deviant verbalizations like neologisms, word substitutions, and incoherence are associated with language production, but are found in only a minority of patients with schizophrenia (Berenbach & Barch, 1995). Furthermore, contrary to the notion of thought disorder being expressed as speech abnormalities, only a small association has been found between thought disorder and language production (Kerns & Berenbaum, 2002).

In an attempt to operationalize the different variants of thought disorder, Andreasen (1986) developed The Scale for the Assessment

of Thought, Language, and Communication (TLC). The TLC has improved the reliable assessment of thought disorder across patient populations and has been widely researched. It consists of 18 different types of thought disorder with the more severe forms listed under the first 11 types (Andreasen, 1986). A factor analytic study of the TLC identified 7 factors that explained 71% of the variance (Peralta *et al.*, 1992). The 7 factors are: *disorganization* (derailment, loss of goal directedness, tangentiality, illogical thinking, circumstantiality and incoherence), *negative* (poverty of speech and content, perseveration), *idiosyncratic* (stilted speech, word approximations), *semantic* (neologisms, clanging), *attentional* (distractibility, blocking), *referential* (self-reference, echolalia), and *verbosity* (pressure of speech). The disorganization factor is considered the most important type of thought disorder, explaining almost 25% of the variance (Peralta *et al.,* 1992).

The types of thought disorder with reference to the TLC are briefly listed (Andreasen, 1986):

1. Poverty of speech (over-concrete and restricted speech),
2. Poverty of content (long replies but conveys little information, repetitive, stereotyped answers),
3. Pressure of speech (rapid speech and difficult to interrupt),
4. Distractible speech (changes the subject in response to external stimuli),

5. Tangentiality (answer questions with irrelevant information),
6. Derailment (spontaneous speech in which ideas do not follow one another),
7. Incoherence (incomprehensible speech, confusing connections between ideas),
8. Illogicality (conclusions do not follow logically in speech),
9. Clanging (speech in which sounds guide choice of words),
10. Neologisms (new word formations),
11. Word approximations (old words used in new way, new words developed following conventional word formation rules),
12. Circumstantiality (speech which is very indirect and delayed in reaching its goal),
13. Loss of goal (wanders off the topic and never returns to it),
14. Perseveration (repetition of words or ideas),
15. Echolalia (speech in which the patient echoes the words or phrases of the interviewer),
16. Blocking (a period of silence interrupting a thread of speech before a thought has been completed),
17. Stilted speech (excessively formal, pompous or distant quality of speech),
18. Self-reference (patient repeatedly refers to himself under the subject of discussion),
19. Phonemic paraphasia (mispronunciation of words because sounds or syllables have slipped out of sequence), and
20. Semantic paraphasia (substitution of an inappropriate word).

THE RELATIONSHIP BETWEEN NEUROCOGNITION AND THOUGHT DISORDER IN SCHIZOPHRENIA

The underlying mechanisms and relationships between neurocognitive impairments and thought disorder remain unclear (Kerns & Berenbaum, 2002; Kiefer *et al.*, 2009). However, special interest has developed over the years in the association between thought disorder and semantic memory as well as executive neurocognitive impairments (Stirling *et al.*, 2006). Thought disorder is not likely to be the cause of neurocognitive deficits (Saykin *et al.*, 1994), nor is it secondary to general neurocognitive impairment (Goldberg *et al.*, 2003; Radanovic *et al.*, 2013). However, the supportive neurocognitive functions of memory, attention, and execution may contribute to language impairments in schizophrenia (Radanovic *et al.*, 2013).

Most research investigating the association between thought disorder and executive function versus the semantic memory system tends to implicate the role of both in the production of speech abnormalities. However, experimental findings have been inconsistent (Stirling *et al.*, 2006; Barrera *et al.*, 2005). This may in part be attributed to differences in patient samples, variable measurements of thought disorder, and different neurocognitive tests purporting to measure aspects of executive or semantic processing.

Executive difficulties in maintaining a stream of thought (working memory), planning speech and inhibiting irrelevant speech, may underlie the speech and language oddities associated with thought disorder (Kerns & Berenbaum, 2002; Barrera *et al.*, 2005). Barrera *et al.* (2009) distinguished between patients with and without thought disorder as well as healthy controls, based on the poorest performance on four executive tests being found in the group with thought disorder. The executive tests included: *The Hayling Sentence Completion test* (Burgess & Shallice, 1997), *The Brixton test* (Burgess & Shallice, 1997), *The Modified Six Elements* (Wilson *et al.*, 1996), and *The Cognitive Estimates test* (Shallice & Evans, 1978). A more recent study (Qwashi *et al.*, 2009) failed to demonstrate an association between thought disorder and executive function using the WCST. Stirling *et al.* (2006) found a positive correlation between patients with more thought disorder and performance on the following executive tests: *Stroop test* (1935), *Trail-making test* (Reitan, 1958), *Design fluency* (Jones-Gotman & Milner, 1977), *Tower of London test* (Shallice, 1982), and *Phonological fluency* (Spreen & Benton, 1969).

The executive neurocognitive underpinnings of thought disorder involve working memory *per se,* but research indicates the strong possibility that an additional inhibition deficit contributes to thought disorder (Roesch-Ely *et al.*, 2010). This is especially the case when the task load is high. Previous studies indicated a high degree of

association between inhibition and thought disorder (Liddle & Morris, 1991), but other studies could not find an association with non-verbal inhibitory tasks using a prepulse inhibition paradigm (Perry & Braff, 1994) and computer-based tasks of interference (Baxter & Liddle, 1998). Thus, excessive interference associated with thought disorder might arise from the inability to suppress verbal responses, but not in suppressing motor responses.

Other neurocognitive models with empirical support have emphasized the role of semantic-lexical processing abnormalities in the development of thought disorder. A meta-analysis conducted by Kerns & Berenbaum (2002) indicated an association between thought disorder and increased / decreased spreading activation, impaired semantic memory, and some studies indicating impaired language production.

Maher (1983) was the first to describe how aberrant spreading activation may lead to irrelevant associations entering into the speech of patients with thought disorder (Soriano, 2008). The automatic spread of activation between two related concepts forms associative nodes in the semantic memory system or world knowledge about concepts (Kerns & Berenbaum, 2002; Kiang, 2010). The amount of activation (measured by response time after exposure to the prime word) and the distance that the activation

spreads (activation of weaker related words) are related but independent from one another.

Research findings on spreading activation and thought disorder have not been consistent. A few studies indicated an association between thought disorder and increased priming for related words (hyperpriming), while on the other hand, decreased semantic priming (hypopriming) has been found in other studies (Kerns & Berenbaum, 2002; Soriano *et al.*, 2008). A decrease or absence of semantic priming results in a breakdown of semantic memory, implying a loss of factual knowledge, which impairs the formation of conceptual meaning in thought disorder (Moss *et al.*, 1995). Kiang *et al.* (2010) also found a higher degree of spreading activation of weaker or more remotely related concepts in people with schizotypal personality disorder. Thus, the under- or over-activation of unrelated concepts could lead to the intrusion of irrelevant associations in speech (Kiang & Kutas, 2005).

Berenbaum & Barch (1995) only found a small number of patients with schizophrenia exhibiting neologisms, word approximation and incoherence, which may be associated with impairment in language production. Semantic-lexical impairment may involve retrieving deficits of lexical / syntactic information or with encoding of phonological information (Kerns & Berenbaum, 2002). Empirical

support for the disruption of the language-lexical system in patients with thought disorder stem mainly from greater impairment with semantic fluency compared to phonemic fluency (Phillips *et al.*, 2004). However, research findings have been contradictory in this regard. A more recent study by Soriano *et al.* (2008) found no difference between patient groups with thought disorder, without thought disorder, and healthy controls when controlling for retrieval deficits and processing speed on fluency tasks.

Research to date on thought disorder has implicated the salience of frontal-executive functions and semantic-lexical processing underlying speech abnormalities. Whether the signs of thought disorder can be related to deficits in working memory versus inhibitory function, hyperpriming or hypopriming, or the result of a breakdown in the semantic-lexical network in speech production, remains unclear.

NEURAL CORRELATES OF THOUGHT DISORDER IN SCHIZOPHRENIA

Several studies have implicated the frontotemporal and temperoparietal language areas in the production of thought disorder. More specifically, these consist of the left superior temporal gyrus (Radanovic *et al.*, 2013), the left planum temporale (Shenton *et al.*, 2001), the orbitofrontal cortex (Nakamura *et al.*, 2008), and the anterior cingulate gyrus (Horn *et al.*, 2009).

Other studies have associated thought disorder with decreased volume in the temporal lobes, in particular the region of the superior temporal gyrus and planum temporale (Shenton *et al.*, 2001), excessive or underactive anterior cingulate activation (Liddle *et al.*, 1992; Kubicki *et al.*, 2006), reduced grey matter volume in Broca's area (Douaud *et al.*, 2007), and decreased activation of the angular gyrus (Liddle *et al.*, 1992). Horn *et al.* (2009), however, found increased activation of the left angular gyrus that is not consistent with the findings of Liddle *et al.* (1992), which showed decreased bilateral activation.

A more recent study exemplified the mediating role of the OFC (monitoring, reward learning, response inhibition, motivation) and its association with the semantic-processing language related areas (Nakamura *et al.*, 2008). A robust finding by Nakamura *et al.* (2008)

correlated severity of thought disorder with a specific pattern of OFC volume deficit, namely the left anterior middle orbital gyrus.

Although several studies have found positive correlations between severity of thought disorder and changes in the left frontal and left temporoparietal language areas (Horn *et al.*, 2009), other studies have indicated a deviance or even reversal of the normal left-lateralization of neural activity during language production in schizophrenia patients (Borofsky *et al.*, 2010). This abnormal lateralization during language processing has also been observed in genetically high-risk individuals (Li *et al.*, 2007).

To date, schizophrenia research using brain imaging to map the areas related to language processing and thought disorder in schizophrenia has been productive, but findings pertaining to hyper/hypoperfusion, increased/decreased volume, or left/right lateralization of language related brain areas have been inconclusive.

However, the notion of disrupted neuro-circuitry underlying thought disorder and language production has received empirical support: which indicates a functional dysconnectivity between frontal, temporal and cingulate regions (Stirling *et al.*, 2006). In support of this model, a study by Kubicki *et al.* (2006) has indicated how hyper-

activation of the superior temporal gyrus during semantic encoding could interact with an OFC failure or suppression of irrelevant associations leading to thought disorder. The mediating role of interneuronal gamma-aminobutyric acid inhibition has been described by Horn *et al.* (2009).

The neural correlates of thought disorder in schizophrenia seem to be concordant with neurocognitive research findings linking frontal/executive function (working memory and inhibition) with semantic encoding (aberrant spreading activation) and impaired semantic memory (conceptual knowledge).

THE USE OF THE RORSCHACH INKBLOT METHOD TO MEASURE THOUGHT DISORDER IN SCHIZOPHRENIA

Overview

The Swiss psychologist, Hermann Rorschach, developed the Rorschach test. He wrote his first book *"Psychodiagnostik"* in 1921 after experimenting with inkblots on 300 patients with a psychiatric disorder and 100 control subjects. From this he selected a set of ten inkblots for their diagnostic value (Rorschach, 1921). The Rorschach test was globally accepted as a method to study human personality in depth (Hertz, 1986).

Since the death of Rorschach, the Rorschach Inkblot Method (RIM) has been further investigated, expanded on, and differentiated as a test of different modes of perception. Its relationship to personality and psychopathology was investigated by Samual Beck and Dr. Bruno Klopfer (Beck, 1937/45/52; Klopfer *et al.*, 1956). Various systems of scoring, classification and interpretation of the RIM were developed. This led to its demise during the 1960's and 70's, because the test was criticized for its lack of reliability, inadequate norms and repeated failures in validating research. Many questioned its clinical utility (Hertz, 1986; Bersoff, 1973; Holt, 1970; Buros, 1970; Aronow & Reznikoff, 1973, Wade & Baker, 1972). However, with the

development of the Rorschach Comprehensive System (RCS) significant refinements were made. The more stringent administration, guidelines for standardization of coding, expansion of normative data and empirically based interpretation of the Rorschach, helped to re-establish it as a clinical tool (Exner, 1974). The RCS is today the most widely used system to code and interpret the test by clinicians globally (Mihura *et al.*, 2012).

Although Exner contributed significantly toward the scientific status of the test as a valid and reliable measure of personality and psychopathology (Exner, 1991/93/95), the debate about its validity, application across cultures, and reliability is ongoing (Mihura *et al.*, 2012).

The method

The RIM uses the same set of 10 inkblot cards originally selected by Hermann Rorschach (1921/1942). Five inkblots are shades of black and grey, two are of black and red ink, and three are multi-coloured, all on a white background. Subjects look at each inkblot and say what it looks like or might be. More than one response may be given per inkblot and the examiner records all responses verbatim. The RCS requires at least one response per inkblot and a minimum of 14 responses (*R*) for the entire protocol to meet adequate test-retest

reliability (Exner, 1988). The average number of responses per protocol is 22 (Exner, 2003).

After the subject has responded to all the inkblots (*free association phase)* the examiner presents the cards again one at a time and the subject is asked to note where he sees what he originally saw and what in the card made it look like that (*inquiry phase*) (Exner, 2003). The examiner again records all responses verbatim for coding and analysis of the responses, using tabulation and a scoring sheet (Exner, 2003).

Coding of responses is done with reference to:

- the level of vagueness or synthesis of multiple images,
- the location of the response [1] (*W, D, Dd, S*),
- the form quality (the degree to which the response is a good match for the actual inkblot),
- the contents of the response (what the subject actually sees in the inkblot, e.g., human detail = *Hd*),
- the determinants of the inkblot that contributed to the formulation of the response [2] (*F, M, FM, m, C*, *CF, FC, Cn, C', C'F, FC', T, TF, FT, V, VF, FV, Y, YF, FY, FD, rF, Fr*),

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[1] Location: W= whole response; D= common detail; Dd= infrequent detail S= use of white space response

2 Determinants: F= pure form; M= human movement; FM= animal movement; m= inanimate movement; C= pure chromatic colour; CF= chromatic colour-form; FC= chromatic form-colour; Cn= chromatic colour naming; C'= pure achromatic colour; C'F= achromatic colour-form; FC'= achromatic form-colour; T= pure texture; TF= texture-form; FT= form-texture; V= pure vista; VF= vista-form; FV= form-vista; Y= pure diffuse shading; YF= undifferentiated shading-form; FY= undifferentiated form-shading; FD= form dimension; rF= reflection-form; Fr= form-reflection.

- the degree of mental organizing activity required in producing the response, and
- any illogical, incongruous or incoherent aspects of responses (Exner, 2003).

Using the scores for these categories[l] the examiner performs a series of calculations producing a structural summary, reflecting ratios, percentages and derivations. Six indices are derived from these various combinations of Rorschach scores: the Perceptual Thinking Index (PTI), Depression Index (DEPI), Coping Deficit Index (CDI), Suicide Constellation (SCON), Hypervigilance Index (HVI), and Obsessive Style Index (OBS) (Exner, 2003).

The RCS places a lot of emphasis on the cognitive triad of information processing (information input), cognitive mediation (how information is transformed), and ideation (conceptualisation of information) (Exner, 2003).

For this reason contemporary views of the RIM have conceptualized the Rorschach test as an external assessment of the person's behaviour (Mihura *et al.*, 2012) that induces the respondent to use available cognitive, affective and representational resources to

formulate a response to an ambiguous task (Vigilone *et al.,* 2003). In this sense, the Rorschach is used as "a high-processing demand, abstract problem-solving test and is conceptualized as a perceptual and cognitive challenge" (Perry *et al.*, 2009). This expels the early notions and traditional classification of the Rorschach as a projective test (Bornstein, 2007; McGrath, 2008). Exner (1993) and others (Smith, 1992; Klepser *et al.*, 1991) have also explicitly denied that the RIM is projective in nature. Meyer *et al.* (2011b) describes the Rorschach as a "behavioural problem-solving task in which respondents must use reasoning and problem-solving skills".

Rorschach indices in schizophrenia research

The search for signs of schizophrenic thinking has long been the subject of investigation using different rating scales, objective and projective tests, and various classifications of deviant verbalizations in psychiatric populations (Bellak, 1969; Weiner, 1966; Andreasen & Grove, 1986). The RIM has followed a similar trend in attempting to systematize and quantify the deviant responses or queer verbalizations found in Rorschach protocols and explaining the psychological processes leading to it (Rappaport *et al.*, 1968). Prior to and after the development of the RCS, various Rorschach indices have been researched and refined in terms of incremental validity and sensitivity in detecting various forms of thought disorder and

signs of psychosis. They are briefly discussed as being the historical precursors of the Rorschach Perceptual Thinking Index.

The delta index

Watkins and Stauffacher (1952) developed the Delta Index in an attempt to quantify the clinical categories of thought disorder as evidenced by deviant verbalizations on patient Rorschach protocols. The Delta Index score is reflected as the sum of all weighted scores for 15 categories of deviant verbalisations, divided by the number of Rorschach responses. Minor deviant verbalizations, e.g., over-elaborate symbolism, will receive a weight of (.25); moderate deviancies, e.g., confabulation, will receive a weight of (.50), and severe forms of deviant verbalisations, e.g., incoherence and absurd responses will receive a weight of (1.0) (Johnston & Holzman, 1979).

The Delta Index has been found to significantly discriminate between groups (normal, neurotic and schizophrenic) with an overall inter-rater reliability of .78 (Watkins & Stauffacher, 1952; Powers & Hamlin, 1955). A cut-off score of 10 on the Delta Index was recommended as a positive indication of schizophrenia, but the false positive rate for non-schizophrenia was found to be high (Powers & Hamlin, 1955). Further refinements to the Delta Index have been

made by other Rorschach researchers (Pope & Jensen, 1957; Kataguchi, 1959).

The Thought Disorder Index

The Thought Disorder Index (TDI) is a revision of the Delta Index and includes 20 categories of communication deviance evidenced on the Wechsler Adult Intelligence Scale (WAIS) and the Rorschach test (Johnston & Holzman, 1979; Solovay *et al.*, 1986). The four level weightings (.25, .5, .75, and 1.0) of the Delta Index have been retained (Watkins & Stauffacher, 1952) and can be used to quantify the severity of disordered thinking and to identify the qualitative features of thought disorder (Makowski *et al.*, 1997). The original research population consisted of 237 subjects, divided into chronically hospitalized schizophrenia patients, recently hospitalized psychiatric patients (schizophrenia, schizoaffective, bipolar), and 27 normal controls (Johnston & Holzman, 1979).

The TDI has been shown to be a valid test for the measurement of thought disorder in adults (Johnston & Holzman, 1979; Solovay *et al.*, 1987) and in children and adolescents (Arboleda & Holzman, 1985). Inter-rater reliability coefficients for the TDI have been in the .80 to .90 range (Johnston & Holzman, 1979; Coleman *et al.,* 1993). A more recent study by Metsȁnen *et al.* (2005) differentiated intra-class

correlation coefficients (ICC): .94 for TDr (number of TD responses), .92 for .25 level, .92 for .50 level, .86 for .75 level, and .66 for 1.0 level responses.

Higher TDI scores have been associated with schizophrenia, psychotic depression and mania compared with nonpsychotic patients and healthy control subjects (Makowski *et al.*, 1997). On the other hand, TDI scores do not discriminate between schizophrenia and mania and schizoaffective disorder (Shenton *et al.*, 1987; Solovay *et al.*, 1987). Studies have found the mean total TDI score for adult patients with schizophrenia to range between 16.8 and 34.6 and a lower mean TDI for adolescent patients with schizophrenia of 20.8. (Johnston & Holzman, 1979; Hurt *et al.*, 1983). Overall, findings have consistently indicated that levels of thought disorder do not distinguish between psychotic patients, but qualitative differences have been found in the ways that patients with schizophrenia and those with mania organize their thoughts (Nuechterlein *et al.*, 1986; Makowski *et al.*, 1997). Furthermore, thought disorders are not restricted to psychiatric disorders but are also evident in healthy individuals in the form of minor cognitive slippages, especially during periods of fatigue or anxiety (Solovay *et al.*, 1987).

Thought disorder appears to be a trait marker in a subgroup of patients with schizophrenia and mania, but could be both a trait and

a state feature in psychotic patients (Metsànen *et al.*, 2005). Severe forms of thought disorder as measured with the TDI in schizophrenia are responsive to neuroleptic treatment (Holzman, 1986; Spohn *et al.,* 1986; Nuechterlein *et al.,* 1986) with residual and less severe forms of thought disorder unmodified by treatment (Nuechterlein *et al.*, 1986; Spohn *et al.*, 1986). The residual thought pathology has been linked to a central nervous system deficit (Holzman, 1986).

The TDI has been found to be a reliable index of various forms of thought disorder. This is observed in patients with chronic schizophrenia and in psychotic patients (Nuechterlein *et al.*, 1986).

The Ego Impairment Index

The Ego Impairment Index (EII) is a composite measure of psychological impairment and thought disturbance, which was derived from factor analysis of the RCS (Perry & Viglione, 1991). The five EII Rorschach sub-component variables are distorted form quality (FQ-); Deviant Verbalizations and Incongruent Thinking (WSum6); Critical Contents score (depressed content e.g. blood, sex); Poor Human Form Perception (M-); and Good-to-Poor Human Experience variable (HEV) (measures positive versus negative aspects of human representation responses) (Viglione *et al.* 2003).

In the original validation study, the total EII score predicted treatment outcome in patients with major depression, with the HEV variable emerging as the strongest predictor (Perry & Viglione, 1991). Studies using the EII extended to include those of patients with schizophrenia and psychotic disorders, since the EII appears to tap into the cognitive functioning of a broad range of thought disordered patients (Kleiger, 1999; Perry *et al.*, 2003). The EII correlated with other known measures of psychotic processing such as the Eckblad-Chapman Scale of Magical Ideation and scales 6 (r= .47), 8 (r= .41), and Ego strength (r= -.44) from the Minnesota Multiphasic Personality Index (MMPI) (Perry *et al.*, 1992). The EII also differentiated between paranoid and non-paranoid patients with schizophrenia. The non-paranoid types achieved higher EII scores (Cohen's d= 1.37; r= .56) (Viglione *et al.*, 2003). Perry *et al.* (1992) found a mean EII score of 1.6 for a heterogeneous sample of schizophrenia patients, which is substantially different from the original depressed sample (Perry & Viglione, 1991).

However, in a study of 85 heterogeneous inpatient and outpatient psychiatric patients, the EII was found to discriminate between inpatients and outpatients but not between psychotic and non-psychotic patients (Adrian & Kaser-Boyd, 1995). More recent research found increased EII scores in the schizophrenia spectrum disorders compared to normal controls and significant differences

between patients with schizophrenia and other schizophrenia spectrum disorders (Perry *et al.*, 2003).

Overall, research findings indicate that the EII is a robust and replicable instrument with adequate reliability and factorial validity (Viglione *et al.*, 2003; Perry *et al.*, 2003), and with temporal stability over the course of symptomatic treatment (Perry *et al.*, 1995). Inter-rater reliability was assessed to be high with ICCs of .93 to .98 found in the original EII study (Perry & Viglioni, 1991).

The EII was further refined by replacing the HEV with the Human Representational variable (HRV), to create the EII-2 (Viglione *et al.*, 2003). The EII-2 is interchangeable with the EII with a correlation that approaches r =1.0 (Viglione *et al.*, 2003). The HRV has been associated with healthy interpersonal relations, interpersonal perception, and psychological well-being (Viglione *et al.,* 2003). The EII-2 has been found to be associated with schizophrenia spectrum disorders, poor response to treatment, thought disorder, cognitive dysfunction, and more prominent positive symptoms (Moore *et al.*, 2012; Viglione *et al.*, 2003). Contrary to intuitive thinking, the EII-2 was not related to social functioning or negative symptoms (Moore *et al.*, 2012).

The psychometric properties of the EII-2 have demonstrated factorial validity and high inter-rater reliability with ICCs of .93 to .98 (Viglione *et al.*, 2003). In conclusion, the use of the EII-2 is relevant to the study of schizophrenia as a measure of cognitive disorganization and perceptual disturbances (Perry *et al.*, 1995; Moore *et al.*, 2012).

The Schizophrenia Index

The Schizophrenia Index (SCZI) (Exner, 1978/1990) consists of 10 Rorschach variables with 6 constellation criteria that assess inaccurate perception, thought disorder, inadequate controls, and interpersonal ineptitude. All of these are regarded as core features of schizophrenia (Exner, 1978).

The TDI overlaps with the SCZI in the WSum6 score, but the SCZI adds a new element with the perceptual accuracy indices, i.e. (X-%), which are regarded as crucial in differentiating psychotic from non-psychotic cognitive processes (Arboleda & Holzman, 1985). The specific clusters of Rorschach variables used to arrive at thought and perceptual disturbances included in the SCZI are a) Form Quality b) Poor Human Form Perception and c) Deviant Verbalizations and Incongruent Thinking (Exner, 1993).

The SCZI was developed using discriminant analyses on samples of schizophrenia patients, non-schizophrenia patients and non-patients, yielding a suggested cut-off of 4, indicating a likelihood of the presence of schizophrenia; and values of 5 or 6 regarded as more definitive (Exner, 1993). In Exner's psychiatric reference group (*n*=320) of schizophrenia patients, 82% have SCZI scores of 4 or more compared to 0.3% of the 700 non-patient adults (Exner, 1995).

Studies have found that the SCZI discriminates between psychotic and non-psychotic patients (Jørgensen *et al.*, 2000; Meyer, 1993). Empirically it relates to a diagnosis of psychotic disorder (Hilsenroth *et al.*, 1998), and it has a high specificity in identifying first-episode schizophrenia (Ilonen *et al.*, 1999).

The SCZI has been found to be internally consistent and can be reliably scored (Ilonen *et al.*, 1999). The psychometric findings have been replicated in child psychiatric patients with slightly lower internal consistency compared to adult patients (Hilsenroth *et al.*, 1998). The SCZI score however needs to be interpreted with caution and not seen as an absolute. Research findings indicate that the correlations between SCZI scores and psychosis are significant in average-length protocols, but non-significant in high (R>29) and low (R<17) protocols (Meyer, 1993). Furthermore the SCZI has been associated with high false negative rates in identifying schizophrenia and high

false positives applied to the cut-off of 4, especially in manic patients (Ilonen *et al.*, 1999; Exner, 2000a). The SCZI has also been found to lack adequate specificity in diagnosing childhood onset schizophrenia (Stokes *et al.*, 2001).

The SCZI is sensitive to the measurement of impaired reality testing and thought disorder, which are not specific to schizophrenia. The renaming of the SCZI as the "*Psychosis Index"* has been argued to be more relevant and a useful dimensional measurement of psychotic indicators of perceptual inaccuracy, disturbed thought processes and impaired reality testing (Hilsenroth *et al.*, 1998).

The Perceptual Thinking Index

Previously the most widely used RCS instrument for the evaluation of psychosis was the SCZI (Exner, 1993; Hilsenroth *et al.*, 1998). Further RCS revisions have led to the development of the Perceptual Thinking Index (PTI), a measure of perceptual oddities and cognitive slippage (Smith *et al.*, 2001). To date, the PTI has replaced the SCZI as the preferred index for assessing thought disturbance in schizophrenia and related disorders (Exner, 2000a).

The PTI comprises eight RCS variables arranged into 5 index scores: Good Form Perception (XA%), Good Form Perception to Whole and

Large Detail (WDA%), Poor Form Perception (X-%), Severe Deviant Verbalizations and Illogical Thinking (Sum2), Fabulised and Implausible Thinking (FAB2), and Sum of 6 Weighted special scores reflecting deviant verbalizations and restraint thinking (WSum6) (Exner, 2003).

The PTI was developed to reduce false positives amongst adults and adolescent psychiatric populations and includes two new RCS variables: XA% and WDA% (Exner, 2000b). To date, research using the PTI in schizophrenia is limited (Dao & Prevatt, 2006).

As far as we are aware, the present study is the first to use the PTI longitudinally in a cohort of FEP patients receiving standardised antipsychotic treatment with assessments at baseline, month 6 and month 12.

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CHAPTER 5:

PURPOSE OF THIS STUDY

INTRODUCTION

This study formed part of a larger prospective study investigating the clinical, biological and functional outcome aspects in a cohort of FEP South African patients with a diagnosis of schizophreniform, schizoaffective or schizophrenia disorder, and their response to treatment with flupenthixol depot according to a fixed protocol over a period of 24 months.

The overall aim of this study was to investigate the occurrence of, and associations between neurocognitive deficits, thought disorder and other symptomatology, and their changes over a 12-month treatment period in FEP.

Null hypothesis:

There exists no relationship between neurocognition, thought disorder and symptoms at baseline and longitudinally.

OBJECTIVES

The primary objectives of this study were:

1. To assess the degree of specific neurocognitive deficits (MCCB) and thought disorder (PTI) in a cohort of South African FEP patients at baseline, prior to treatment.
2. To investigate the correlations between MCCB and PTI scores at baseline with demographic factors (age, sex, HLOE, ethnicity), DUP, substance abuse, and remission status.
3. To investigate the correlations between MCCB and PTI scores with PANSS scores at baseline, month 6 and month 12 respectively..
4. To assess changes in MCCB and PTI scores, as well as changes in PANSS factor scores, Social and Occupational functioning (SOFAS) and Quality of Life (WHOQOL), at baseline, month 6 and month 12 respectively.
5. To investigate the correlations between the degree of change in MCCB and PTI scores with the degree of change in PANSS, SOFAS and WHQOL scores.

The secondary objectives of the study were:

1. To determine the value of baseline MCCB, PTI and PANSS scores with demographic factors in predicting treatment outcome after 12 months in terms of:

    i. Symptom severity (PANSS total).

ii. Social and occupational functioning (SOFAS).

iii. Quality of life (WHOQOL).

iv. Remission status.

2. To determine the value of baseline PTI subscale scores in predicting MCCB total scores at month 12.

3. To determine the value of improvement (difference between baseline and month 6 scores) on the MCCB, PTI, and PANSS in predicting treatment outcome after 12 months, in terms of:

i. Symptom severity (PANSS total).

ii. Social and occupational functioning (SOFAS).

iii. Quality of life (WHOQOL).

iv. Remission status.

CHAPTER 6:

STUDY DESIGN

This was a prospective, non-comparative, longitudinal study of patients with FEP treated with a single long-acting FGA according to a fixed protocol, over a period of 12 months.

PATIENTS

A total of 47 patients were recruited over a period of 18 months. Thirteen patients were recruited from first admissions to Tygerberg and Stikland hospitals. A further 34 patients presenting at the community clinics, falling within the catchment area were recruited. The catchment area includes the metro and rural areas of the North Eastern part of Cape Town, the Winelands, and the Cape West Coast. Patients who presented with FEP at any of these service points were referred to the research unit for psychiatric assessment and enrolment into the study.

Approval to conduct the study was obtained from the Human Research Ethics Committee of Stellenbosch University Faculty of Medicine and Health Sciences **(N06/08/148)**. The study was conducted in accordance with the International Conference on Harmonization guidelines on good clinical practice (GCP) and was

registered at the South African National Clinical Trials Register (DOH-27-0710-1957) (International Conference on Harmonization, 1996).

URL: www.sanctr.gov.za/SAClinicalTrials/tabid/169/Default.aspx

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Inclusion criteria

a. Male or female in-or-outpatients.
b. Aged between 16 and 45 years.
c. A first-episode of schizophreniform disorder, schizophrenia, or schizoaffective disorder according to the Diagnostic and Statistical Manual of Mental Disorders Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000).
d. Prior lifetime antipsychotic exposure of 4 weeks or less.
e. Patients with an educational level of at least Grade 7.

Exclusion criteria

a. Patients who have been treated with a long-acting depot antipsychotic.
b. Patients with a psychotic disorder other than schizophreniform, schizophrenia or schizoaffective disorder (bipolar mania, major depressive disorder with psychotic features, substance-induced psychotic disorder, psychotic disorder due to a general medical condition).

c. Positive substance screen with a significant history of current and ongoing substance abuse.
d. Significant physical illness (e.g., AIDS, neurodegenerative disease, tuberculosis) after physical examination at screening.
e. Mental retardation.
f. Patients who were not fluent in English or Afrikaans. The administration, coding and scoring of the RCS and MCCB is limited to the use of either English or Afrikaans. The patient thus requires an understanding of either instructional language during test administration.

DATA COLLECTION

Patients were assessed with the Structured Clinical Interview for DSM-IV disorders (SCID-P) (First *et al.,* 1994). The following information additional information was obtained:

a. Demographic data included age, gender, ethnicity, first language, educational level, occupational history, marital status, and current living conditions.
b. Psychiatric history including current complaints, history of current illness, duration of untreated psychosis, previous, and current treatment.
c. Record of previous and current substance abuse.
d. Family history of psychiatric and medical illnesses, and treatment received.
e. Collateral history from the patient's family members regarding psychiatric and early developmental history (birth and developmental milestones).

Routine drug screening was performed on all patients at baseline and thereafter at 3-month intervals for the duration of the study. During each of the follow-up visits, patients were asked about substance use since the previous visit.

Assessment instruments

The following rating scales and measurements were administered at baseline, month 6 and month 12. Administration of the PANSS included a month 3 rating as well, as seen in the study plan (see Table 6.2):

A. The Positive and Negative Syndrome Scale for Schizophrenia.

The PANSS (Kay *et al.,* 1987) was conducted by a trained psychiatrist. The PANSS consists of a 30-item clinician rating of the patient's interpersonal behaviour, cognitive-verbal processes, thought content, physical behaviour, and responses to structured questioning, as well as collateral information obtained from the primary caregiver. It assesses three main domains: the positive subscale (P1-P7), the negative subscale (N1-N7), and a general psychopathology subscale (G1-G16). A forced five-factor model based on the equamax method was used for this study (Emsley, *et al.,* 2003). The five factors are: negative, positive, disorganized (or cognitive), excited and anxiety/depression factors (see Table 6.1). Inter-rater reliability for the PANSS ratings was established by training clinicians to administer the PANSS and achieve an inter-rater reliability of .70 or higher before enrolling patients into the study.

	PANSS item	Factor loadings
Negative (alpha=.89)	N4: social withdrawal	.80
	N2: emotional withdrawal	.78
	N1: blunted affect	.74
	N6: lack of spontaneity	.71
	N3: poor rapport	.69
	G16: active social avoidance	.67
	G7: motor retardation	.62
	G13: disturbance of volition	.51
	% of variance	15.4%
Disorganized (alpha=.80)	G11: poor attention	.74
	N7: stereotyped thinking	.63
	P2: conceptual disorganization	.62
	N5: difficulty in abstract thinking	.56
	G15: preoccupation	.50
	G10: disorientation	.40
	G5: mannerisms and posturing	.38
	% of variance	11.4%
Positive (alpha=.78)	P1: delusions	.84
	G9: unusual thought content	.74
	P3: hallucinatory behaviour	.65
	P6: suspiciousness	.63
	P5: grandiosity	.45
	G12: lack of insight and judgement	.41
	% of variance	10.8%
Excited (alpha=.71)	P7: hostility	.80
	G14: poor impulse control	.69
	P4: excitement	.63
	G8: uncooperativeness	.57
	% of variance	9.0%
Anxiety/Depression (alpha=.66)	G2: anxiety	.81
	G4: tension	.67
	G6: depression	.59
	G3: guilt feelings	.56
	G1: somatic concern	.43
	% of variance	8.4%

(cumulative= 54.7%)

Table 6.1: PANSS forced five factor model

B. The MATRICS Consensus Cognitive Battery (MCCB).

Research psychologists administered the MCCB to measure specific neurocognitive deficits. The researcher (RO) supervised the administration and scoring of all MCCB protocols. The MCCB has been endorsed by the National Institute of Mental Health (NIMH) of the USA as the standard measurement of cognition in all treatment research of schizophrenia (Green *et al.,* 2004).

The MCCB battery consists of 10 individual subtests making up 7 domain scores:

1. Speed of Processing: Trail Making Test Part A (Spreen & Straus, 2006), Brief Assessment of Cognition in Schizophrenia (Keefe, 1999), and Category Fluency (public domain);
2. Attention/Vigilance: Continuous Performance Test (Cornblatt, 2006);
3. Working Memory: Wechsler Memory Scale (Third edition) Spatial Span (Harcourt Assessment, 1997) and Letter-Number Span (Gold, 1997);
4. Verbal Learning: Hopkins Verbal Learning Test - Revised (Brandt & Benedict, 2001);
5. Visual Learning: Brief Visuospatial Memory Test (Brandt & Benedict, 1997);
6. Reasoning - and Problem Solving Neuropsychological Assessment Battery-Mazes (Stern & White, 2003); and

7. Social Cognition: Mayer-Salovey-Caruso Emotional Intelligence Test (Mayer *et al.*, 2005).

The tests have been carefully selected from a list of established neuropsychological tests based on the psychometric properties of sensitivity, specificity, minimal practice effect, reproducibility and the practical convenience of the tests when measuring changes in neurocognitive abilities in schizophrenia trials. Nine of the tests are pencil-and-paper tests, while the Continuous Performance Test (CPT) is a computerized test. Randomized alternate forms were used on repeat testing for the subtests: Verbal Learning, Visual Learning, and Reasoning-and-Problem Solving (Nuechterlein & Green, 2006).

The MCCB Computer Scoring Program was used to convert raw scores into T-scores for the 7 cognitive domains, and to derive an overall Composite T-score. Double data entry was adhered to, and age-and-gender corrected norms were selected on the computer program (Nuechterlein & Green, 2006). The MCCB standardization norm, which consists of 3000 non-psychiatric randomly selected United States citizens (Green *et al.,* 2004), has been used as a reference norm for this study. The MCCB has good psychometric properties in terms of test-retest reliability and validity (Nuechterlein & Green, 2006). It has also been found to

have a strong correlation with functional outcome in schizophrenia research (Nuechterlein & Green, 2006). All test instructions were translated into Afrikaans to make provision for the majority of Afrikaans speaking patients in the study cohort.

C. The Rorschach Comprehensive System (RCS).

The researcher (RO) administered the Rorschach according to the standardized RCS (Exner, 1993/2000a/2000b/2003). An independent, blinded rater (a registered clinical psychologist trained and experienced in the RCS) coded the Rorschach protocols. The independent rater coded all the Rorschach protocols and then entered the coded responses into the software program of the Rorschach Interpretation Assistance Program (RIAP5) (Exner, *et al.,* 2008). The RIAP5 transformed the scores for each patient into a structural summary (ratios, percentages and derivations), and a constellation table with six summary index scores: Suicide Constellation, Depression Index, Hypervigilance Index, Obsessive Style Index, Coping Deficit Index, and Perceptual Thinking Index (Exner, 2003).

For the purpose of this study, only the Perceptual Thinking Index (PTI) scores were entered into analysis as the primary measure of

thought and perceptual disorder. The PTI comprises of 5 subcategory criterion rated scores:

i) Good Form Perception (XA% <.70) and Good Form Perception to Whole and Large Detail (WDA% <.75) =1 point.

ii) Poor Form Perception (X- % >.29) =1 point.

iii) Severe Deviant Verbalizations and Illogical Thinking (Sum2 >2) and Fabulised and Implausible Thinking (FAB2 >0) =1 point.

iv) Number of responses (R <17) and Sum of 6 Weighted scores reflecting Deviant Verbalizations and Illogical Thinking (WSum6 >12) or (R >16) and (WSum6 >16) = 1 point.

v) Poor Human Form Perception (M- % >1) or Poor Form Perception (X- % >.40) = 1 point.

The PTI Total score has a range from 0 to 5 with a suggested cut-off of 3 or more, indicating the likelihood of psychosis (Dao & Prevatt, 2006).

Research on the PTI has found that the number of responses (R) in a protocol is a strong moderator, accounting for almost 50% of the variance in test scores (Meyer, 1992a/1993). No significant bivariate correlation (two-tailed) was found ($p<0.05$) between PTI

and R, so there was no need to partial out the effect of R in the analyses of PTI total. To control for the possible effect of R on Sum2, FAB2, WSum6, and M- scores, and to make statistical comparison with WA%, WDA% and X-% possible, we averaged the totals for Sum2, FAB2, WSum6, and M- scores as a percentage of R for each patient. All the PTI Total and PTI sub-category scores (percentages and averaged percentages for Sum2, FAB2, WSum6) were captured on a spreadsheet and entered into analyses.

We calculated the Lambda (ratio of pure form responses to the frequency of all responses) for each patient, and in addition used F% (percentage of pure form responses in a protocol) as an equivalent for Lambda because of its suitability in parametric analyses (Meyer *et al.*, 2001). A higher Lambda reflects a tendency to a guarded or defensive approach to the Rorschach task, which may mask some of the manifestations of psychotic thinking (Rosenbaum *et al.*, 2012). We, however, did not exclude protocols with Lambda higher than .99 because of the large number of protocols with values exceeding this figure. Other studies have also found that inclusion of protocols with Lambda >.99 did not affect the results compared to analyses of the initial subset (Dao & Prevatt, 2006).

Inter-rater reliability of 13 variables critical for the PTI was done by making use of a second blind rater who coded and scored 20 randomly selected Rorschach protocols. Intraclass correlation reliability analysis was conducted with intraclass correlation coefficients (ICC) ranging from .55 (WSum6), to .74 (F-) and .80 (F+). Considering Cicchetti's (1994) guidelines, these coefficients would be considered fair to excellent (Cicchetti, 1994).

The PTI can be regarded as a valid Rorschach composite score to detect psychosis (Mihura, *et al.,* 2012; Viglione & Meyer, 2008). It measures different components of thought disorder, as manifested in the verbal responses given to the stimulus cards (use of peculiar language, neologisms, derailment, combining stimulus details in an illogical or implausible manner) and perceptual accuracy (how good the response matches the stimulus outline and perception of conventional responses).

The Rorschach does not have alternate forms, but test-retest reliability values of .77 to .97 have been found (Grønnerød, 2003) and excellent inter-rater reliability (mean kappa of .88) exists for ten Rorschach response segments (Meyer, 1997a).

Normative data from a sample of 700 non-patient American adults (ages 18-70, measured during the 1970s and 1980s, representative of the United States demographic distribution including 19% of African American, Hispanic, and Asian American respondents) has been used as reference norm for this study (Exner, 1993/2000a/2000b/2003).

D. Social and Occupational Functioning Assessment Scale

The Social and Occupational Functioning Assessment Scale (SOFAS) was used as a secondary measure to provide a global rating of illness severity, improvement, and response to treatment. This is a clinician rated scale, requiring the clinician to compare the subject to the clinician's past experience with patients who have the same diagnosis (American Psychiatric Association, 2000).

The SOFAS is a clinician rating of social and occupational functioning independent of symptom severity, on a scale from 0 to 100. The SOFAS score is represented on a continuum of 100 (superior functioning in a wide range of activities), to 50 (serious impairment in social and occupational functioning) to 10 (persistent inability to maintain minimal personal hygiene, unable to function independently) (American Psychiatric Association,

2000). Impairment can be due to mental and/or physical limitations and reflects current functioning at the time of assessment (Goldman *et al.*, 1992).

E. The World Health Organization Quality of Life

The World Health Organization Quality of Life (WHOQOL-BREF) (World Health Organization, 1998) is a self-administered scale consisting of 26 items, which are rated by the patient from 0 (not at all satisfied) to 5 (completely satisfied). Items are summed to arrive at 4 domain scores:

1) *Physical health*: activities of daily living, dependence on medicinal substances / medical aids, energy and fatigue, mobility, pain and discomfort, sleep and rest, work capacity;
2) *Psychological health*: bodily image and appearance, negative feelings, positive feelings, self-esteem, spirituality/ religion/ personal beliefs, thinking, learning, memory and concentration,
3) *Social relationships*: personal relationships, social support, and sexual activity and
4) *Environment*: financial resources, freedom, physical safety and security, health and social care, home environment, opportunities for acquiring new information and skills, participation in and opportunities

for recreation/ leisure activities, physical environment (World Health Organization, 1998).

The four domain scores were converted to transformed scores of 0-100 (Bergner *et al.*, 1981) to make comparison with the comprehensive WHOQOL version possible. For regression analysis the four domain scores were averaged to arrive at an index score for WHOQOL as the dependent variable.

TREATMENT

The patients were treated according to a specific algorithm, in order to standardise treatment as far as possible. Initially, there was a wash-out phase (of up to 7 days) during which all psychotropic medications were discontinued. Thereafter, treatment was initiated with oral flupenthixol, 1 to 4 mg/day for a 1 week prior to the first long-acting flupenthixol decanoate (FD) depot to rule out hypersensitivity to flupenthixol. The starting dose of FD was 10mg every second week, with dose increases allowed at 6-week intervals. Dose increases were determined according to clinical response and tolerability. Oral flupenthixol was given between visits, if the treating psychiatrist deemed it necessary due to acute exacerbations of symptoms. Patients who did not respond to FD by month 6 were offered clozapine. Concomitant medication for known physical illnesses (e.g. hypertension, hypothyroidism) were allowed and lorazepam was prescribed for additional sedation, if clinically so required. Extraparydamil side effects (EPSE) were treated with orphenadrine and/or biperidine and propranolol could be prescribed for akathisia. Antidepressant medication was permitted. No anticholinergic medication or lorazepam / propranolol were given 12 hours before a neurocognitive assessment. Medications that were not permitted were: other antipsychotics, mood stabilizers, and psychostimulants.

STUDY PLAN

The MCCB and RCS were administered in close proximity to one another (within the same week): at baseline, month 6 and month 12. The MCCB took an average 60 minutes to complete and the RCS about 90 minutes. If the patients were found to be too psychotic to complete the MCCB or RCS, these tests were postponed until the psychiatrist deemed the patient to have stabilized enough for formal testing to continue.

Visit	Baseline D-7 to D-0	Wk 2	Wk 4	Wk 6	Mnth 3	Mnth 6	Mnth 9	Mnth 12
Consent	X							
Demography	X							
Physical exam	X							
Psychiatric / Medical Hx + SCID	X							
DUP	X							
PANSS	X				X	X		X
SOFAS	X					X		X
WHOQOL-BREF	X					X		X
MCCB	X					X		X
RCS	X					X		X
Adverse Events	X	X	X	X	X	X	X	X
Concomitant treatment	X	X	X	X	X	X	X	X
Oral treatment	X and intermittentlyas required							
Depot treatment		X	X	X	X	X	X	X

Table 6.2: Study plan as part of the larger study

DATA ANALYSES

All data was recorded in case record format. A research assistant conducted data entry for the MCCB onto a spreadsheet. The researcher (RO) was responsible for the data management of the RCS and MCCB. Analyses of data was performed according to intention to treat and last observed cases carried forward method.

Statistical analyses were conducted with the assistance of a biostatistician. Statistical analyses were performed with the Statistica version 12 (Statsoft) software (Statistica, 2013). A 5% significance level ($p<.05$) was used as the guideline for determining significant differences. The following analyses were performed:

a. Spearman correlational analyses were conducted to explore significant relationships with regard to Age, HLOE and DUP on baseline measures of MCCB, PTI and PANSS. Differences in Gender, Ethnicity, drug screen, and Remission Status for the same baseline measures (MCCB, PTI, PANSS) were tested with one-way analyses of variance.
b. To explore the relationships between MCCB and PTI scores at baseline and between MCCB/PTI scores with PANSS, SOFAS, and WHOQOL scores at baseline, Spearman correlational analyses were conducted.

c. To explore the relationships between degree of improvement in PANSS, MCCB and PTI scores from baseline to month 6, Spearman correlational analyses were conducted.

d. To assess changes in neurocognitive deficits and thought disorder over time: observed cases (OC) analyses at each time point, and mixed model repeated measures analyses of variance were conducted to examine mean changes in MCCB and PTI Total and subscale scores. In addition, changes in PANSS Total and factor scores, and changes in SOFAS and WHOQOL scores over time were assessed.

e. To assess the value of neurocognitive deficits, degree of thought disorder and symptom severity at baseline in predicting outcome at month 12, multiple linear regression analysis with all the independent variables (including demographic variables, DUP, drug screen) was done with the PANSS Total, SOFAS and WHOQOL scores at month 12 as the dependent variables. For Remission Status, a general discriminant analysis was conducted with the same independent variables.

f. To assess the value of baseline measures of thought disorder in predicting outcome in MCCB Total score at month 12, multiple linear regression analysis with the PTI Total and PTI sub-category scores at baseline was conducted.

g. To assess the value of the degree of improvement from baseline to month 6 scores for the MCCB, PTI, and PANSS in predicting outcome at month 12, multiple linear regression analysis with all the independent variables (including demographic variables, DUP, drug screen any time) was done with the PANSS, SOFAS, and WHOQOL scores at month 12 as the dependent variables. For Remission Status, a general discriminant analysis was conducted with the same independent variables.

ETHICAL CONSIDERATIONS

Written informed consent was obtained from all patients, and/or their legal guardians. Ample opportunity was allowed to answer any questions before informed consent was signed. Patient anonymity was assured by non-disclosure of personal identifying detail. The patients were informed of the potential risks and benefits of the study and were assured that refusal to participate would not affect their current or future treatment in any way. Patients were also informed that treatment would be ongoing upon completion of the study and that they would be offered other clinical treatment should they decide to withdraw from the study. Patients were given the choice of completing all assessments in either English or Afrikaans and translation was offered when indicated.

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CHAPTER 7:

RESULTS: DEMOGRAPHIC DATA

A total of 47 patients were recruited for this study. Of these, five were failed screens: two refused consent, one was under age, one was later diagnosed with a drug induced psychosis, and one was withdrawn early form the study due to insufficient response. Of the final sample (N=42) a total of 40 patients completed baseline MCCB and 30 patients received baseline PTI assessments (ten were excluded due to the low number of responses on Rorschach protocols (R<14) (Exner, 2003).

Patient attrition

A total of 26 patients completed the study, reflecting a patient attrition rate of 38% over a period of 12 months, with 11 (23%) lost to follow-up, 5 (11%) refused further participation, 1 (2%) developed tardive dyskinesia, and 4 (9%) provided insufficient data.

Age and gender

Gender was disproportionally distributed with 8 (19%) females and 34 (81%) males. The mean age of the sample was 24.91 years ±6.93 depicted in figure 7.1.

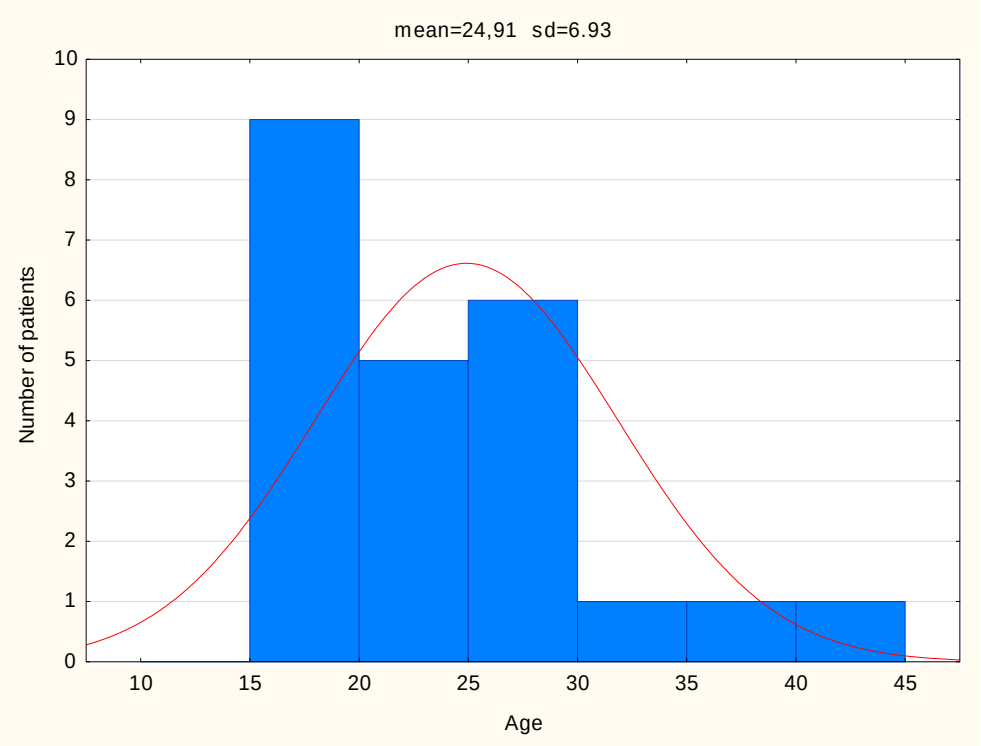

Figure 7.1: Age distribution of patients

There was a significant correlation between Age and overall neurocognitive ability at baseline (MCCB Cognitive Composite score: r=0.32; p=0.05), between Age and Attention/Vigilance at baseline (MCCB A/V score: r=0.33; p=0.04), and between Age and Working Memory at baseline (MCCB WM score: r=0.39; p=0.01). Age did not correlate significantly with thought disorder at baseline (PTI Total and sub-category scores) or with symptom severity (PANSS Total score) at baseline.

One-way analysis of variance revealed no significant gender differences on measures of neurocognitive ability (p=0.66), thought

disorder (p=0.91) or symptom severity (p=0.18.) at baseline. These results must be interpreted with caution due to the small number of females in the sample.

Education and ethnicity

The patients had a mean educational level of 10.78 ±2.10 years of formal schooling depicted in figure 7.2.

Educational level did not correlate significantly with any baseline measures of neurocognitive ability (MCCB Total and subscale scores), thought disorder (PTI Total and sub-category scores) or symptom severity (PANSS Total and factor scores).

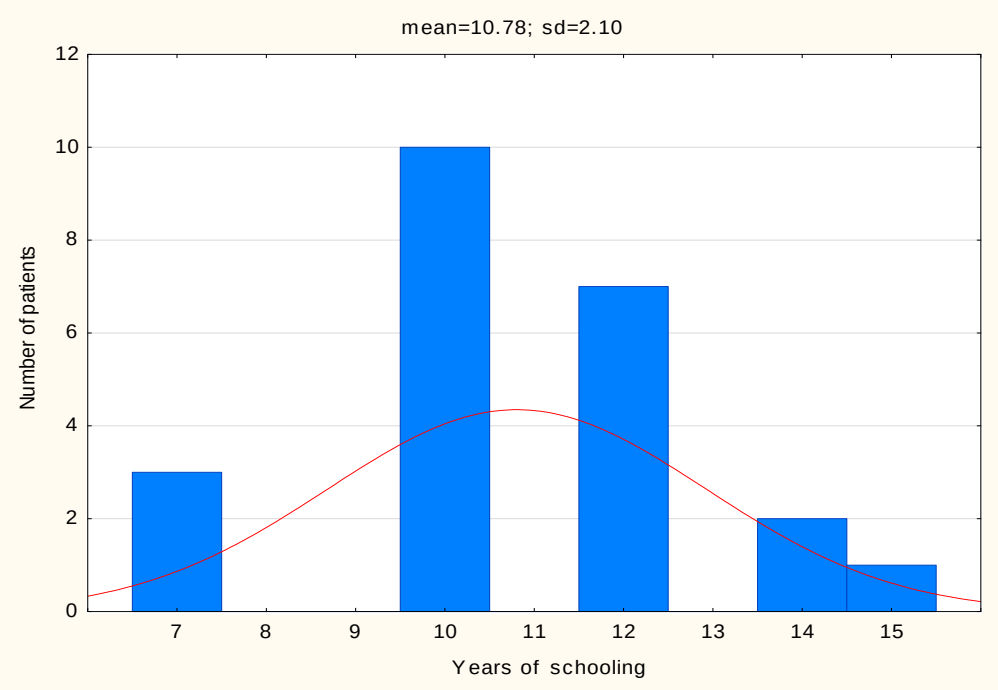

Figure 7.2: Educational level of patients

The patient's ethnic background reflected the demographic distribution of the catchment area with 67% mixedethnicity, 26% African and 7% Caucasian depicted in figure 7.3.

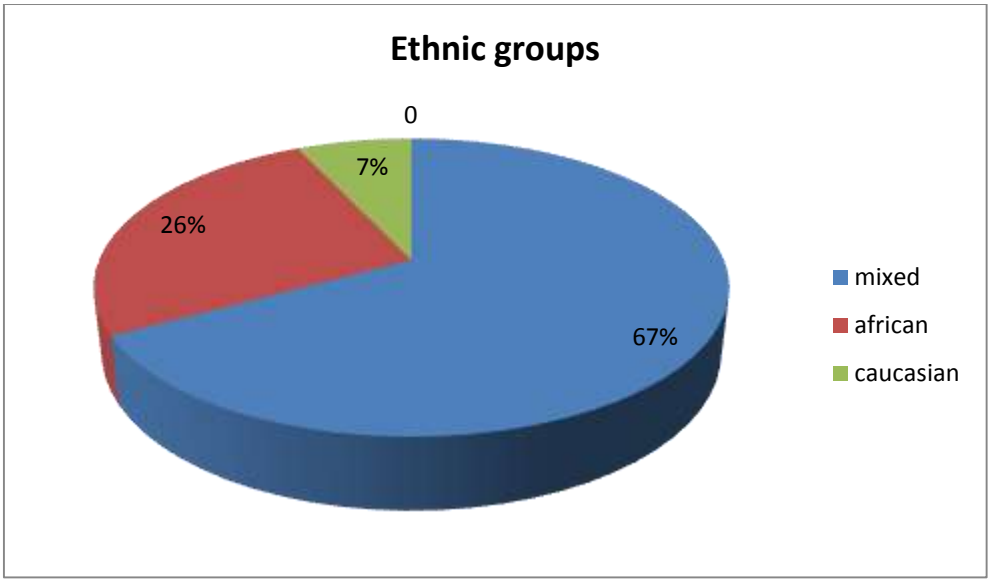

Figure 7.3: Ethnic representation

Educational level and ethnicity did not correlate significantly with any baseline measures of symptom severity or thought disorder.

One way analysis of variance revealed significant differences between ethnic groups ($F(2,37)=4.27$, $p=0.02$) on baseline measures of neurocognitive ability with regard to Reasoning and Problem Solving (MCCB RPS scores: Caucasian (mean=44.66); mixed

(mean=33.80); and african (mean=28.14)) (see figure 7.4). It may be that language differences have influenced the results.

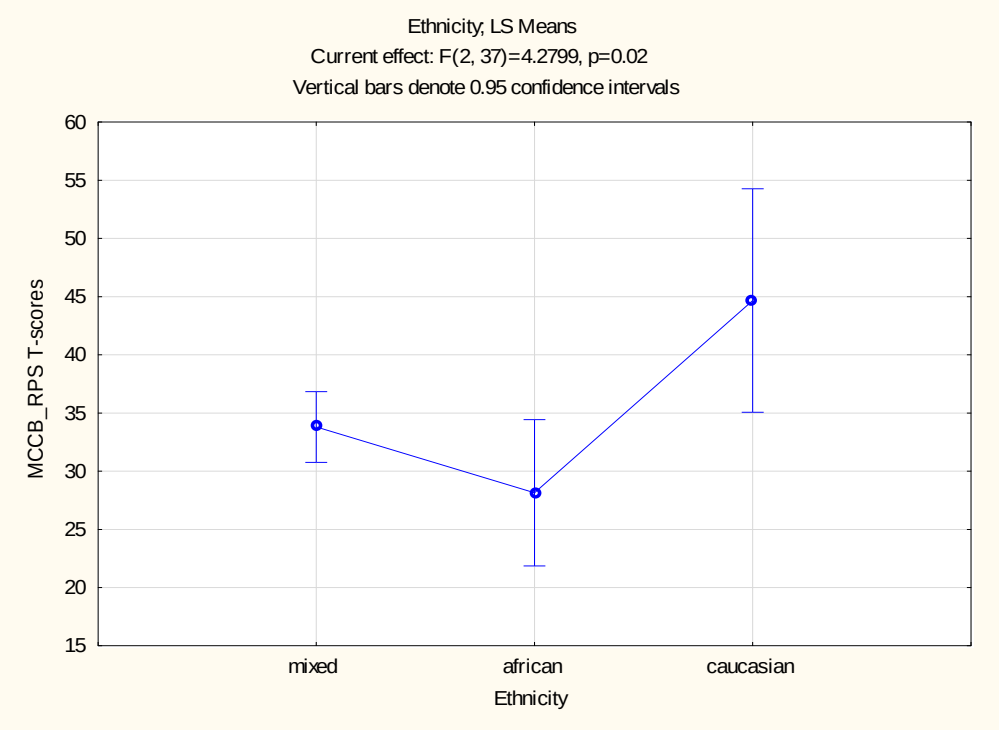

Figure 7.4: Ethnicity differences on baseline MCCB RPS scores

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MCCB RPS: Matrics Consensus Cognitive Battery Reasoning and Problem Solving

These results should be interpreted with caution due to the small number of Caucasian patients represented in the sample.

A smaller but significant effect (F(2,37)=2.84, p=0.04) was found between ethnicity and baseline neurocognitive measures of Verbal

Learning (MCCB Vrbl Lrng scores: Caucasian (mean=43.66); mixed (mean=34.80); and african (mean=39.14).

Duration of untreated psychosis

The mean duration of untreated psychosis (DUP) was 237 days ±269 with a minimum of 8 days and a maximum 1307 days.

There was a significant correlation between DUP and baseline neurocognitive measures of Attention/Vigilance (MCCB A/V: r=0.33, p=0.04), Reasoning and Problem Solving (MCCB RPS: r=0.42, p=0.01) and Speed of Processing (MCCB SoP: r=0.32, p=0.04).

DUP was not significantly correlated with baseline measures of thought disorder (PTI Total and sub-category scores) and symptom severity (PANSS Total and factor scores).

Use of illegal drugs

At baseline (urine drug screen) a total of 4 patients tested positive for use of illicit drugs: cannabis (N=3); methaqualone (N=0); and methamphetamine (N=1).

No significant differences were found between illicit drug users and non-users at baseline on measures of neurocognitive ability (MCCB Total and subscale scores), thought disorder (PTI Total and sub-category scores) and symptom severity (PANSS Total and factor scores).

These results should be interpreted with caution due to the small number of patients who were using illegal drugs at baseline.

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CHAPTER 8:

RESULTS: SYMPTOM SEVERITY, NEUROCOGNITIVE IMPAIRMENT AND SEVERITY OF THOUGHT AND PERCEPTUAL DISORDER AT BASELINE

Symptom severity

The PANSS Total mean score at baseline was 89.06±16.89 with PANSS factor mean scores shown in table 8.1.

	N	mean	sd
PANSS Total	42	89.06	16.89
PANSS N	42	22.27	7.73
PANSS D	42	21.37	7.52
PANSS P	42	23.14	6.96
PANSS E	42	7.39	3.91
PANSS A/D	42	11.16	5.78

Table 8.1: PANSS Total and factor mean scores

PANSS: Positive and Negative Syndrome Scale; PANSS N: PANSS Negative factor; PANSS D: PANSS Disorganized factor; PANSS P: PANSS Positive factor; PANSS E: Excited factor; PANSS A/D: PANSS Anxiety/Depression factor.

Neurocognitive impairment

The MCCB Composite mean score at baseline was 15.48±15.84 with MCCB mean subscale scores depicted in table 8.2.

	N	mean	Sd
MCCB Composite	37	15.48	15.84
MCCB AV	40	26.30	11.41
MCCB SoP[2]	40	22.67	14.23
MCCB Vis Lrng	40	32.50	15.35
MCCB Vrbl Lrng	40	36.22	7.42
MCCB WM	40	25.75	15.22
MCCB RPS[2]	40	33.62	8.87
MCCB SC	40	26.86	15.10

Table 8.2: MCCB Composite and subscale mean T-scores

MCCB: Matrics Consensus Cognitive Score; MCCB AV: Attention/Vigilance; MCCB SoP: Speed of Processing; MCCB Vis Lrng: Visual Learning;MCCB Vrbl Lrng: Verbal Learning; MCCB WM: Working Memory; MCCB RPS: Reasoning and Problem Solving;MCCB SC: Social Cognition

The MCCB Composite score was more than 3 standard deviations below the reference group norm at baseline (Nuechterlein & Green, 2006).

The following MCCB subscale scores were positively correlated with the MCCB Composite score: Attention/Vigilance (MCCB A/V), Speed of Processing (MCCB SoP) and Working Memory (MCCB WM) scores shown in figure 8.1.

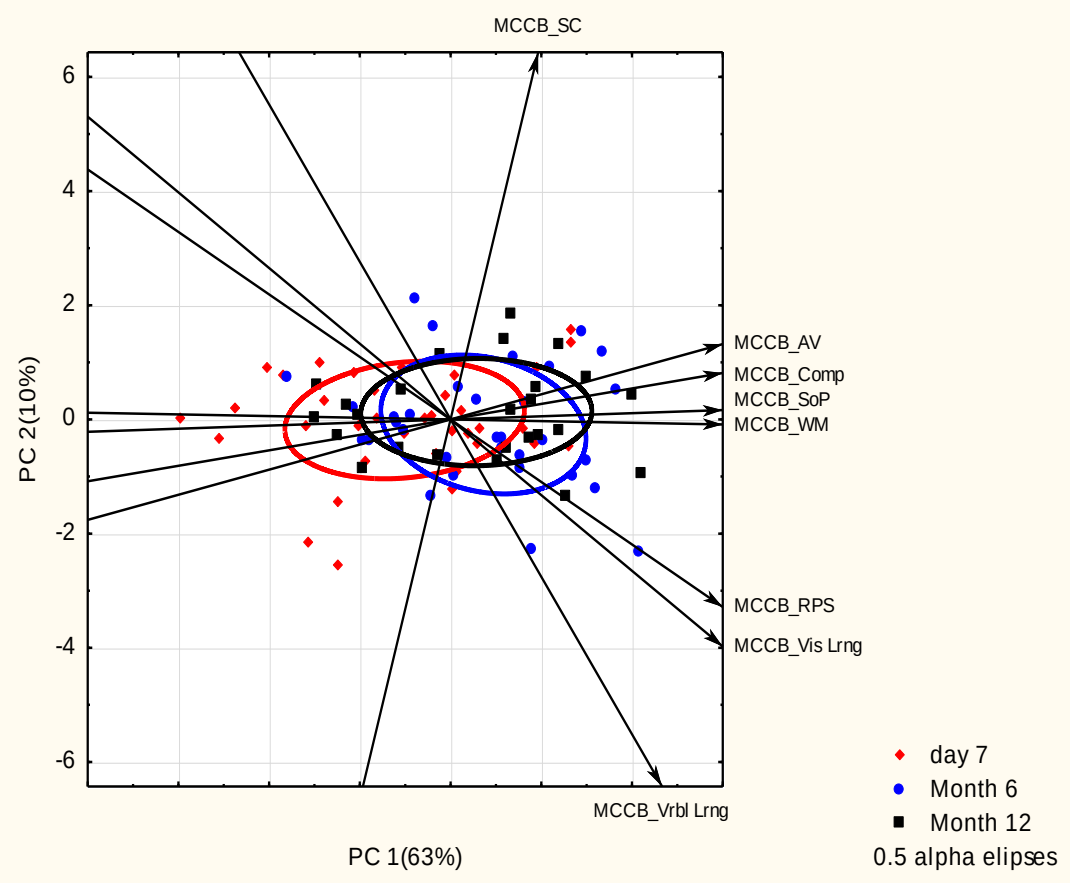

Figure 8.1: PCA biplot of baseline neurocognitive measures

Reasoning and Problem Solving (MCCB RPS), Visual Learning (MCCB Vis Lrng) and Verbal Learning (MCCB Verb Lrng) had weaker correlations with the MCCB Composite scores, and Social Cognition (MCCB SC) scores showed the weakest correlation with MCCB Composite scores at baseline.

A one way repeated measures analysis of variance (ANOVA) between MCCB subscale scores revealed significantly higher baseline scores on Reasoning and Problem Solving (MCCB RPS mean=33.62), Visual Learning (MCCB Vis Lrng mean=32.50) and Verbal Learning (MCCB Vrbl Lrng mean=36.22) shown in table 8.2 and figure 8.2.

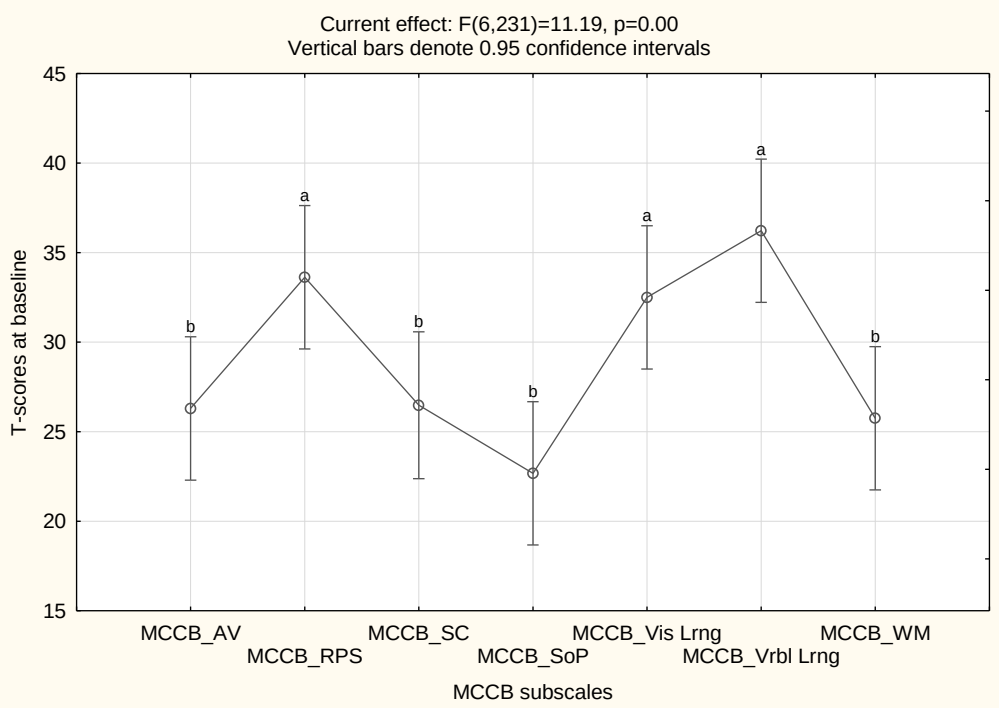

Figure 8.2: Baseline differences between MCCB subscale scores

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MCCB: Matrics Consensus Cognitive Battery; MCCB AV: Attention/Vigilance; MCCB SoP: Speed of Processing; MCCB Vis Lrng: Visual Learning;MCCB Vrbl Lrng: Verbal Learning; MCCB WM: Working Memory; MCCB RPS: Reasoning and Problem Solving;MCCB SC: Social Cognition.

Fisher's least squared differences (LSD) with p-values for MCCB subscale means at baseline are depicted in table 8.3.

Cell No.	LSD test; MCCB Subscale scores at baseline							
	subscale	{1} 26.30	{2} 33.62	{3} 26.48	{4} 22.67	{5} 32.50	{6} 36.22	{7} 25.75
1	MCCB_AV		0.00	0.93	0.08	0.00	0.00	0.79
2	MCCB_RPS	0.00		0.00	0.00	0.59	0.21	0.00
3	MCCB_SC	0.93	0.00		0.07	0.00	0.00	0.73
4	MCCB_SoP	0.08	0.00	0.07		0.00	0.00	0.14
5	MCCB_Vis Lrng	0.00	0.59	0.00	0.00		0.07	0.00
6	MCCB_Vrbl Lrng	0.00	0.21	0.00	0.00	0.07		0.00
7	MCCB_WM	0.79	0.00	0.73	0.14	0.00	0.00	

Table 8.3: LSD p-values for MCCB subscale mean scores

MCCB: Matrics Consensus Cognitive Battery; MCCB AV: Attention/Vigilance; MCCB SoP: Speed of Processing; MCCB Vis Lrng: Visual Learning;MCCB Vrbl Lrng: Verbal Learning; MCCB WM: Working Memory; MCCB RPS: Reasoning and Problem Solving;MCCB SC: Social Cognition.

Overall neurocognitive ability (MCCB Composite score) had significant inverse correlations with PANSS Total ($p=0.05$), PANSS Disorganization ($p<0.01$) and PANSS Negative factors ($p=0.05$) at baseline shown in table 8.4.

Variable 1	Variable 2	N	Spearman value	Spearman p-value
MCCB Comp	PANSS Total	37	-0.33	0.05
MCCB Comp	PANSS N	37	-0.32	0.05
MCCB Comp	PANSS D	37	-0.44**	<0.01
MCCB AV	PANSS Total	40	-0.35*	0.03
MCCB AV	PANSS N	40	-0.39*	0.01
MCCB AV	PANSS D	40	-0.52**	<0.01
MCCB SoP	PANSS D	40	-0.32	0.05
MCCB WM	PANSS Total	40	-0.31	0.05
MCCB WM	PANSS N	40	-0.42**	<0.01
MCCB WM	PANSS D	40	-0.47**	<0.01
MCCB Vis Lrng	PANSS Total	40	-0.32*	0.04
MCCB Vis Lrng	PANSS N	40	-0.32*	0.04
MCCB Vis Lrng	PANSS D	40	-0.40*	0.01
MCCB Vrbl Lrng	PANSS Total	40	-0.34*	0.03
MCCB Vrbl Lrng	PANSS D	40	-0.33*	0.04
MCCB Vrbl Lrng	PANSS A/D	40	-0.31	0.05
MCCB RPS	PANSS E	40	-0.32	0.05

* p<0.05 ** p<0.01

Table 8.4: Correlations between MCCB and PANSS scores

MCCB: Matrics Consensus Cognitive Battery; MCCB AV: Attention/Vigilance; MCCB SoP: Speed of Processing; MCCB Vis Lrng: Visual Learning;MCCB Vrbl Lrng: Verbal Learning; MCCB WM: Working Memory; MCCB RPS: Reasoning and Problem Solving;MCCB SC: Social Cognition; PANSS N: PANSS Negative factor; PANSS D: PANSS Disorganized factor; PANSS P: PANSS Positive factor; PANSS E: Excited factor; PANSS A/D: PANSS Anxiety/Depression factor.

The strongest correlations ($p<0.01$) were found between MCCB (Composite; Attention/Vigilance; Working Memory) and PANSS Disorganization factor scores at baseline depicted in table 8.4.

There were no significant correlations between baseline neurocognitive measures (MCCB Composite and subscale scores) and baseline scores on PANSS Positive, PANSS Excited or PANSS Anxiety/Depression factor scores.

Neurocognitive measures that assess Learning (MCCB Vis Lrng, MCCB Vrbl Lrng, MCCB WM) and Attention/Vigilance (MCCB A/V) were highly correlated with PANSS Disorganization and PANSS Negative factors. Reasoning and Problem Solving (MCCB RPS) and Speed of Processing (MCCB SoP) had weaker and fewer correlations with PANSS factor scores shown in table 8.4.

Social Cognition (MCCB SC) poorly correlated with symptom severity (PANSS Total) or PANSS factor scores at baseline.

Thought disorder

The mean number of Rorschach responses (R) was 23.16±8.22, with a range of 14 to 45. No significant bivariate correlation was found between Rorschach PTI and R shown in figure 8.3.

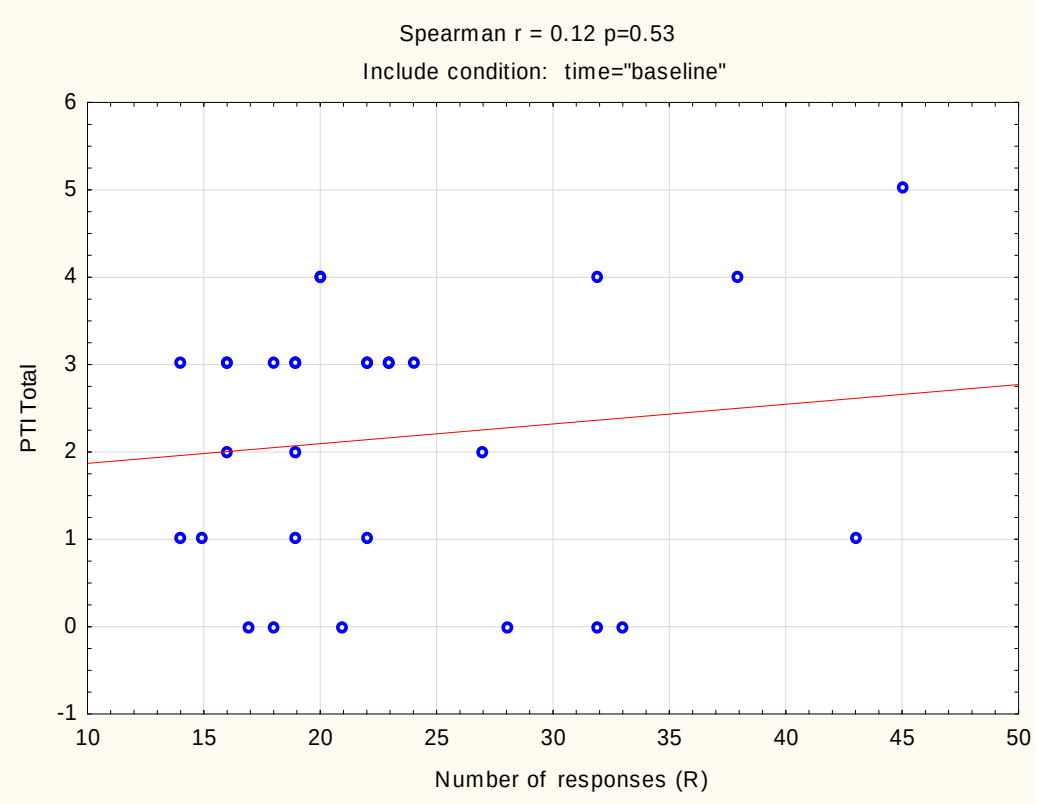

Figure 8.3 Correlation between PTI Total and R

PTI: Perceptual Thinking Index; R: number of Rorschach responses.

At baseline the mean Lambda was 2.28±3.23 and the mean F% was 54.58.

The PTI Total mean score at baseline was 2.16±1.48 with mean percentages for PTI sub-categories: X- % (mean=38.30), M- % (mean=2.52), XA% (mean=60.03), WDA% (mean=62.60), WSum6% (mean=59.77), Sum2% (mean=6.16), and FAB2% (mean=0.48) shown in table 8.5.

	N	Mean	Sd
PTI Total	30	2.16	1.48
X- %	30	38.30	17.84
M- %	30	2.52	4.18
XA%	30	60.03	18.25
WDA%	30	62.60	18.64
WSum6%	30	59.77	47.62
Sum2%	30	6.16	7.95
FAB2%	30	0.48	1.61

Table 8.5: PTI Total mean and subcategory mean percentages

PTI: Perceptual Thinking Index; X- : % poor form perception; M-: % poor human form perception; XA: % good form perception; WDA:% good form perception to whole and large detail; WSum6: % deviant verbalizations and illogical thinking; Sum 2: % severe deviant verbalizations and illogical thinking; FAB2: % fabulised and implausible thinking.

A mild degree of perceptual and thought disorder was evident at baseline (PTI Total mean=2.16, cut-off score>3) (Dao & Prevatt, 2003).

Recalculated cut-off scores for PTI sub-categories (Exner, 2003) indicated significant impairment for baseline scores that assess perceptual accuracy (X- %, XA%, WDA%) shown in table 8.6.

	N	Mean	cut-off scores
PTI total	30	2.16	equal or > 3
X- %	30	38.30*	> 29
M- %	30	2.52	> 4.3
XA%	30	60.03*	< 70
WDA%	30	62.60*	< 75
WSum6%	30	59.77	>73.4
Sum2%	30	6.16	> 8.6
FAB2%	30	0.48*	> 0

* significant impairment at baseline

Table 8.6: Recalculated cut-off scores based on mean R

PTI: Perceptual Thinking Index; X- : % poor form perception; M-: % poor human form perception; XA: % good form perception; WDA:% good form perception to whole and large detail; WSum6: % deviant verbalizations and illogical thinking; Sum 2: % severe deviant verbalizations and illogical thinking; FAB2: % fabulised and implausible thinking; R: number of Rorschach responses.

PTI sub-categories assessing perceptual accuracy indices (X- %; XA% and WDA%) accounted the most for raised PTI total scores depicted in table 8.5 and table 8.6.

Fabulised and Implausible Thinking scores (FAB2%) were also slightly raised at baseline as shown in table 8.6.

There were no significant correlations between baseline thought disorder (PTI Total score) and baseline scores of symptom severity (PANSS Total score).

Perceptual accuracy indices (XA% and WDA%) had significant positive correlations with PANSS Positive factor scores and Poor Form Perception (X- %) had a significant inverse correlation with PANSS Positive factor scores at baseline depicted in table 8.7.

Variable 1	Variable 2	N	Spearman value	Spearman p-value
PTI X- %	PANSS P	30	-0.42*	0.02
PTI XA%	PANSS P	30	0.40*	0.03
PTI WDA%	PANSS P	30	0.42*	0.02

* $p < 0.05$ ** $p < 0.01$

Table 8.7: Correlations between PTI and PANSS scores

PTI: Perceptual Thinking Index, X- : % poor form perception; M-: % poor human form perception; XA: % good form perception; WDA:% good form perception to whole and large detail;PANSS: Positive and Negative Syndrome Scale; PANSS P: PANSS Positive factor.

Thought disorder (PTI Total and PTI sub-category scores) were not significantly correlated with PANSS Disorganization, PANSS Negative, PANSS Excited and PANSS Anxiety/Depression factors at baseline.

Thought disorder at baseline (PTI Total score) correlated inversely with overall neurocognitive ability (MCCB Composite, $p<0.01$), Speed of Processing (MCCB SoP, $p<0.01$), Visual Learning (MCCB Vis Lrng, $p<0.01$) and Working Memory (MCCB WM, $p=0.02$) at baseline as shown in table 8.8.

Variable 1	Variable 2	N	Spearman value	Spearman p-value
PTI Total	MCCB Comp	30	-0.54**	<0.01
PTI Total	MCCB SC	30	-0.42*	0.03
PTI Total	MCCB SoP	30	-0.55**	<0.01
PTI Total	MCCB Vis Lrng	30	-0.63**	<0.01
PTI Total	MCCB WM	30	-0.42*	0.02
PTI X- %	MCCB Comp	30	-0.56**	<0.01
PTI X- %	MCCB SoP	30	-0.57**	<0.01
PTI X- %	MCCB Vis Lrng	30	-0.46*	0.01
PTI X- %	MCCB WM	30	-0.44*	0.02
PTI XA%	MCCB Comp	30	0.58**	<0.01
PTI XA%	MCCB SoP	30	0.59**	<0.01
PTI XA%	MCCB Vis Lrng	30	0.55**	<0.01
PTI XA%	MCCB WM	30	0.48**	<0.01
PTI WDA%	MCCB Comp	30	0.55**	<0.01
PTI WDA%	MCCB SoP	30	0.55**	<0.01
PTI WDA%	MCCB Vis Lrng	30	0.53**	<0.01
PTI WDA%	MCCB Vrbl Lrng	30	0.37	0.05
PTI WDA%	MCCB WM	30	0.46*	0.01

* p <0.05 ** p <0.01

Table 8.8: Correlations between PTI and MCCB scores

PTI Total: Perceptual Thinking Index total score; X- : % poor form perception; M-: % poor human form perception; XA: % good form perception; WDA:% good form perception to whole and large detail; MCCB Comp: Matrics Consensus Cognitive Battery Composite;MCCB SoP: Speed of Processing; MCCB Vis Lrng: Visual Learning;MCCB Vrbl Lrng: Verbal Learning; MCCB WM: Working Memory; MCCB SC: Social Cognition

The significant inverse correlation between PTI Total and Social Cognition (MCCB SC, Spearman p= -0.42, p=0.03) at baseline is clinically inconsistent with the correlations between MCCB subscale and PTI Total scores at baseline, and should therefore be interpreted with caution as depicted in table 8.8.

The perceptual accuracy indices (X-%, XA%, WDA%) had significant correlations with overall neurocognitive ability (MCCB Composite, p<0.01), Speed of Processing (MCCB SoP, p<0.01), Working Memory (MCCB WM, p=0.02, p<0.01, p=0.01) and Visual Learning (MCCB Vis Lrng, p=0.01, p<0.01) at baseline (see table 8.8).

PTI Total and PTI sub-category scores did not correlate significantly with Verbal Learning (MCCB Verb Lrng) at baseline except for a relatively weak correlation with Good Form Perception to Whole and Large Detail (WDA%, Spearman=0.37, p=0.05) (see table 8.8).

Various indices of Deviant Verbalizations and Illogical Thinking (WSum6%, Sum2%, FAB2%) were not significantly correlated with baseline measures of neurocognitive ability.

Social and occupational functioning

The mean score of Social and Occupational Functioning (SOFAS) at baseline was 48.67±13.53, which indicates serious impairment (Goldman *et al.,* 1992).

Social and Occupational Functioning correlated positively at baseline with overall neurocognitive ability (MCCB Composite, p=0.04), Attention/Vigilance (MCCB A/V, p<0.01) and Visual Learning (MCCB Vis Lrng, p=0.04) as depicted in table 8.9.

Variable 1	Variable 2	N	Spearman value	Spearman p-value
SOFAS	MCCB Comp	37	0.35*	0.04
SOFAS	MCCB AV	40	0.42**	<0.01
SOFAS	MCCB Vis Lrng	40	0.32*	0.04

* p <0.05 ** p <0.01

Table 8.9: Correlations between SOFAS and MCCB scores

SOFAS: Social and Occupational Functioning Scale; MCCB Comp: Matrics Consensus Cognitive Battery Composite; MCCB Vis Lrng: Visual Learning; MCCB AV: Attention / Vigilance.

The strongest correlation at baseline was found between Attention/Vigilance (MCCB A/V) and SOFAS.

Measures of Thought Disorder (PTI Total and PTI sub-categories) were not significantly correlated with SOFAS at baseline.

Quality of life

The mean transformed scores for Quality of Life at baseline ranged from 46.91 to 53.24 for the four domains as depicted in table 8.10.

	N	Mean	sd
WHOQOL Domain 1 - Physical	42	46.91	13.29
WHOQOL Domain 2 - Psychological	42	53.24	17.30
WHOQOL Domain 3 - Social relations	42	47.33	23.72
WHOQOL Domain 4 - Environment	42	48.06	21.50

Table 8.10: WHOQOL mean transformed domain scores

WHOQOL: World Health Organization Quality of Life Questionnaire

Overall Quality of Life as reported by patients at baseline reflected a moderate degree of dissatisfaction with Physical, Psychological, Social and Environmental well-being (Bergner *et al.,* 1981).

Question1 (rating of quality of life) had a mean of 3.24±1.00 and Question2 (rating of health satisfaction) had a mean of 3.33±1.26, which indicate a neutral response to these questions at baseline by most patients.

Quality of Life (Environment) correlated significantly with overall neurocognitive ability (MCCB Comp, p=0.03) and Social Cognition (MCCB SC, p<0.01) at baseline (see table 8.11). Quality of Life (Physical) also correlated with Social Cognition (MCCB SC, p=0.04) at baseline.

Variable 1	Variable 2	N	Spearman value	Spearman p-value
QOL Domain 4	MCCB Comp	36	0.35*	0.03
QOL Domain 4	MCCB SC	36	0.45**	<0.01
QOL Domain 1	MCCB SC	36	0.35*	0.04

* p<0.05 ** p<0.01

Table 8.11: Correlations between QOL domain and MCCB

QOL Domain 1: Quality of Life Physical; QOL Domain 4: Quality of Life Environment; MCCB Comp: Matrics Consensus Cognitive Battery Composite score; MCCB SC: Social Cognition

All four QOL domains (Physical, Psychological, Social, Environment) had significant inverse correlations with thought disorder (PTI Total) at baseline depicted in table 8.12.

Variable 1	Variable 2	N	Spearman value	Spearman p-value
QOL Domain 1	PTl Total	30	-0.49**	<0.01
QOL Domain 2	PTI Total	30	-0.55**	<0.01
QOL Domain 3	PTI Total	30	-0.51**	<0.01
QOL Domain 4	PTI Total	30	-0.41*	0.03
QOL Domain 1	X- %	30	-0.45*	0.01
QOL Domain 2	X- %	30	-0.49**	<0.01
QOL Domain 4	X- %	30	-0.41*	0.02
QOL Domain 1	XA%	30	0.44*	0.01
QOL Domain 2	XA%	30	0.49**	<0.01
QOL Domain 4	XA%	30	0.36	0.05
QOL Domain 1	WDA%	30	0.49**	<0.01
QOL Domain 2	WDA%	30	0.47**	<0.01
QOL Domain 4	WDA%	30	0.39*	0.03
QOL Domain 3	FAB2%	30	-0.43*	0.02

* p<0.05 ** p<0.01

Table 8.12: Correlations between QOL domain and PTI scores

QOL Domain 1: Quality of Life Physical; QOL Domain 2: Quality of Life Psychological; QOL Domain 3: Quality of Life Social; QOL Domain 4: Quality of Life Environment; PTI Total: Perceptual Thinking Index total score; X- : % poor form perception; XA: % good form perception; WDA:% good form perception to whole and large detail; FAB2: % fabulised and implausible thinking.

Poor Form Perception (X- %) had significant inverse correlations with Physical (QOL Domain 1, p=0.01), Psychological (QOL Domain 2, p<0.01) and Environment (QOL Domain 4, p=0.02) as depicted in table 8.12.

The Perceptual Accuracy indices (XA%, WDA%) had significant positive correlations with Physical (QOL Domain 1), Psychological (QOL Domain 2), and Environment (QOL domain 4) at baseline as depicted in table 8.12.

Various degrees of Deviant Verbalizations and Illogical Thinking (WSum2%, Sum2%, FAB2%) were not significantly correlated with QOL domains at baseline except for Fabulised and Implausible Thinking (FAB2%) which had an inverse correlation with Social (QOL Domain 3, p=0.02) shown in table 8.12.

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CHAPTER 9:

RESULTS: TREATMENT RESPONSE AND OUTCOME

Decrease in symptom severity

A mixed model repeated measures ANOVA revealed a significant decrease in symptom severity (PANSS Total mean) from 89.06±16.89 at baseline to 44.17±11.52 at month 12 as depicted in figure 9.1.

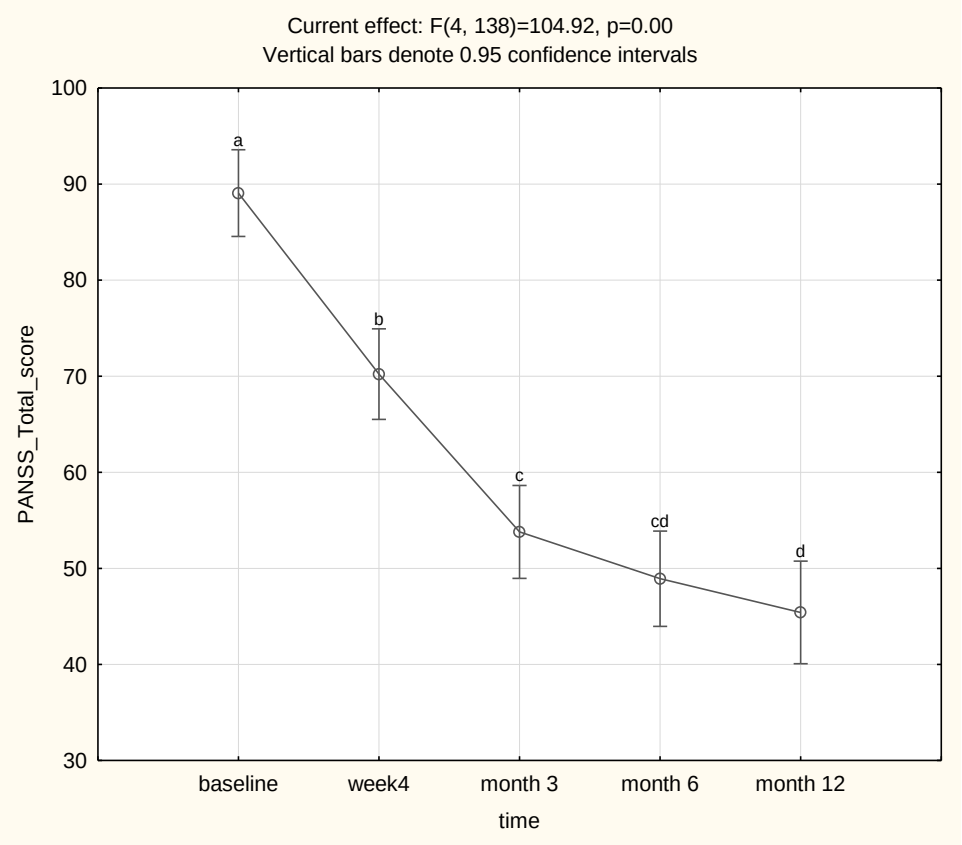

Figure 9.1: Change in PANSS Total mean scores over time

PANSS Total: Positive and Negative Syndrome Scale total score

The degree of symptom severity reached levels of minimal psychopathology at month 12 (mean PANSS Total= 44.17) (Kay, 1987).

Most of the change occurred within the first 3 months after treatment with 41.8% improvement within the first month, 79.5% within the first 3 months and 91.0% after 6 months as shown in table 9.1.

Effect	Descriptive Statistics: PANSS Total scores			
	Level of Factor	N	PANSS_Total_score Mean	PANSS_Total_score Std.Dev.
time	baseline	42	89.06	16.89
time	week4	41	70.29	16.10
time	month 3	38	53.36	16.036
time	month 6	35	48.20	12.48
time	month 12	28	44.17	11.52

Table 9.1: PANSS Total mean scores over time

PANSS Total: Positive and Negative Syndrome Scale total score

No significant change in symptoms occurred between month 3 and month 6, or between month 6 and month 12 as shown in table 9.2.

	LSD test; variable PANSS_Total_score			
Assessment Effect: Time	1st Mean	2nd Mean	Mean Differ.	P
{1}-{2}	baseline	week4	18.84	0.00
{1}-{3}	baseline	month 3	35.27	0.00
{1}-{4}	baseline	month 6	40.14	0.00
{1}-{5}	baseline	month 12	43.65	0.00
{2}-{3}	week4	month 3	16.43	0.00
{2}-{4}	week4	month 6	21.30	0.00
{2}-{5}	week4	month 12	24.81	0.00
{3}-{4}	month 3	month 6	4.87	0.05
{3}-{5}	month 3	month 12	8.38	0.00
{4}-{5}	month 6	month 12	3.51	0.20

Table 9.2: LSD p-values for PANSS Total mean scores over time

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PANSS Total: Positive and Negative Syndrome Scale total score

Change in the PANSS factors scores (Positive, Negative, Disorganization, Excited, Anxiety/Depression) followed a similar trend with most improvement occurring within the first 3 months after treatment.

PANSS Positive factor scores improved significantly between baseline and month 12, with most improvement between baseline and month 3 as shown in figure 9.2.

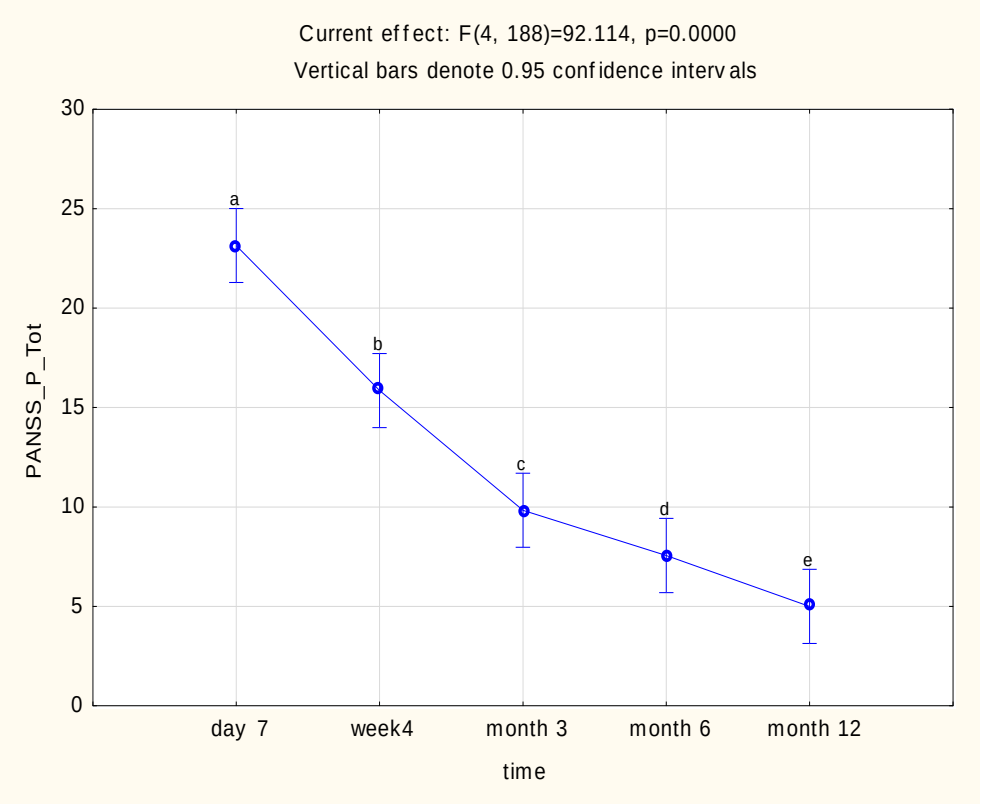

Figure 9.2: Change in PANSS Positive factor scores over time

PANSS Negative factor scores improved significantly from baseline to month 12 with most improvement occurring within the first 3 months after treatment as shown in figure 9.3.

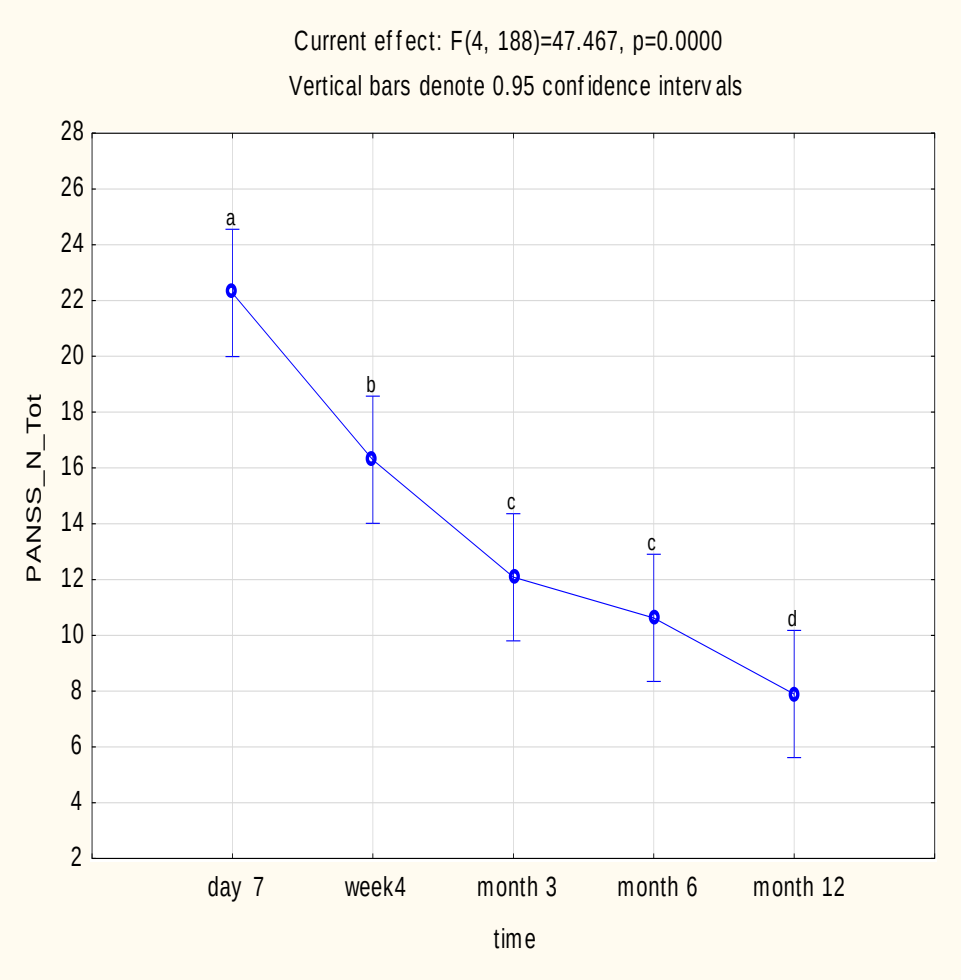

Figure 9.3: Change in PANSS Negative factor scores over time

Change in PANSS Negative factor scores were not significant between month 3 and month 6 (p=0.20).

PANSS Disorganization factor scores improved significantly from baseline to month 12 with most change occurring within the first 3 months after treatment as shown in figure 9.4.

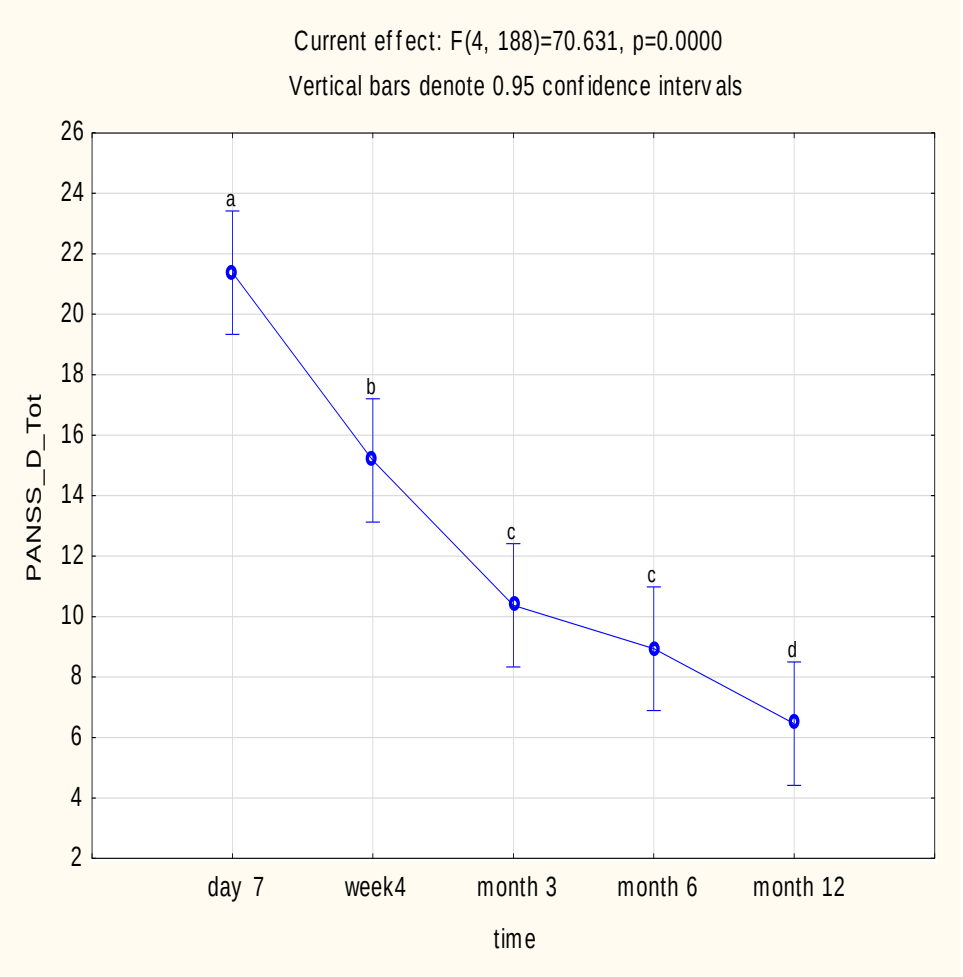

Figure 9.4: Change in PANSS Disorganization factor scores over time

Change in PANSS Disorganization factor scores were not significant between month 3 and month 6 (p=0.14).

PANSS Anxiety / Depression factor scores improved signicantly from baseline to month 12 with most improvement occurring within the first 3 months after treatment as shown in figure 9.5.

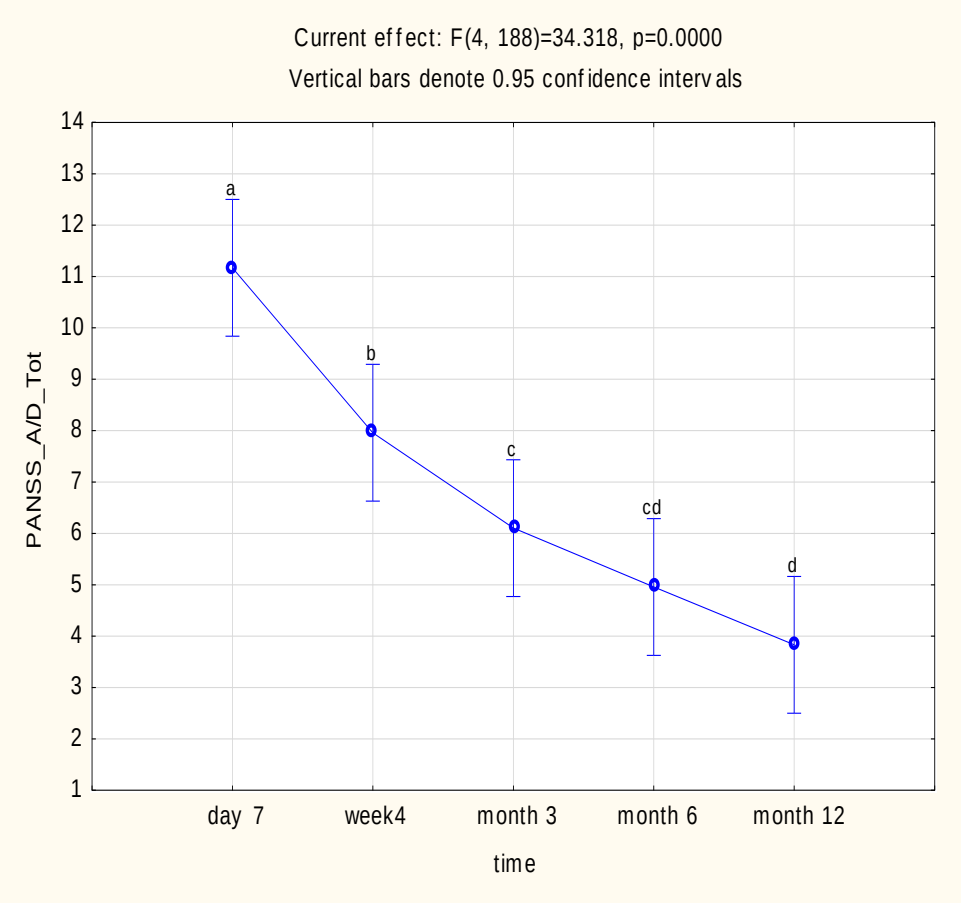

Figure 9.5: Change in PANSS Anxiety / Depression factor scores over time

Change in PANSS Anxiety / Depression factor scores were not significant between month 3 and month 6 (p=0.1) and between month 6 and month 12 (p=0.1).

PANSS Excited factor scores improved significantly from baseline to month 12 with most improvement occurring within the first 4 weeks after treatment as shown in figure 9.6.

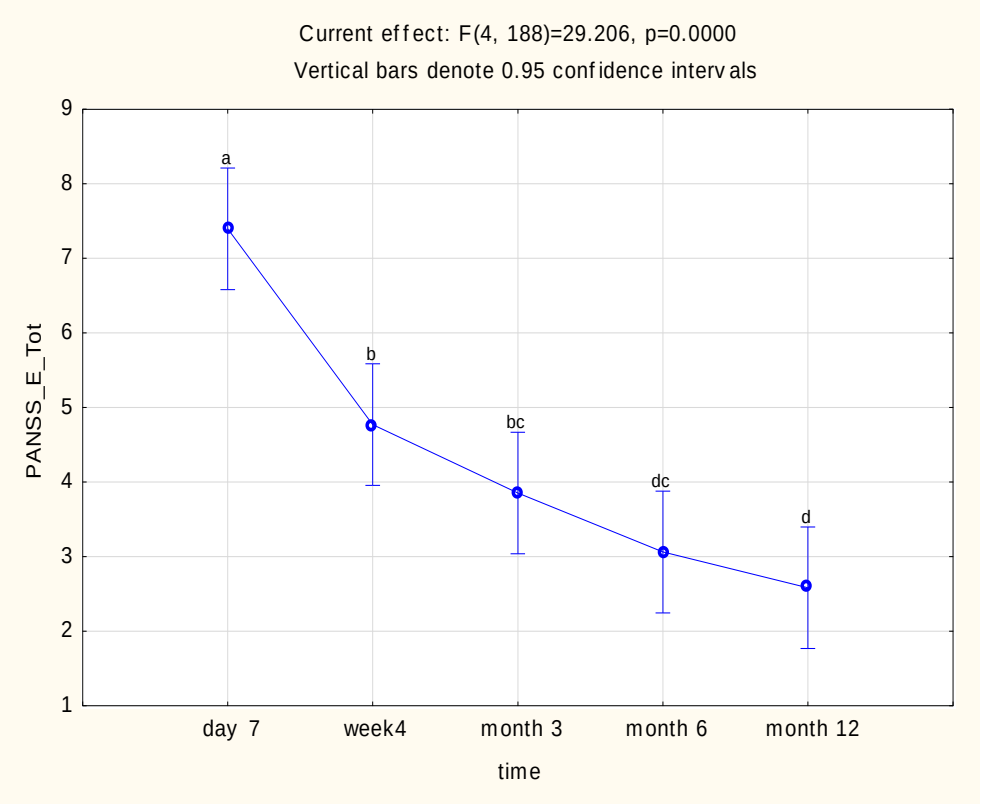

Figure 9.6: Change in PANSS Excited factor scores over time

Change in PANSS Excited factor scores were not significant between month 1 and month 3 (p=0.06), between month 3 and month 6 (p=0.11) and between month 6 and month 12 (p=0.33).

Predictors of various outcome measures:

Best subsets regression with all the independent variables identified baseline scores for Social Cognition (MCCB SC), highest level of education (HLOE), Working Memory (MCCB WM), thought disorder (PTI total) and Attention/Vigilance (MCCB A/V) as predictors accounting for 40.5% of the variance (adjusted R^2=0.40, F(5,14)=3.58, p<0.02) of symptom severity (PANSS Total) at month 12 as shown in table 9.4.

N=20	Regression Summary for PANSS_Total_score R^2= .561 Adjusted R^2= .405 F(5,14)=3.58,p<0.02			
	b*	B	p-value	# times in best 20 models
Intercept		77.17	0.00	
MCCB_AV	-0.19	-0.22	0.33	8
MCCB_SC	0.42	0.29	*0.04*	20
MCCB_WM	-0.22	-0.18	0.30	13
HLOE	-0.54	-2.93	*0.00*	20
PTI_Tot	0.23	1.59	0.24	10

***** standard beta

Table 9.4: Beta and p-values of baseline predictors of PANSS Total score at month 12

PANSS: Positive and Negative Syndrome Scale; MCCB WM: Working Memory; MCCB SC: Social Cognition; MCCB AV: Attention / Vigilance; HLOE: highest level of education; PTI Tot: Perceptual Thinking Index total score.

Of the predictors only Social Cognition (MCCB SC) and HLOE were significant independently and the same two variables were also the

only ones to appear in all 20 of the best models as depicted in figure 9.7.

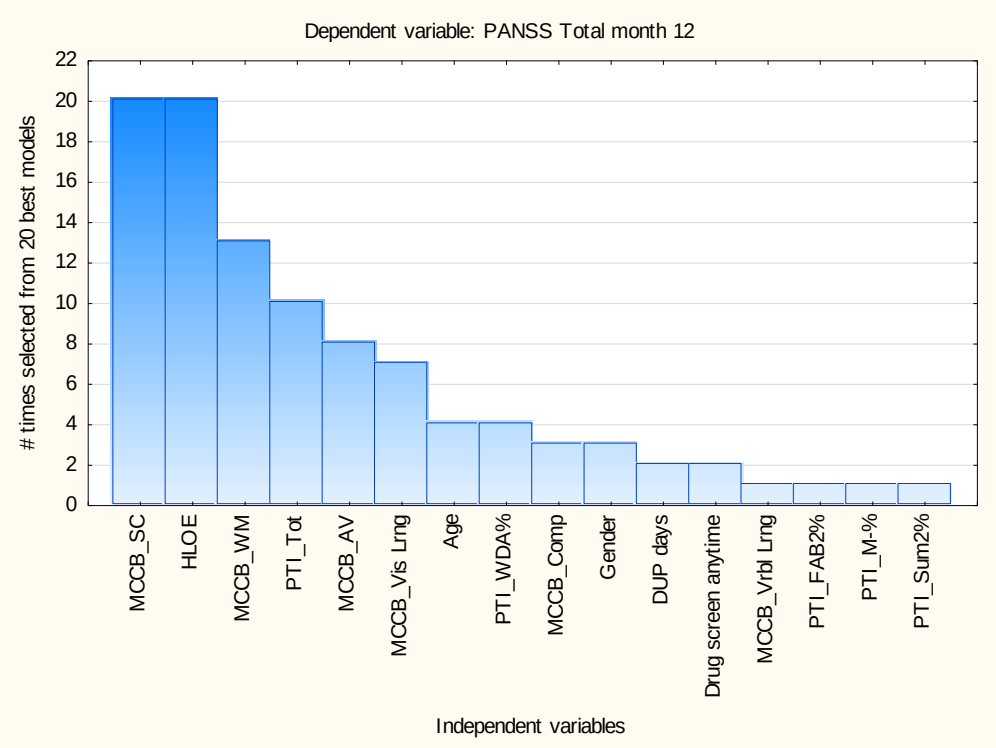

Figure 9.7: Predictors of PANSS Total score at month 12

PANSS: Positive and Negative Syndrome Scale; MCCB SC: Social Cognition; HLOE: highest level of education, MCCB WM: Working Memory; PTI Tot: Perceptual Thinking Index total score; MCCB A/V: Attention / Vigilance; MCCB Vis Lrng: Visual Learning.

However, while Social Cognition (MCCB SC) was a significant predictor (b=0.42, p=0.04) it was in a positive direction – i.e. better performance in the social cognition domain predicted more severe symptoms at month 12. This is counter-intuitive, and the role of Social Cognition as a predictor of symptom severity at month 12 should be interpreted with caution.

When entering change from baseline to month 6 in total and subscale scores for PANSS, MCCB and PTI with the same independent variables and PANSS Total at month 12 as dependent variable, the predictive power in a best subsets regression increased (adjusted R^2 =0.73, $F(4,13)=16.41$, $p<0.01$) compared to baseline predictors only (adjusted R^2 =0.40, $F(5,14)=3.58$, $p<0.05$) as depicted in table 9.5.

N=18	Regression Summary for Dependent Variable: PANSS_Total (M12) R^2= .834 Adjusted R^2= .783 $F(4,13)=16.41$ $p<0.01$			
	b*	b	p-value	# times in best 20 models
Intercept		69.36	0.00	
HLOE	-0.57	-3.08	0.00	15
Sum2% (M6- baseline)	-0.53	-1.03	0.00	15
WDA% (M6- baseline)	0.72	0.53	0.00	14
PANSS_E (M6- baseline)	-0.35	-0.94	0.01	2

* standard beta

Table 9.5: Beta and p-values for change predictors of PANSS Total score at month 12

PANSS: Positive and Negative Syndrome Scale; PANSS E: Excited factor; HLOE: highest level of education; Sum2: % deviant verbalizations and illogical thinking; WDA: % good form responses to whole and large detail.

The following change variables explained 78.3% of the variance in PANSS Total score at month 12: Highest level of education (HLOE), Severe Deviant Verbalizations and Illogical Thinking (Sum2%),

Good Form Perception to Whole and Large Detail (WDA%) and PANSS Excited factor (PANSS E) as shown in table 9.5. All of these predictors were significant and also appeared in the best 20 models depicted in figure 9.8.

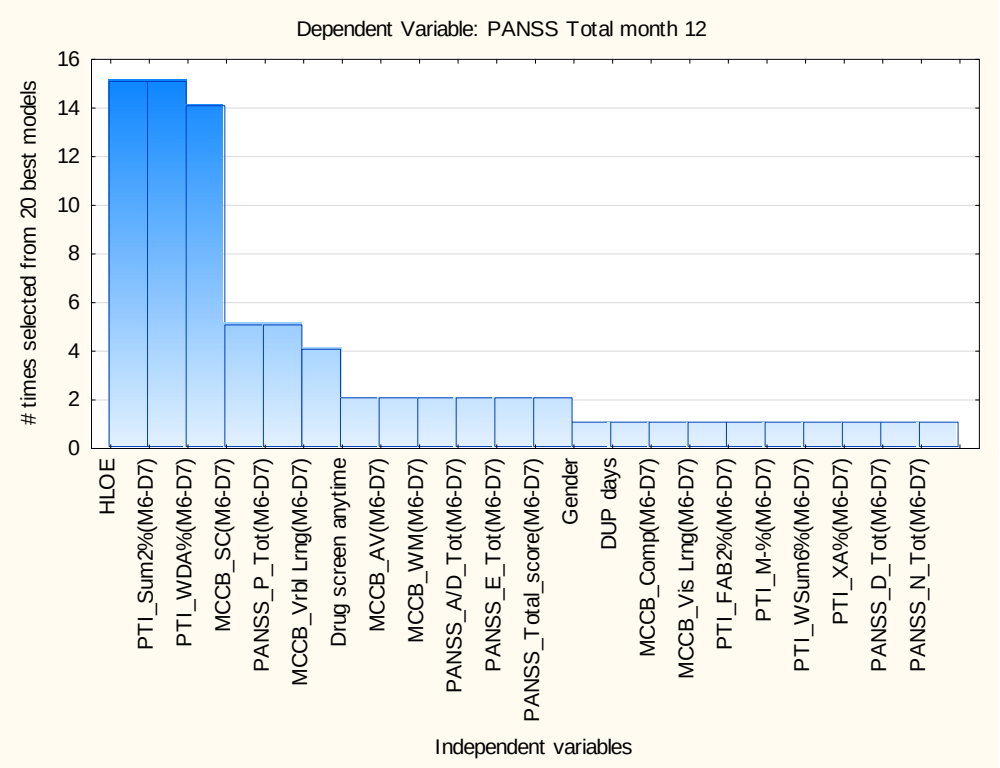

Figure 9.8: Change predictors of PANSS Total score at month 12

PANSS Total: Positive and Negative Syndrome Scale total score; Sum2: % severe deviant verbalizations and illogical thinking; WDA: % good form responses to whole and large detail; MCCB SC: Social Cognition; PANSS P: Positive factor; MCCB Vrbl Lrng: Verbal Learning.

The degree of improvement (increase from baseline to month 6 scores) in WDA had a positive influence (beta=0.72, $p<0.01$) on the

variance which is clinically inconsistent with the negative influence of improvement in Sum2 (beta= -0.53, p=<0.01).

The predictive validity of degree of improvement in WDA from baseline to month 6 should therefore be interpreted with caution.

Improvement in neurocognitive performance

Overall neurocognitive ability (MCCB Composite score) improved significantly from a baseline mean of 15.48±15.84 to a mean of 26.28±15.20 at month 12 as shown in figure 9.9.

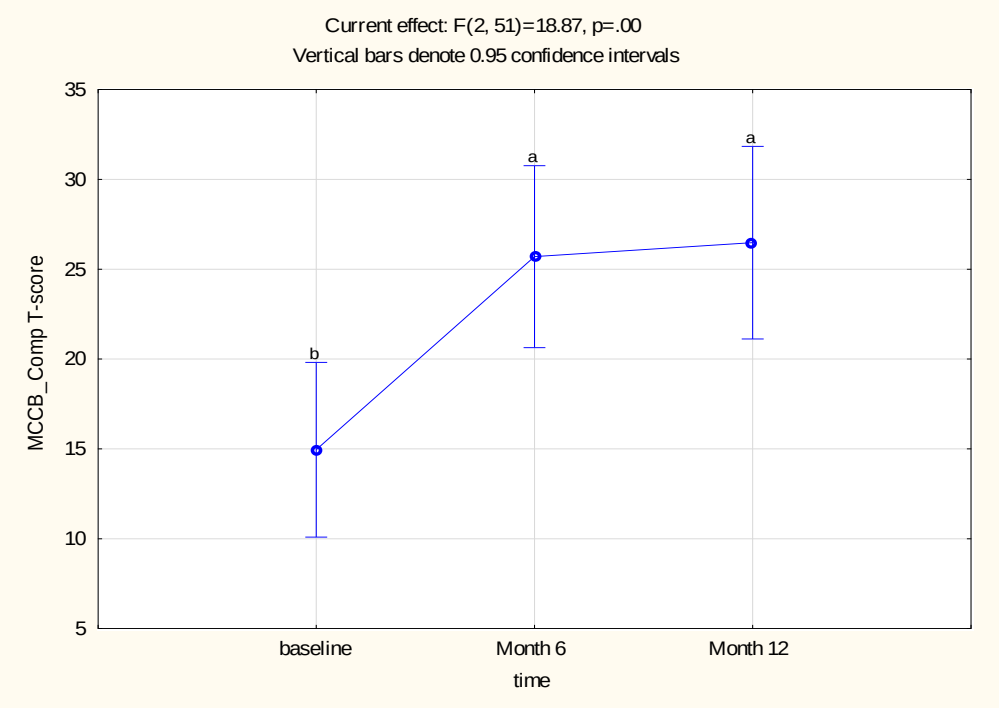

Figure 9.9: Change in neurocognitive ability over time

MCCB Comp: Matrics Consensus Cognitive Battery composite score.

Most of the improvement in overall neurocognitive ability occurred early with 100% improvement observed during the first 6 months depicted in table 9.6.

Effect	Descriptive Statistics: MCCB Composite scores			
	Level of Factor	N	MCCB_Comp Mean	MCCB_Comp Std.Dev.
Total		94	22.36	15.71
time	Baseline	37	15.48	15.84
time	month 6	32	27.25	13.30
time	month 12	25	26.28	15.20

Table 9.6: MCCB Composite mean T-scores over time

MCCB Composite: Matrics Consensus Cognitive Battery composite score.

A degree of impairment in overall neurocognitive ability was evident at month 12 (MCCB Composite T score, mean=26.29) which is 2-3 standard deviations (<1st percentile) below the reference norm (Nuechterlein & Green, 2006).

For the MCCB subscales most improvement occurred within the first 6 months: Attention/Vigilance (MCCB A/V=85.5%), Speed of Processing (MCCB SoP=100%), Working Memory (MCCB WM=100%), Verbal Learning (MCCB Vrbl Lrng=100%), Visual Learning (MCCB Vis Lrng=100%), Reasoning-and Problem Solving (MCCB RPS=100%), and Social Cognition (MCCB SC=86.6%) as shown in table 9.7.

	Descriptive Statistics: MCCB Subscale scores							
Effect Time	N	AV Mean	SoP Mean	Vrbl Lrng Mean	Vis Lrng Mean	WM Mean	RPS Mean	SC Mean
Total	97	32.03	27.87	38.58	36.39	32.23	37.34	29.72
baseline	40	26.30	22.67	36.22	32.50	25.75	33.62	26.86
month 6	32	35.50	31.75	41.43	39.81	37.03	40.21	31.28
month 12	25	36.76	31.24	38.72	38.24	36.48	39.60	31.96

Table 9.7: MCCB Subscale mean T-scores over time

MCCB AV: Attention / Vigilance; MCCB SoP: Speed of Processing; MCCB Vrbl Lrng: Verbal Learning; MCCB Vis Lrng: Visual Learning; MCCB WM: Working Memory; MCCB RPS: Reasoning and Problem Solving; MCCB SC: Social Cognition.

The mean differences between baseline and month 6 scores were significant at a 95% confidence interval for all domains except for Social Cognition (MCCB SC) which did not show significant improvement from baseline to month 6, but did so at month 12 as shown in figure 9.10.

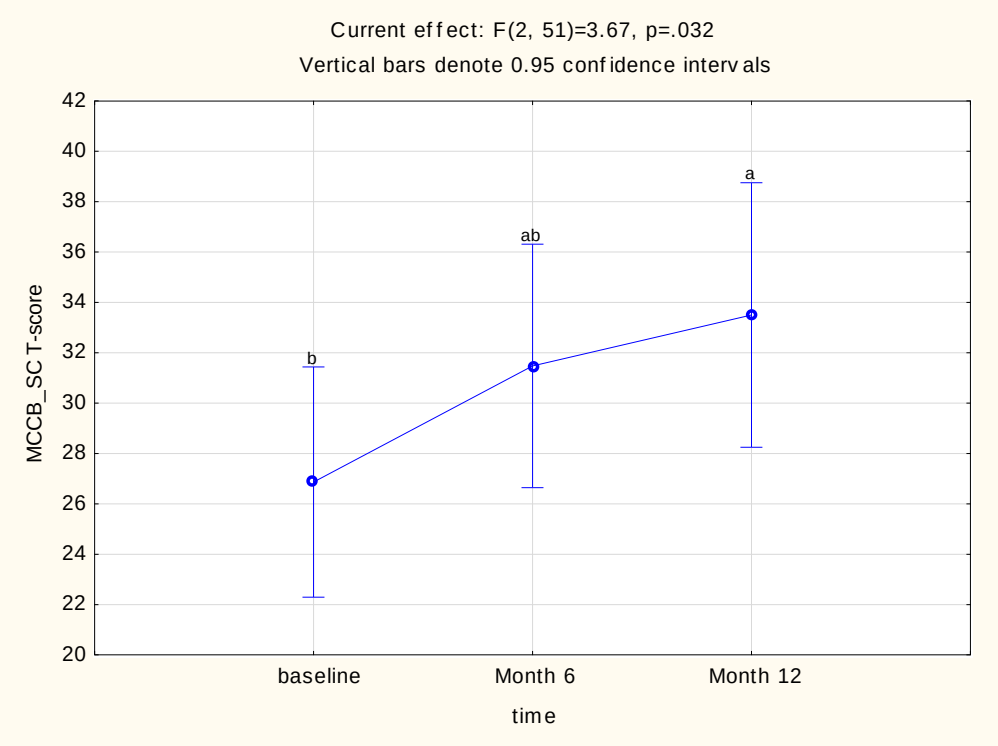

Figure 9.10: Change in Social Cognition scores over time

The degree of change in neurocognitive performance (MCCB Composite and subscale scores) and symptoms (PANSS Total and factor scores) revealed the following significant inverse correlations: improvement in MCCB Composite and subscales measuring Learning (MCCB Visual Learning, MCCB Verbal Learning, MCCB Working Memory) correlated significantly with improvement in PANSS Negative and Disorganization factors depicted in table 9.8.

Variable 1	Variable 2	N	Spearman value	Spearman p-value
MCCB Comp (M6 - baseline)	PANSS D (M6 - baseline)	30	-0.41*	0.03
MCCB Vis Lrng (M6 - baseline)	PANSS D (M6 - baseline)	30	-0.44*	0.01
MCCB Vis Lrng (M6 - baseline)	PANSS N (M6 - baseline)	30	-0.48**	<0.01
MCCB Vrbl Lrng (M6 - baseline)	PANSS N (M6 - baseline)	30	-0.51**	<0.01
MCCB WM (M6 - baseline)	PANSS N (M6 - baseline)	30	-0.44*	0.01

***** $p < 0.05$ ** $p < 0.01$

Table9.8: Correlations between MCCB and PANSS change scores

MCCB Comp: Matrics Consensus Cognitive Battery composite score; MCCB Vis Lrng: Visual Learning; MCCB Vrb Lrng: Verbal Learning; MCCB WM: Working Memory; PANSS D: Disorganization factor; PANSS N: Negative factor.

A best subsets regression with MCCB Composite score at month 12 as the dependent variable and baseline PTI Total and sub-category scores as independent variables had a relative weak predictive power with 21% of the variance explained by PTI variables as shown in table 9.9.

N=21	Regression Summary for Dependent Variable: MCCB_Comp M12 R^2= .329 Adjusted R^2= .211 F(3,17)=2.78, p<0.07			
	b*	B	p-value	# times in best 20 models
Intercept		-10.36	0.45	
FAB2%	-0.32	-2.67	0.21	10
WDA%	0.62	0.54	0.01	8
WSum6%	0.30	0.10	0.24	9

* standard beta

Table 9.9: PTI predictors of MCCB Composite score at month 12

FAB2: % fabulised and implausible thinking; WDA: % good form responses to whole and large detail; WSum6: % deviant verbalizations and illogical thinking; MCCB Comp: Matrics Consensus Cognitive Battery composite score.

Of the PTI predictor variables only Good Form Perception to Whole and Large detail (WDA) was significant (p=0.01) as shown in table 9.9.

Improvement in perceptual and thought disorder

Perceptual and thought disorder index scores (PTI Total) decreased significantly from a baseline mean of 2.16±1.48 to 1.65±1.44 at month 6 and 1.31±1.49 at month 12 shown in figure 9.11.

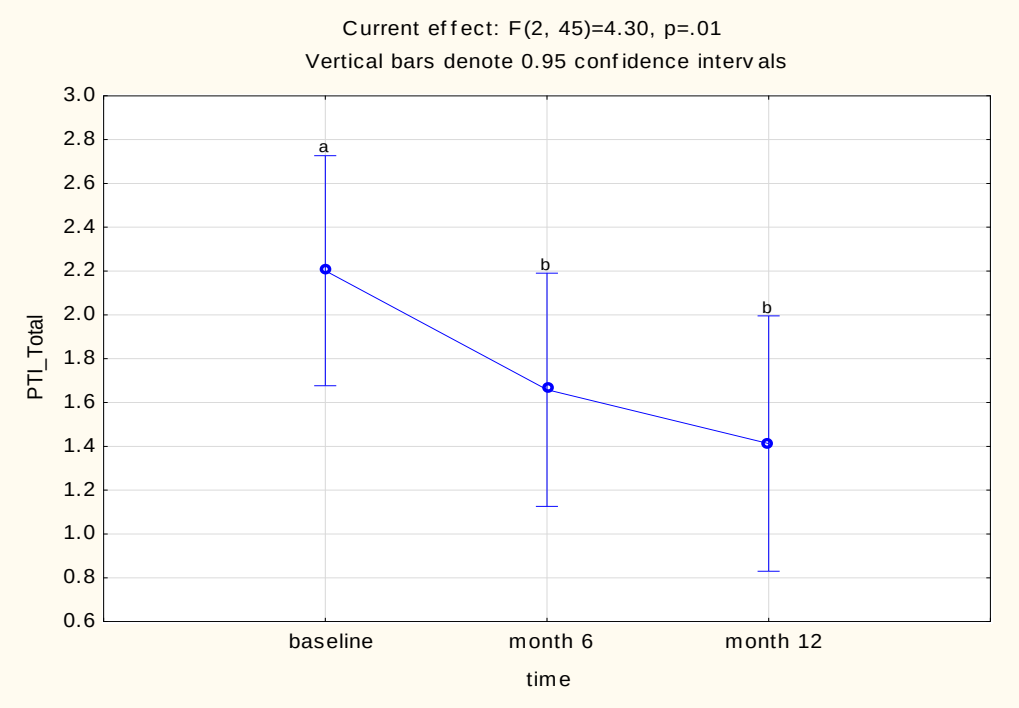

Figure 9.11: Change in PTI Total scores over time

PTI Total: Perceptual Thinking Index total score

Most of the improvement in perceptual and thought disorder (PTI Total) occurred early with a 60% decrease at month 6 and a 40% decrease in perceptual and thought disorder at month 12 as depicted in table 9.10.

Effect	Descriptive Statistics: Thought disorder scores			
	Level of Factor	N	PTI_Tot Mean	PTI_Tot Std.Dev.
Total		81	1.75	1.49
time	baseline	30	2.16	1.48
time	month 6	29	1.65	1.44
time	month 12	22	1.31	1.49

Table 9.10: PTI total mean scores over time

PTI Total: Perceptual Thinking Index total score

The decrease in perceptual and thought disorder score was significant between baseline and month 6 (p=0.04) but not between month 6 and month 12 (p=0.38) as shown in table 9.11.

Comparisons Cell {#1}-{#2}	LSD test; variable PTI_Total Effect: time			
	1st Mean	2nd Mean	Mean Differ.	p
{1}-{2}	Baseline	month 6	0.54	0.04
{1}-{3}	Baseline	month 12	0.78	0.00
{2}-{3}	month 6	month 12	0.24	0.38

Table 9.11: LSD p-values for change in PTI total scores over time

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PTI Total: Perceptual Thinking Index total score

The distribution of Lambda was skewed (see figure 9.12) and in order to calculate a mixed model repeated ANOVA, we used a statistically corrected Lambda mean which is more suitable for parametric analysis.

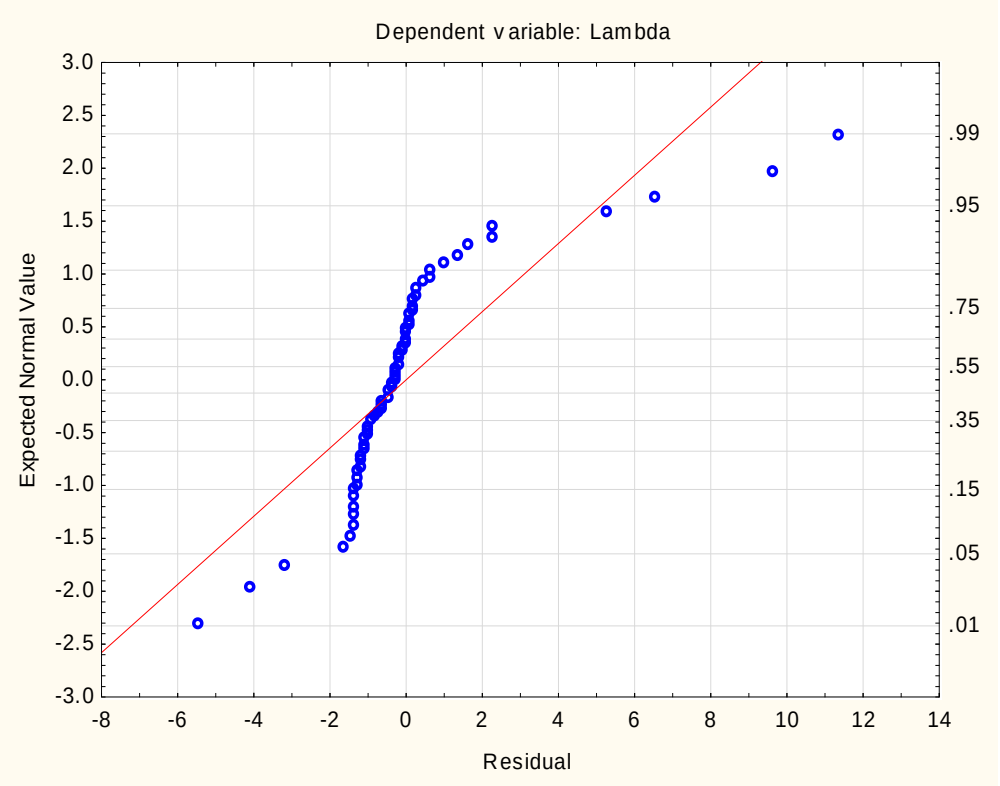

Figure 9.12: Distribution of Lambda scores at baseline

Lambda increased significantly from baseline to month 6 whereafter it reached a plateau as depicted in figure 9.13.

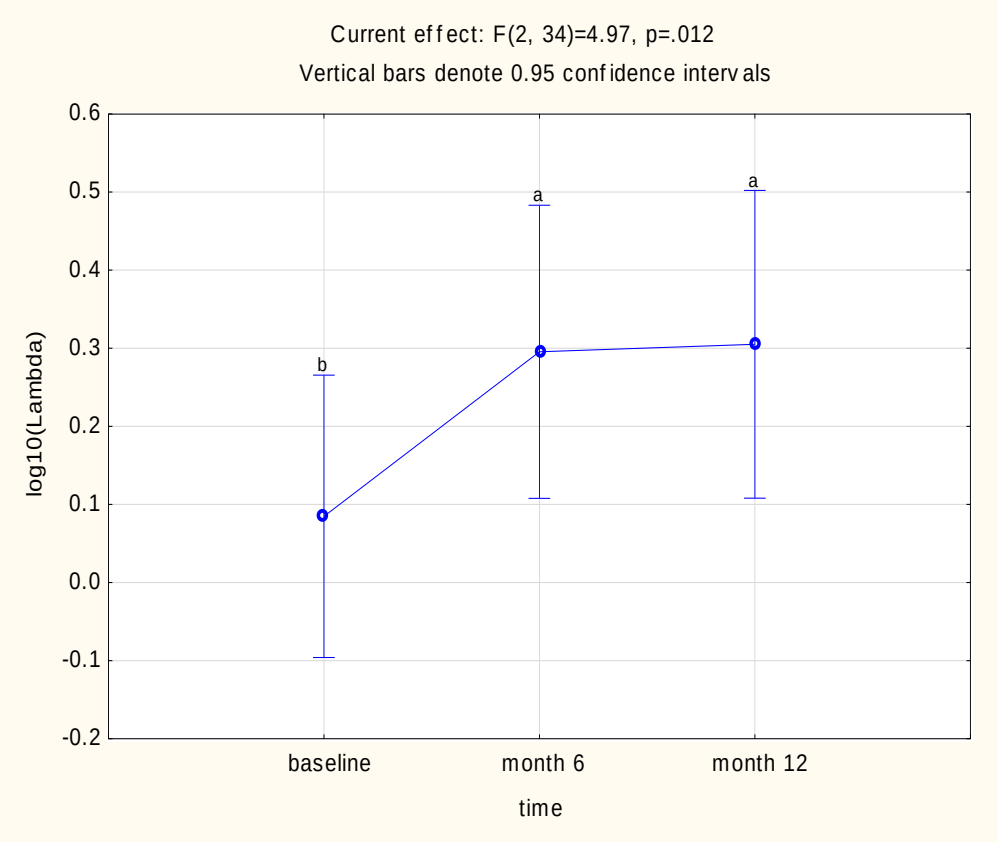

Figure 9.13: Change in Lambda scores over time

Of the PTI sub-categories, improvement from baseline to month 6 was most evident for Poor Human Form Perception (M-%=100%), Severe Deviant Verbalizations and Illogical Thinking (Sum2% =77.8%), and Fabulised and Implausible Thinking (FAB2% =100%) as depicted in table 9.12.

	Descriptive Statistics: PTI Sub-category scores							
Effect Time	N	X- % Mean	XA % Mean	WDA % Mean	M- % Mean	WSum 6 % Mean	Sum2 % Mean	FAB2 % Mean
Total	81	33.83	63.17	65.11	1.62	39.14	3.59	0.20
baseline	30	38.30	60.03	62.60	2.52	59.77	6.16	0.48
month 6	29	33.17	62.41	64.68	1.03	36.20	2.53	0.00
month 12	22	28.63	68.45	69.09	1.16	14.90	1.50	0.11

Table 9.12: PTI Sub-category mean percentages over time

PTI: Perceptual Thinking Index; X- : % poor form perception; M-: % poor human form perception; XA: % good form perception; WDA:% good form perception to whole and large detail; WSum6: % deviant verbalizations and illogical thinking; Sum 2: % severe deviant verbalizations and illogical thinking; FAB2: % fabulised and implausible thinking.

Deviant Verbalizations and Illogical Thinking (WSum6%: LSD $p<0.01$), Severe Deviant Verbalizations and Illogical Thinking (Sum2%: LSD $p<0.01$) and Fabulised and Implausible Thinking (FAB2%: LSD $p=0.04$) showed significant improvement from baseline to month 6 at a 95% confidence interval (see table 9.12).

Improvement in the Perceptual Accuracy indices occurred later with most improvement evident between month 6 and month 12 for XA% (71.8%) and WDA% (68%) as depicted in table 9.12.

Improvement between month 6 and month 12 was significant for Good Form Perception (XA%, LSD p=0.03, CI=0.95) as shown in figure 9.14.

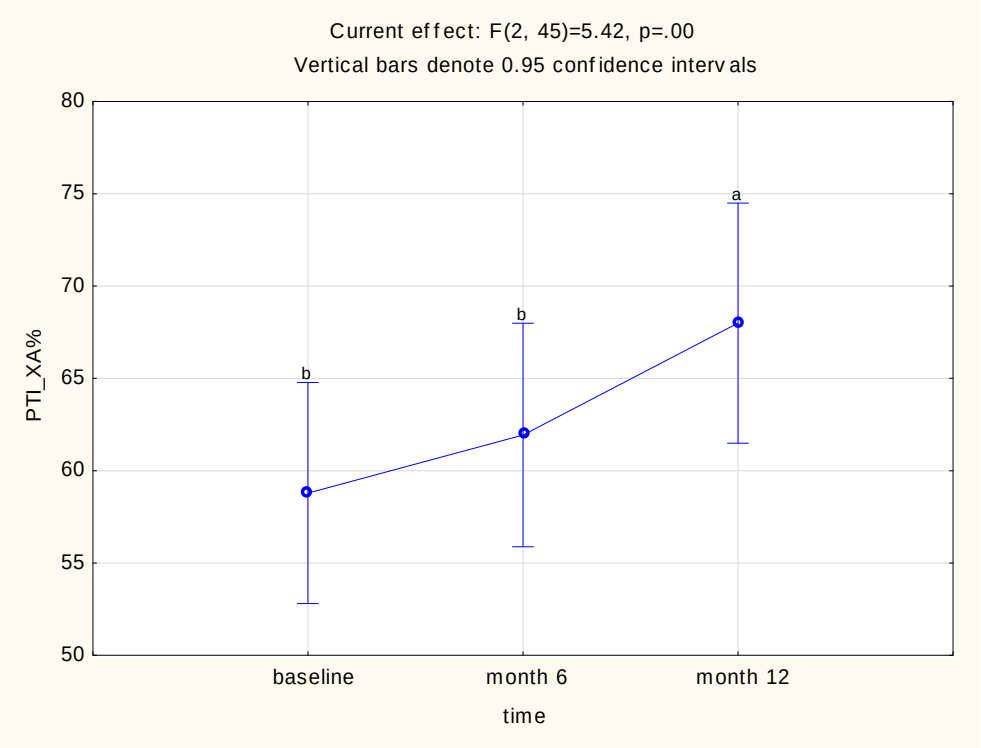

Figure 9.14: Change in Good Form Perception (XA%) over time

PTI XA: % good form responses

At month 12 residual thought and perceptual impairment was evident with Good Form Perception (XA% mean=68.45, cut-off <70), Good Form Perception to Whole and Large Detail (WDA% mean=69.09, cut-off <75) and Fabulised and Implausible Thinking (FAB2% mean=0.11, cut-off >0) as depicted in table 9.12 (Exner, 2003).

No significant correlations were found between degree of improvement in thought disorder (difference between baseline and month 6 for PTI Total and sub-category scores) and improvement in symptoms (difference between baseline and month 6 for PANSS Total and factor scores).

No significant correlations were found between improvement in thought disorder (difference between baseline and month 6 for PTI Total and sub-category scores) and improvement in neurocognitive performance (difference between baseline and month 6 for MCCB Total and subscale scores), except for significant correlations between improvement in Poor Human Form Perception (M- %) and improvement in Reasoning-and-Problem Solving (MCCB RPS), and improvement in Good Form Perception to Whole and Large Detail (WDA%) which was correlated to improvement in Working Memory (MCCB WM) as shown in table 9.13.

Variable 1	Variable 2	N	Spearman value	Spearman p-value
M- % (M6 - baseline)	MCCB RPS (M6 - baseline)	24	0.50*	0.01
WDA% (M6 - baseline)	MCCB WM (M6 - baseline)	24	0.54**	<0.01

* p< 0.05 ** p< 0.01

Table 9.13: Change correlations between PTI and MCCB scores

M-: % poor human form responses; WDA: % good form responses to whole and large detail; MCCB RPS: Reasoning and Problem Solving; MCCB WM: Working Memory

The correlation between M- % and MCCB RPS should be interpreted with caution due to the small variance in mean M- % scores over time (see table 9.12).

Improvement in Social and Occupational Functioning

Social and Occupational Functioning (SOFAS) improved significantly from a baseline mean of 48.67±13.53 to a mean of 70.46±12.43 at month 12 as depicted in figure 9.15.

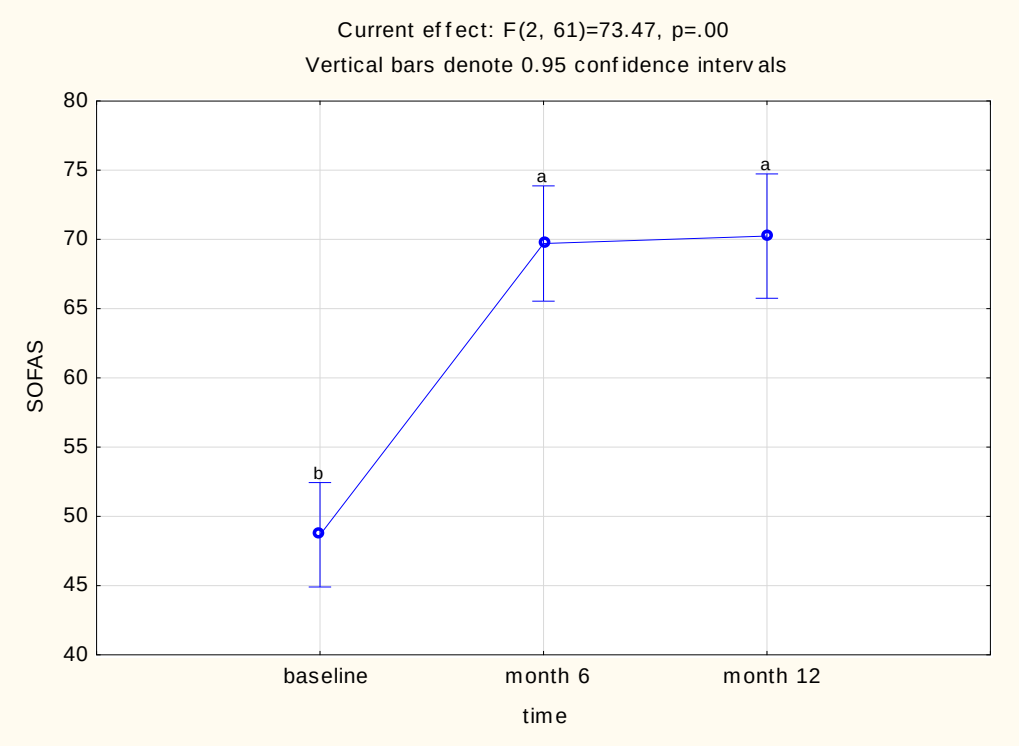

Figure 9.15: Change in SOFAS scores over time

SOFAS: Social and Occupational Functioning Scale

Most of the improvement (96%) in Social and Occupational Functioning occurred within 6 months after treatment as indicated in table 9.14.

Effect	Descriptive Statistics: SOFAS			
	Level of Factor	N	CGI_SOFAS Mean	CGI_SOFAS Std.Dev.
Total		109	60.99	16.54
time	baseline	46	48.67	13.53
time	month 6	35	69.60	12.18
time	month 12	28	70.46	12.43

Table 9.14: SOFAS mean scores over time

SOFAS: Social and Occupational Functioning Scale

SOFAS scores at month 6 (mean=69.60) indicated considerably improved Occupational and Social Functioning although substantial impairments remained (Goldman *et al*., 1992).

A best subsets regression with all the independent variables and SOFAS score at month 12 as the dependent variable explained 56.5% of the variance with the following five predictors: Overall neurocognitive ability (MCCB Composite), Reasoning and Problem Solving (MCCB RPS), highest level of education (HLOE), positive drug screen anytime, and thought and perceptual disorder (PTI Total) as shown in table 9.15.

N=20	Regression Summary for Dependent Variable: SOFAS(M12) R^2= .679 Adjusted R^2= .565 F(5,14)=5.93 p< .003			
	b*	B	p-value	# times in best 20 models
Intercept		49.13	0.00	
MCCB_Comp	-0.91	-0.89	0.00	11
MCCB_RPS	0.64	0.73	0.01	15
HLOE	0.37	2.21	0.05	5
Drug screen anytime	0.37	8.96	0.04	3
PTI_Tot	-1.11	-8.29	0.00	20

b* = standard beta

Table 9.15: Predictors of SOFAS at month 12

MCCB Comp: Matrics Consensus Cognitive Battery composite score; MCCB RPS: Reasoning and Problem Solving; HLOE: highest level of education, PTI Tot: Perceptual Thinking Index total score.

The negative influence of MCCB Composite score (beta= -0.91) is clinically inconsistent with MCCB RPS (shown in table 9.15) and should therefore be interpreted with caution. The MCCB subscales have a multicolinear relationship and therefore should be in the same direction as the MCCB Composite score.

Of the significant predictors only PTI Total, MCCB RPS and MCCB Composite appeared frequently in the best 20 models depicted in see figure 9.16.

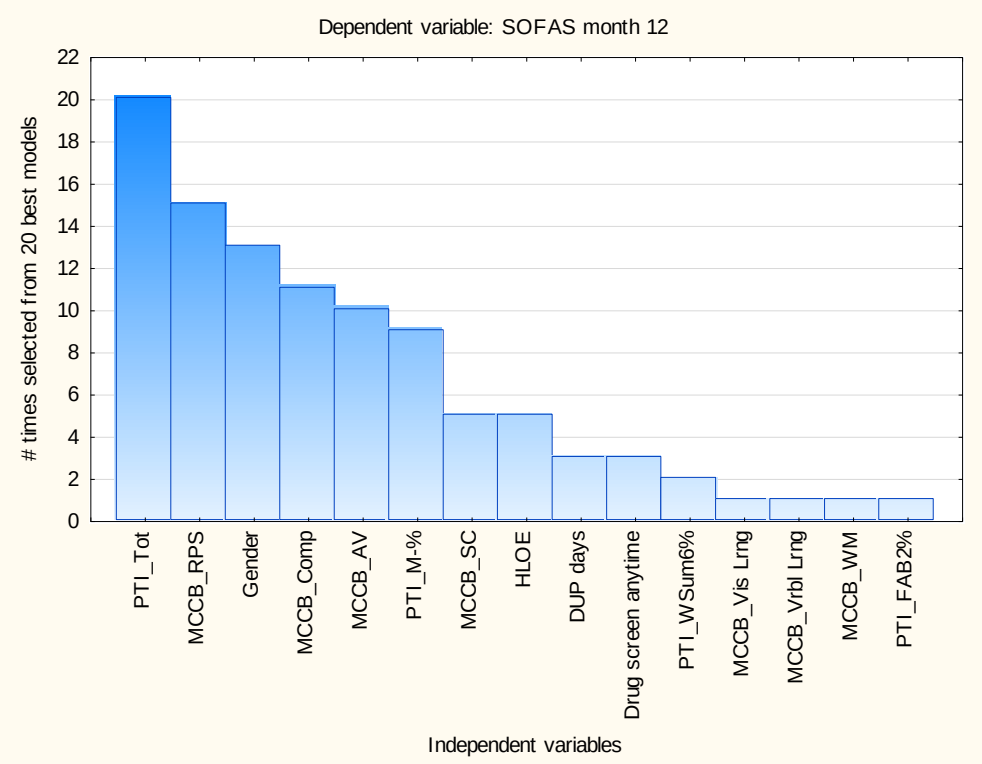

Figure 9.16: Predictors of SOFAS scores at month 12

SOFAS: Social and Occupational Functioning Scale; PTI Tot: Perceptual Thinking Index total score; MCCB RPS: Reasoning and Problem Solving, MCCB Comp: Matrics Consensus Cognitive Battery composite score; MCCB AV: Attention/Vigilance; M- :% poor human form responses.

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When entering change scores (difference between baseline and month 6 scores) for PANSS Total and factor scores, MCCB Composite and subscale scores, and PTI Total and sub-category scores with all the independent variables in a best subsets regression, the predictive power increased (adjusted R^2=0.82, F(5,12)=16.83, p<0.01) compared to baseline predictors only (adjusted R^2=0.56, F(5,14)=5.93, p<0.01) (see table 9.16).

N=18	Regression Summary for Dependent Variable: SOFAS(M12) R^2= .875 Adjusted R^2= .823 F(5,12)=16.837 p<.01			
	b*	b	p-value	# times in best 20 models
Intercept		13.52	0.060	
MCCB_AV (M6-baseline)	0.80	1.06	0.00	20
MCCB_SoP (M6-baseline)	-0.52	-0.55	0.00	7
MCCB_WM (M6-baseline)	0.41	0.50	0.00	11
PANSS_E (M6-baseline)	0.39	1.16	0.00	8
PANSS_Total (M6-baseline)	-1.12	-1.21	0.00	17

Table 9.16: Change predictors of SOFAS score at month 12

SOFAS: Social and Occupational Functioning Scale; MCCB AV: Attention/Vigilance; MCCB SoP: Speed of Processing; MCCB WM: Working Memory; PANSS E: Excited factor; PANSS Total: Positive and Negative Syndrome Scale total score.

Improvement in Attention/Vigilance (increase from baseline to month 6 scores for MCCB A/V), improvement in Speed of Processing (increase from baseline to month 6 scores for MCCB SoP),

improvement in Working Memory (increase from baseline to month 6 scores for MCCB WM), improvement in PANSS Excited (decrease from baseline to month 6 scores for PANSS E) and improvement in symptom severity (decrease from baseline to month 6 scores for PANSS Total) explained 82.3% of the variance of SOFAS scores at month 12 shown as depicted in table 9.16.

The negative influence of MCCB SoP (b= -0.52) is clinically inconsistent with the positive influence of MCCB A/V and MCCB WM, therefore the predictive validity of MCCB SoP should be interpreted with caution in this regression analysis. The MCCB subscales have a multicolinear relationship and therefore should be in the same direction as the MCCB Composite score.

All the significant predictors also appeared in a best 20 model as shown in figure 9.17.

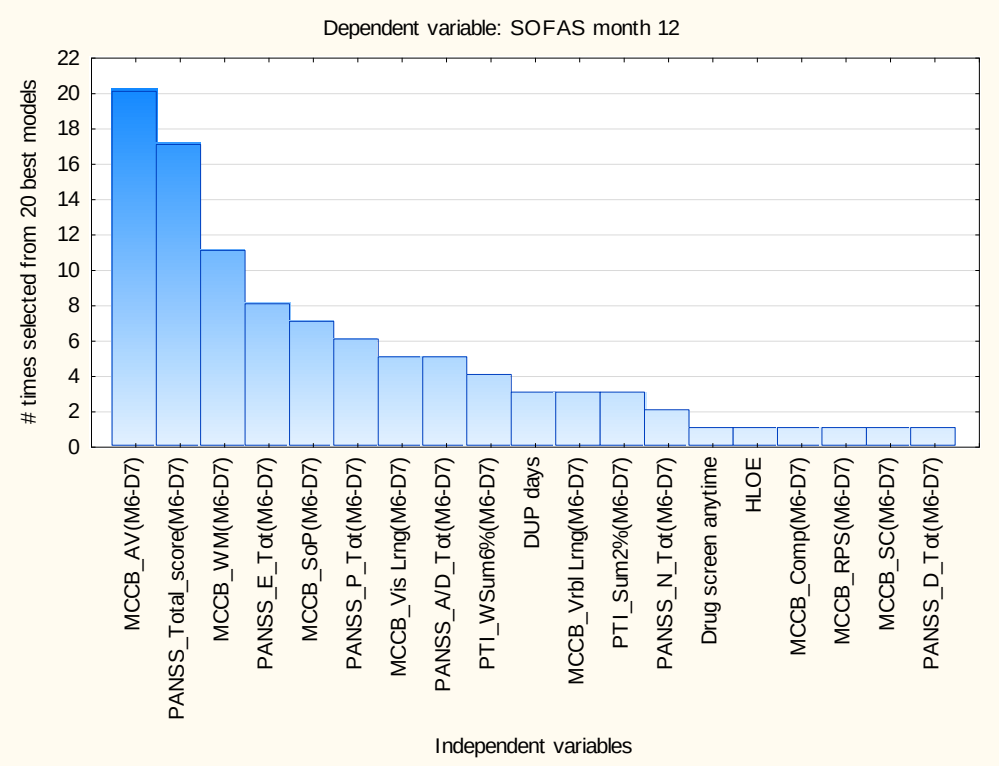

Figure 9.17: Change predictors of SOFAS at month 12

SOFAS: Social and Occupational Functioning Scale; MCCB AV: Attention/Vigilance; PANSS Total: Positive and Negative Syndrome Scale total score; MCCB WM: Working Memory; PANSS E: Excited factor'MCCB SoP: Speed of Processing; PANSS P: Positive factor

Improvement in Quality of Life

Quality of Life (WHOQOL) transformed scores improved in all four domains from baseline to month 12 as shown in table 9.17.

Effect	Descriptive Statistics: WHOQOL					
	Level of Factor	N	Physical Mean	Psychological Mean	Social Mean	Environment Mean
Total		108	49.33	54.13	52.24	54.00
time	Baseline	42	46.91	53.24	47.33	48.06
time	month 6	35	49.74	53.34	56.00	57.97
time	month 12	28	52.71	56.57	55.42	58.60

Table 9.17: WHOQOL mean transformed scores over time

WHOQOL: World Health Organization Quality of Life.

Most of the improvement occurred between baseline and month 6 with regards to WHOQOL Social (LSD p=0.03) and WHOQOL Environment (LSD p<0.01) depicted in table 9.18.

Comparisons	LSD test; variables: Domain Social (a) Effect: time			
	1st (a) Mean	2nd (a) Mean	Mean Differ.	p
{1}-{2}	baseline	month 6	-8.97	0.03
{1}-{3}	baseline	month 12	-5.82	0.20
{2}-{3}	month 6	month 12	3.15	0.50
Comparisons	Domain Environment (b)			
	1st (b) Mean	2nd (b) Mean	Mean Differ.	p
{1}-{2}	Baseline	month 6	-9.31	0.00
{1}-{3}	Baseline	month 12	-9.45	0.01
{2}-{3}	month 6	month 12	-0.14	0.97

Table 9.18: LSD p-values for WHOQOL Social and Environment

WHOQOL: World Health Organization Quality of Life.

At month 12 the four mean transformed domain scores ranged from 55.42 to 58.60 (shown in table 9.17), which falls at least one standard deviation below the mean for the reference group (Bergner *et al.*, 1981).

A best subsets regression with all the independent variables and averaged WHOQOL 4 domain scores at month 12 as the dependent variable, identified Verbal Learning (MCCB Verbal Learning: b= -0.72, p<0.01), HLOE (b=0.63, p<0.01), positive drug screen (b=0.74, p<0.01), Good Form Perception to Whole and Large Detail (WDA%: b=0.91, p<0.01) and Deviant Verbalizations and Illogical Thinking (WSum6%: b=0.37, p=0.02) as significant predictors accounting for 69.4% of the variance in WHOQOL at month 12 as depicted in table 9.19.

N=20	Regression Summary for Dependent Variable: WHOQOL domain average (M12) R^2= .775 Adjusted R^2= .694 F(5,14)=9.65 p<.01			
	b*	b	p-value	# times in best 20 models
Intercept		-20.43	0.35	
MCCB_Vrbl Lrng	-0.72	-2.11	0.00	19
HLOE	0.63	6.58	0.00	20
Drug screen anytime	0.74	30.66	0.00	18
WDA%	0.91	1.02	0.00	16
WSum6%	0.37	0.16	0.02	3

b* = standard beta

Table 9.19: Predictors of averaged WHOQOL scores at month12

WHOQOL: World Health Organization Quality of Life; MCCB Vrb Lrng: Verbal Learning; HLOE: highest level of education; WDA: % good form responses to whole and large detail; WSum6: % deviant verbalizations and illogical thinking.

Of all the predictors ($p<0.05$) only highest level of education (HLOE, b=0.63) and Good Form Perception to Whole and Large Detail, WDA%, b=0.91) had an influence on the variance in the direction anticipated.

The predictive power did not increase when entering change scores (difference between baseline and month 6 for: PANSS Total and factor scores, MCCB Composite and subscale scores, and PTI Total and sub-category scores) with all the independent variables in a best subsets regression (adjusted R^2=.67, $F(5,12)=8.20$, $p<0.01$) compared to baseline measures only (adjusted R^2=.69, $F(5,14)=9.65$, $p<0.01$) (depicted in table 9.20).

N=18	Regression Summary for Dependent Variable: Domain average WHOQOL(M12) R^2= .773 Adjusted R^2= .679 F(5,12)=8.20 p<0.01			
	b*	b	p-value	# times in best 20 models
Intercept		-52.42	0.02	
Age	0.44	1.29	0.01	6
HLOE	0.49	4.99	0.00	11
MCCB_Vrbl Lrng (M6-baseline)	0.51	1.03	0.00	16
M-% (M6-baseline)	0.89	5.74	0.00	14
PANSS_D (M6-baseline)	-0.34	-2.13	0.04	2

*b= standard beta

Table 9.20: Change predictors of WHOQOL scores at month 12

WHOQOL: World Health Organization Quality of Life; HLOE: highest level of education; MCCB Vrbl Lrng: Verbal Learning; M- :% poor human form responses; PANSS D: Disorganization factor.

All the change predictors were significant (p<0.05) and revealed clinically congruent beta values: Age (b=0.44), HLOE (b=0.49), improvement in Verbal Learning (b=0.51), and improvement in M- % (b=0.89), except for PANSS D (b= -0.34) which is clinically unanticipated.

The predictive validity of improvement in Poor Human Form Perception (M-%) should be interpreted with caution due to the small variance in mean differences over time (refer to Table 9.12, page 272).

Of the significant predictors the following variables appeared more frequently in the best 20 models: improvement in MCCB Verbal Learning, improvement in M- %, and HLOE as depicted in figure 9.18.

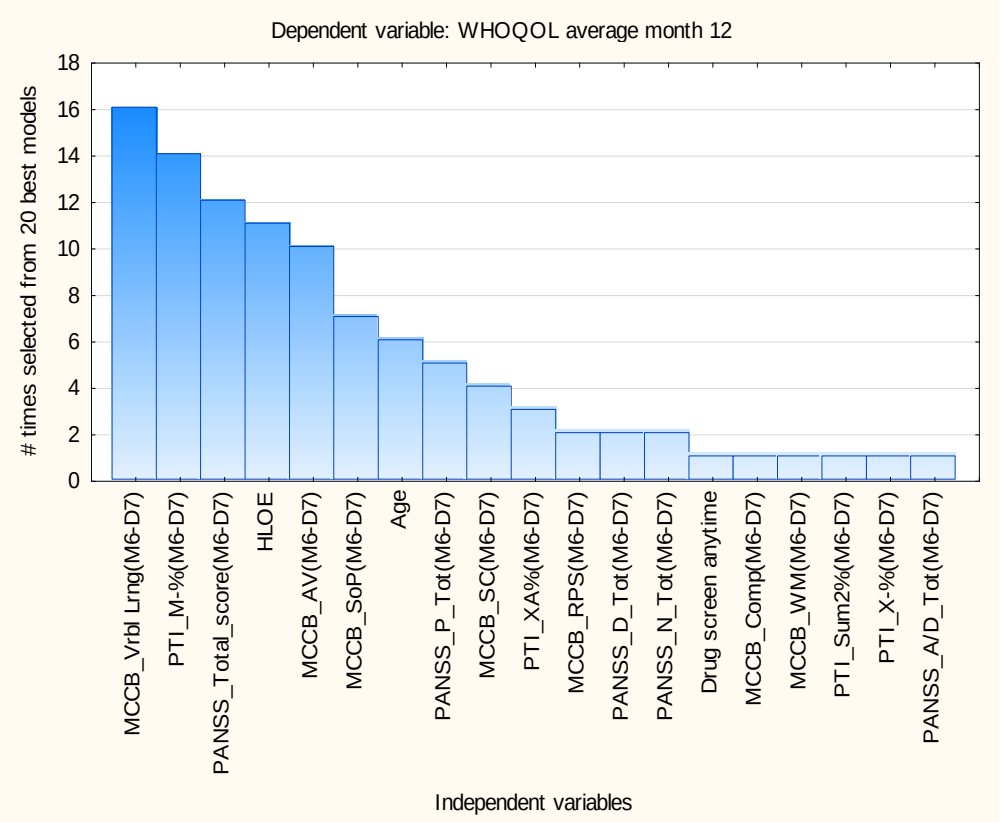

Figure 9.18: Change predictors of average WHOQOL scores at month 12

WHOQOL: World Health Organization Quality of Life; MCCB Vrbl Lrng: Verbal Learning; M- :% poor human form responses; PANSS Total: Positive and Negative Syndrome scale total score; HLOE: highest level of eduction; MCCB: AV: Attention/Vigilance; MCCB SoP: Speed of Processing

Remission status

A total of 47.6% of the patients achieved symptom remission when using the criteria of the Remission in Schizophrenia Working Group (Andreasen *et al.*, 2005).

A general discriminant analysis revealed that duration of untreated psychosis (DUP, Wilks F=5.40, p=0.02) and Fabulised and Implausible Thinking (FAB2%, Wilks F=5.96, p=0.02) predicted Remission Status at a 95% confidence interval level shown in table 9.21.

	Multivariate Tests of Significance: Remission Status			
Effect	Test	Value	F	p
Intercept	Wilks	0.75	7.03	0.01
MCCB_Vrbl Lrng	Wilks	0.93	1.44	0.24
Age	Wilks	0.88	2.92	0.10
Gender	Wilks	0.91	2.08	0.16
DUP days	Wilks	0.80	5.40	0.02
FAB2%	Wilks	0.78	5.96	0.02

Table 9.21: Predictors of Remission Status

MCCB Vrbl Lrng: Verbal Learning; DUP: duration of untreated psychosis; FAB2: % fabulised and implausible thinking.

The two significant predictors (DUP and FAB2%) also appeared in the best 20 models as depicted in figure 9.19.

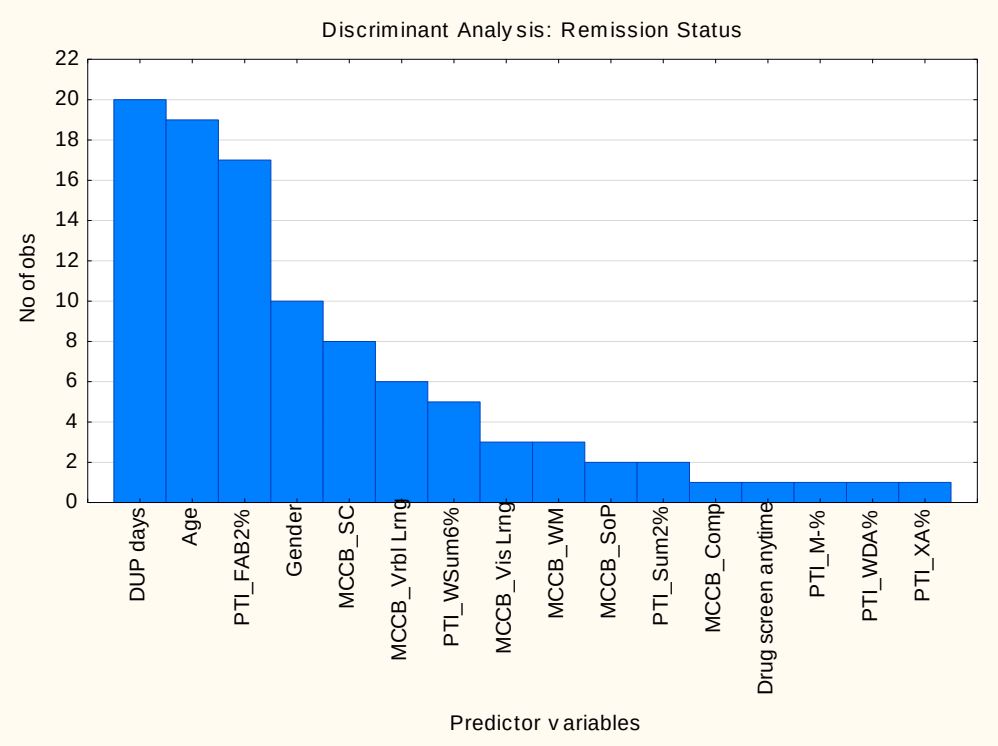

Figure 9.19: Predictors of Remission Status

DUP: duration of untreated psychosis; FAB2: % fabulised and implausible thinking; MCCB SC: Social Cognition; MCCB Vrbl Lrng: Verbal Learning; WSum6: % deviant verbalizations and illogical thinking.

General discriminant analyses of Remission Status with change variables (difference between baseline and month 6 for PANSS Total and factor scores, MCCB Composite and subscale score, and PTI Total and sub-category scores) with all the independent variables strengthened the predictive power with the strongest predictor (improvement in PANSS Total: Wilks F=31.67, p<0.01) as depicted in table 9.22).

Effect: Change scores	Multivariate Tests of Significance: Remission status			
	Test	Value	F	P
Intercept	Wilks	0.356	32.46	0.00
Age	Wilks	0.73	6.53	0.01
MCCB_AV (M6-baseline)	Wilks	0.74	6.28	0.02
PANSS_E (M6-baseline)	Wilks	0.62	11.01	0.00
PANSS_Total (M6-baseline)	Wilks	0.36	31.67	0.00

Table 9.22: Change predictors of Remission Status

MCCB AV: Attention/Vigilance; PANSS E: Excited factor; PANSS Total: Positive and Negative Syndrome Scale total score.

Improvement in PANSS Excited factor (Wilks F=11.01), improvement in MCCB A/V (Wilks F=6.26) and Age (WIlks F=6.53) were also significant predictors of Remission Status.

Of the significant change predictors only MCCB A/V and PANSS Total appeared more frequently in the best 20 models (depicted in figure 9.20).

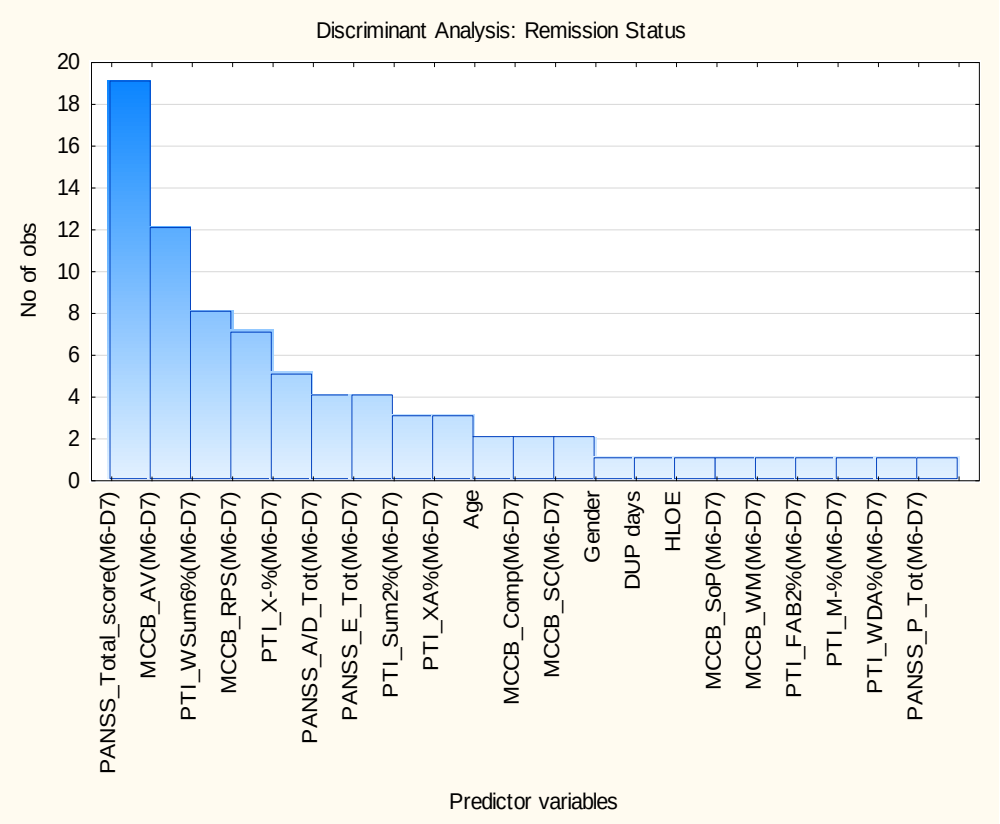

Figure 9.20: Change predictors of Remission Status

PANSS Total: Positive and Negative Syndrome Scale total score; MCCB AV: Attention/Vigilance; WSum6: % deviant verbalizations and illogical thinking; MCCB RPS: Reasoning and Problem Solving; X- : % poor form responses.

Remission Status appears to be correctly predicted by improvement in PANSS Total and Attention/Vigilance from baseline to month 6.

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CHAPTER 10:

DISCUSSION

In this chapter the main findings pertaining to impairments in neurocognitive performance and thought and perceptual disturbances, their significance and course after treatment, their underlying associations, and their relationships to symptoms and outcome measures are discussed.

GENERAL

Patient demographics

The gender distribution of the cohort was skewed with the majority (81%) represented by male patients. This is not unlike other first-episode cohorts, and is consistent with epidemiological studies that have found that the onset of schizophrenia for males is typically before the age of 25, whereas the onset for females usually peaks later, typically after age 35 (Häfner *et al.*, 1998; Sadock & Sadock, 2007). The mean age of this FEP cohort was 25 years with 25% lying between age 16 and 20 years. Although schizophrenia can have its onset at any age, the neurodevelopmental model postulates that the first psychotic "break", which marks the clinical onset of the disease, usually occurs in late puberty or early adulthood (Piper *et al.*, 2012).

The age distribution of this FEP cohort supports the neurodevelopmental model of delayed disease onset during the critical period of brain maturation in adolescence/early adulthood. The mean age of the cohort is, however, not an accurate reflection of the age at the time of first psychotic episode. Considering the mean DUP of 237 days, the age at FEP will be slightly lower than the reported age distribution.

There were no significant gender differences on baseline measures of symptom severity, neurocognitive impairment, and thought disorder. However, older patients tended to do better on composite neurocognitive scores, as well as on measures of Attention/Vigilance and Working Memory. This finding contradicts that of other studies reporting an inverse correlation between neurocognition as measured by the MCCB and age. A cross-sectional study by Rajji *et al.* (2013), with 235 stable schizophrenia patients and 333 healthy controls, found poorer performances on most of the MCCB subtests in patients and healthy controls who were of older age. The co-norming of the MCCB on 300 U.S citizens (Nuechterlein & Green, 2006) found similar aging effects on all 7 neurocognitive domains. However, it is important to note that these studies were conducted in older, chronic schizophrenia samples.

The positive correlation between age and neurocognitive ability in this FEP cohort may point to more impairment in younger patients with schizophrenia. Although this finding cannot be stated unequivocally, it mirrors previous studies of early-onset psychosis that have found significant impairments in social relations (Hollis, 1995), language and motor development (Nicholson *et al.*, 2000) and lower IQ (Reichenberg *et al.*, 2005; Asarnow *et al.*, 1994). Older age may also be associated with a higher educational level obtained by patients in this cohort, which generally has a curvilinear relation to IQ and measures of neurocognitive ability. However, educational level did not correlate with measures of neurocognitive ability or degree of symptoms in this study, therefore age may be considered an independent factor co-varying with neurocognitive ability.

Significant ethnic differences were found on neurocognitive measures of Reasoning and Problem Solving; and Verbal Learning that favoured Caucasian patients in comparison to African and ethnic groups of mixed origin. The ethnic spread was representative of the catchment area with the majority of patients from mixed (67%), African (26%) and Caucasian (7%) origin. The significant differences found between ethnic groups on neurocognitive measures should be interpreted with caution due to the small number of Caucasian patients in this cohort. Also, socio-economic factors and educational inequalities are likely to have played a role here. The possible effect

of ethnicity on MCCB scores should be replicated with further studies on patient and non-patient samples in a South African context.

There were no significant differences between ethnic groups on Rorschach measures of thought disorder. Critics of the Rorschach test have questioned its applicability to ethnic groups other than the original RCS United States normative sample (Wood & Lilienfield, 1999) and its use in non-American countries (Weiner, 2001). However, the results from this study render support to literature favouring the cross-cultural use of the Rorschach without adjusting the RCS (Meyer & Archer, 2001; Viglione & Hilsenroth, 2001). In a study comparing 188 RCS variables between European Americans, African Americans, and non-European Americans, no evidence of cultural bias was found after controlling for relevant demographic factors (Meyer, 2002).

Of all the relevant demographic variables, only educational level was identified as a strong predictor of treatment outcome at month 12. However, no significant correlations were found between educational level and baseline measures of neurocognition and symptoms. It can therefore be concluded that FEP patients had significant impairment at baseline regardless of educational level, but patients with a higher education had a better response to treatment.

Extrapolations between clinical variables and demographic factors to the broader schizophrenia population should however be scrutinized carefully because of the small sample size which may introduce selection bias if the demographic factors are not representative of the whole population.

Duration of untreated psychosis

There was a significant correlation between DUP and neurocognitive measures (Attention/Vigilance, Reasoning and Problem Solving, Speed of Processing). DUP was also found to be a predictor of Remission Status. These findings would seem to underscore the neurotoxic concept of longer DUP leading to progression of underlying neuropathologies and poorer treatment response (Lieberman *et al.*, 2001; Perkins *et al.*, 2005). However, the results from this study did not fully support the association between longer DUP and more severe and persistent symptoms documented elsewhere (Loebel *et al.*, 1992), as DUP was not significantly correlated with changes in PANSS scores.

Use of ilicit drugs

Substance use is a risk factor for FEP and has been associated with poorer outcome, treatment non-adherence and higher rates of relapse (Tarricone *et al.*, 2014). Its influence on the course of FEP

and neurocognition however remains unclear. The majority of studies reported better neurocognitive performances in cannabis using patients compared to non-users (Rabin *et al.*, 2011; Ferraro *et al.*, 2013) and fewer brain abnormalities (Cunha *et al.*, 2013) in FEP. Other studies have reported poorer neurocognitive performance (Mata *et al.*, 2008) or no difference between cannabis using patients and non-using patients (Sevy *et al.*, 2007).

This study did not find any differences between substance using patients and non-users on neurocognitive measures or symptom severity. Substance use also did not predict outcome in terms of symptom severity or general functioning after 12 months of treatment. However, the low percentage of illegal substance using patients in our sample is much lower than what has been documented elsewhere (Barnes *et al.,* 2006) which could explain the absence of significant group differences.

At baseline, 9% of patients used illegal substances with the majority of patients using cannabis, followed by a smaller number using methamphetamine. Longitudinally the incidence of substance use increased to 19% over 12 months. Ongoing substance use was identified as one of the main contributors leading to the patient attrition rate (38%): a third of the patients who were lost to the study could be directly or indirectly related to ongoing substance use. These results confirm the use of substances in FEP as an

independent risk factor, leading to inter alia treatment non-adherence. Further studies investigating the relapse rate of patients who dropped out of the study due to ongoing substance use will add valuable data on the course of schizophrenia in defaulting substance-abusing patients.

Cannabis is the most commonly used drug among schizophrenia patients with a lifetime use reported to be as high as 64% (Barnes *et al.*, 2006). The catchment area of the cohort is annexed within the geographical boundaries of the Western Cape. The South African Community Epidemiology Network on Drug Use (Dada *et al.*, 2011) reported methamphetamine as the primary drug of abuse in 8407 treatment admissions in the Western Cape, followed by cannabis as the second highest ranking drug being used. In patients under the age of 20 years, the prevalence of methamphetamine and cannabis was almost equal. The results of this study confirm the preference for cannabis use among FEP patients, but the reported prevalence rate might be an underrepresentation of real world substance use for the area. Also, it may be that the drug-screening assay was more sensitive to detecting cannabis than methamphetamine.

NEUROCOGNITION

FEP patients scored 1-2 standard deviations below the U.S. community age/gender corrected norm (Nuechterlein & Green, 2006) on all the MCCB neurocognitive domains. The MCCB Composite mean T-score of 15.48±15,84 at baseline, which is a more robust measure of neurocognitive ability, was at least 3 standard deviations below the U.S.community population reference norm. These findings confirmed the presence of significant neurocognitive impairment in this cohort of FEP patients, which was generalized across neurocognitive domains.

Numerous other studies have found similar general neurocognitive deficits in schizophrenia patients with scores falling 1-2 standard deviations below the population norm (Holmen *et al.*, 2010; Rajji *et al.*, 2013; Dickinson *et al*., 2008). In stable schizophrenia outpatients, Keefe *et al.* (2011) found a mean MCCB Composite T-score of 26.7±12.4 and MCCB mean domain T-scores have been reported to range from 33.4 to 39.3 (Kern *et al.,* 2011). In a study of FEP, which is comparable to this study, Vesterager *et al.* (2012) reported a MCCB Composite mean T-score of 42.8±5.5, which is considerably higher than the neurocognitive scores found in this FEP cohort. The sample studied by Vesterager *et al.* (2012) had relatively fewer symptoms at baseline with a reported PANSS mean total score of 54.2±12.4. Furthermore, more than 89% of that sample had received

prior antipsychotic medication, which might explain why the patients achieved better neurocognitive performances at baseline and less severe symptoms as measured by the PANSS. A systematic review of 118 clinical trials found mean MCCB composite T-scores ranging from 20.8±8.5 to 31.0±12.6 (Keefe *et al.*, 2013). The majority of these studies included patient samples of older stabilized schizophrenia patients.

South African studies using the MCCB across patient and non-patient samples are still lacking, thereby making comparison to this study difficult. The only other South African study that could be traced documented neurocognitive deficits in FEP of similar severity to this study, with MCCB domain T-scores ranging from 12.4 to 31.9 (Schoeman, 2011).

Numerous studies have documented differentially impaired neurocognitive deficits in schizophrenia patient samples with impairment accentuated in executive function, WM, verbal memory, visual memory, attention/vigilance, speed of processing and social cognition (Barch & Smith, 2008; Reichenberg & Harvey, 2007; Savla *et al.*, 2012). In a systematic review of neurocognition in FEP patients, Aas *et al.* (2014) noted that differences exist between studies and within neurocognitive domains, also suggesting that neurocognitive impairment might be consolidated over the course of

the illness. In other FEP studies, verbal and visual memories have been found to be more impaired (Hovington *et al.*, 2013; Benoit *et al.*, 2014). Impairment in speed of processing has been found to be a core feature of FEP (Townsend *et al.*, 2001). Speed of processing and non-verbal WM deficits have also been identified as a risk factor for psychosis in an adolescent sample with psychotic symptoms (Kelleher *et al.*, 2012). The results of this study confirm the presence of marked impairments in attention/vigilance, speed of processing and WM deficits in FEP patients. Impairments in these neurocognitive domains were significantly greater than those found in verbal memory, visual memory, and reasoning-and-problem solving at baseline. This study offers the advantage of assessing schizophrenia spectrum psychosis without the confounding variables associated with chronicity. Therefore, it can be assumed that the neurocognitive impairments found at baseline are a reflection of underlying cerebral pathology and not the effect of treatment or institutionalism. The differentially severe impairments found in the neurocognitive domains of attention/vigilance, WM and speed of processing suggest the involvement of the prefrontal cortex (Ren *et al.,* 2013). These findings, coupled with age of illness onset documented elsewhere in this study, support the hypothesis of 'hypofrontality' and the neurodevelopmental model of disease pathogenesis.

This study did not assess general IQ, thereby making it difficult to determine whether the poor neurocognitive performance in this FEP cohort was a reflection of low IQ. The question of IQ and its co-variance with measures of neurocognitive ability has long been debated. Available literature has consistently indicated lower premorbid IQ and lower IQ after FEP schizophrenia when compared to healthy controls (Aas *et al.*, 2014). Longitudinally, a decline in IQ has been found in FEP and chronic schizophrenia patients, but not more than from the expected effect of aging (Kurtz, 2005). Several studies have found that neurocognitive impairments are related to IQ but also independent from IQ in terms of the magnitude of impairment across neurocognitive domains (Holmen *et al.*, 2010; Gray *et al.*, 2013). Further support for differential neurocognitive impairment in schizophrenia patients, over and above IQ, is documented by Hedman *et al.* (2013). In this meta-analytic study, schizophrenia patients show a relative lack of gain from a 'learning or practice effect' with repeated IQ measures when compared to healthy controls. It can therefore be assumed that the mean IQ will be lower in this patient cohort when compared to healthy controls, and that the degree of neurocognitive impairment will remain significant after controlling for IQ.

Social cognition has emerged as a key factor in schizophrenia research and has been found to be a strong predictor of functional outcome, and more specifically related to social outcome (Combs *et*

al., 2011; Vesterager *et al.*, 2012). In a study of FEP schizophrenia patients, Bliksted *et al.* (2014) found that social cognition explained 24% of the variance in real world functioning when entered with neurocognition, IQ, and clinical symptoms into principal component analysis. In our study, social cognition was measured by the Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT) (Mayer *et al.*, 2005). We found that social cognition, as measured by the MCCB, was not significantly related to clinical symptoms, other neurocognitive domains, or outcome in FEP patients. The validity of the measurement of social cognition in this cohort is questionable. Firstly, many patients had difficulty in following the test instructions and many test items were answered randomly. A similar difficulty has been encountered by Holmen *et al.* (2010), who used the MSCEIT with early-onset psychosis. Secondly, it is suggested that, in future, assessment tools should be used that limit the possible language and cultural barriers in the measurement of social cognition in a South African context. Also, other elements of social cognition such as perception of emotion, facial recognition and theory of mind, as co-primary MCCB measures, may render more promising findings in future FEP schizophrenia studies.

This study treated patients with a long acting, low dose flupenthixol decanoate depot, thereby assuring treatment adherence. The low-dosing strategy ensured minimal extrapyramidal symptoms and less cognitive interfering effects of concomitant anticholinergic

medication. Current data suggest improvement in neurocognition after antipsychotic dose reduction (Nielsen, 2011), which could explain significant neurocognitive gain in our FEP schizophrenia cohort. Improvement was significant across the neurocognitive domains with the exception of social cognition. Significant improvements in neurocognition after antipsychotic treatment has been documented elsewhere (Keefe *et al.*, 2006), but the cognitive enhancing effects of typical and atypical antipsychotic medication remains controversial (Bozikas & Andreou, 2011). Most of the improvement occurred within the first 6 months after treatment, whereafter a plateau was reached. Longitudinally, neurocognition was relatively stable between month 6 and month 12 with scores falling 2-3 standard deviations below the US population reference norm (Nuechterlein & Green, 2006). This would be in line with the 'static encephalopathy' view of schizophrenia and in support of numerous studies indicating stability of neurocognitive impairments after treatment in FEP schizophrenia (Bozikas & Andreou, 2011; Barder *et al.*, 2013).

Some of the improvement might be explained by a practice effect that is seen with repeat assessments of neurocognitive ability. In a systematic review of neurocognition in FEP, Bozikas & Andreou (2011) found that in most studies that included a healthy control group, improvement was of similar magnitude to improvement found in the patient group. Similarly, comparative effect sizes between FEP

patients (.35) and healthy controls (.33) have been found on neurocognitive testing after treatment with olanzapine and risperidone (Goldberg *et al.*, 2007). A few studies have found that patients benefit less from a practice effect compared to healthy controls (Bozikas & Andreou, 2011). The MCCB has the advantage of alternate forms for verbal memory, visual memory and, reasoning-and-problem solving, to minimize the practice effects associated with serial testing. The MCCB manual reports minimal practice effects across subtests with effect sizes ranging from .00 to .22 (Nuechterlein & Green, 2006). A small practice effect (.18) on the MCCB composite score was also confirmed by Keefe *et al.* (2011) in a 29-site antipsychotic trial of stable schizophrenia patients. Goldberg *et al.* (2010) in their literature review found that practice effects occurred even when alternate forms were used. It is therefore likely that although significant changes in neurocognitive scores were found, improvement cannot be stated unequivocally, due to unknown variance that could be accounted for by a practice and/or placebo effect. Further FEP studies including a matched healthy group are paramount to determine the magnitude of change, over and above observed practice effects.

THOUGHT AND PERCEPTUAL DISTURBANCE

A mild degree degree of perceptual and thought disorder was present in the patients at baseline with a mean PTI Total score of 2.16(±1.48). This is slightly below the psychosis threshold score of 3 or more, suggested by Dao & Prevatt (2006). Research using the PTI is scarce, despite its growing validity in the study of schizophrenia (Dao *et al.*, 2008). Studies have been mostly conducted on stable schizophrenia patients with PTI total scores ranging from 1.0 (Benedik *et al.*, 2013), to 1.7 (Dao & Prevatt, 2006), 1.94 (Ilonen *et al.*, 2010) and 2.95 (Dao *et al.*, 2008). These studies vary across the schizophrenia spectrum, inpatient and outpatient status, and duration of illness, treatment regimes, patient demographics, and so on. Few studies have used the PTI longitudinally in FEP schizophrenia. The only other FEP study that could be traced that is comparable to our study, found a mean PTI total score of .82 at baseline (Rosenbaum *et al.*, 2012). This low PTI total score found in a Danish FEP schizophrenia population (N=34) may arguably be a reflection of the effect of antipsychotic medication or raised Lambda scores (L=1.02; F%=50) during an acute psychotic state. A high Lambda, or 'guardedness' in Rorschach responses, is commonly associated with psychosis, which may result in impoverished Rorschach protocols (Dao & Prevatt, 2006). However, in our study we found raised Lambda scores of greater magnitude at baseline than the Danish study (L=2.28; F%=54.5). The Danish study followed treatment with a low dose antipsychotic and baseline Rorschach assessments took

place within 2 weeks after treatment, similar to our study. A possible explanation for the failure of the Danish study to find significant elevations in Rorschach variables reflecting perceptual and thought disturbances, were the inclusion of protocols with less than 14 responses. These might invalidate the results (Exner, 1993). Rorschach protocols with higher response frequency are generally known to result in more manifestations of perceptual and thought disturbances (Lilienfeld *et al.*, 2000).

The variables comprising the Rorschach PTI, measure two dimensions: perceptual accuracy (X-%, XA%, WDA%, M-%) and manifestations of thought disorder or illogical reasoning (Sum2, FAB2, WSum6) (Smith *et al.*, 2001). In our study the perceptual accuracy scores contributed mostly to a raised PTI Total score when measured against the threshold for psychosis (Smith *et al.*, 2001). Visual-perceptual deficits have been described elsewhere in schizophrenia research, with numerous studies indicating abnormalities in visual scanning and eye movements (Minassian *et al.*, 2005), visual form recognition (Gabrovska *et al.*, 2003), and figure-ground perception (Malaspina *et al.*, 2004). Kimhy *et al.* (2007) found that good visual form perception as measured by the Rorschach (XA%) was decreased in the clinical high risk group for psychosis and the decrease in XA% was found to be relatively stable in the FEP schizophrenia group (duration of illness < 2 years). In a recent study by Ilonen *et al.* (2010) similar results were found in

adolescents at high risk for psychosis with a mean XA%(.71), WDA%(.74) and X-%(.28). This is slightly lower than the degree of perceptual inaccuracy we found at baseline, with a mean XA%(.60), WDA%(.62) and X-%(.38). Results from our study confirmed the elevation of poor form perception in FEP schizophrenia.

The relative stability of thought disorder has been documented in previous research using a variety of rating scales and indices across schizophrenia samples (Docherty *et al.*, 2003; Maeda *et al.*, 2007). Antipsychotic treatment has been found to have an ameliorating effect on more severe forms of thought disorder during acute phases of the illness, with the presence of residual thought pathology evident after treatment (Marengo & Harrow, 1997; Spohn *et al.*, 1986) and some improvement found in FEP patients (Goldstein *et al.*, 2002). Research on the temporal development and stability of perceptual and thought disturbances in schizophrenia as measured by the Rorschach PTI is limited. In our study we found significant improvement in perceptual and thought disturbances over time with thought disorder (Sum2, FAB2, WSum6) improving relatively early (first 6 months) and perceptual accuracy improving later (between month 6 and month 12). By month 12, residual impairment in perceptual accuracy scores XA%(.68), WDA%(.69), X-%(.28) was evident but manifestations of thought disorder (Sum2, FAB2, WSum6) were within normal limits when compared to the published norms (Exner, 2003). Our findings contradict the findings of a recent

FEP study that documented no improvement in Rorschach PTI variables after treatment (Rosenbaum *et al.*, 2012), and another study which showed worse form perception (X-%) in schizophrenia inpatients on antipsychotic or antidepressant treatment (Ilonen *et al.*, *2*010).

Our findings support the findings by Kimhy *et al.* (2007) that perceptual inaccuracies in schizophrenia reflect a trait factor and thought disturbances are manifestations of disease expression. We found that indices of thought disorder as measured by the PTI improved early (between baseline and month 6) and reached normal limits by month 12, whilst perceptual inaccuracies improved later (between month 6 and month 12) with residual perceptual impairment evident by month 12.

Future studies are needed to replicate our findings in larger FEP schizophrenia samples. Differential treatment effects on thought disorder should be investigated in comparative clinical trials.

RELATIONSHIPS BETWEEN SYMPTOMS, NEUROCOGNITION AND DISTURBANCES IN THOUGHT AND PERCEPTION

The neurocognitive correlates of schizophrenia symptoms and thought disorder *per se* have been studied extensively in schizophrenia research. To date, the temporal stability of neurocognitive, thought and perceptual disturbances have been widely documented, indicating both trait and state like features. The underlying association between neurocognitive deficits, thought and perceptual disturbances, and clinical symptoms over the course of treatment after FEP schizophrenia, however, remains unclear.

The majority of studies have found correlations with small to modest effect sizes between neurocognitive impairment and negative and disorganization symptoms, and little or no correlation with positive symptoms (O'Leary *et al.*, 2000; Kerns & Berenbaum, 2002; Keshavan *et al.*, 2008). Thought disorder has been correlated with executive, WM and semantic-lexical processing deficits (Kerns & Berenbaum, 2002; Roesch-Ely *et al.*, 2010) but its relation to general neurocognitive deficits remains unclear. Furthermore the correlation between measures of thought disorder and PANSS derived scores is controversial (Stirling *et al.*, 2006; Horn *et al.*, 2009; Palaniyappan, 2009). Research on Rorschach measures of thought disorder and the correlation with PANSS scores is scarce. Perry *et al.* (2009) found that perceptual inaccuracy (X-%) accounted for 35% of the

variance in positive symptoms as measured by the Scale for the Assessment of Positive Symptoms. The only other study we could trace documented improvement in PANSS symptoms after FEP, but no change in form perception (Rosenbaum *et al.*, 2012).

In our study we found significant inverse correlations ($p<0.05$) between the MCCB composite score and PANSS factor derived negative and disorganization symptoms. This finding supports current literature on the association between neurocognitive impairment and symptoms of schizophrenia. The association was evident across the neurocognitive domains of attention/vigilance, speed of processing, working memory, visual learning and verbal learning. This finding is similar to previous studies (Nielsen, 2011) using the MCCB with the exception of reasoning and problem solving, for which we found no significant correlation. We also found that perceptual accuracy (form perception) as measured by the Rorschach PTI was significantly correlated to overall neurocognition, speed of processing, visual learning and working memory ($p<0.01$), but perceptual accuracy did not share the correlation with negative and disorganization symptoms. The PTI subscales reflecting thought disturbances (WSum6, Sum2, FAB2) did not correlate with PANSS Disorganization factor scores, which is not suprising when scrutinizing the Disorganization factor items (G11, N7, P2, N5, G15, G10 and G5) which are considered to reflect more a cognitive factor (Good *et al*., 2004) and not formal thought disorder as much.

Perceptual accuracy was significantly correlated to PANSS factor derived positive symptoms (P1, G9, P3, P6, P5, P6, G12) with X-% (poor form perception) having an inverse correlation (Spearman= -0.42, p=0.02) and XA% (good form perception) a positive correlation (Spearman= 0.40, p=0.02). This finding is clinically counter intuitive and extremely unexpected since accurate form perception on the Rorschach is seen as a measure of reality testing (Benedik *et al.*, 2013). It is generally expected that acutely psychotic patients will have poor reality testing and more severe positive symptoms (delusions and hallucinations). Our findings indicate that patients with poor reality testing (X-%) had less severe positive symptoms during FEP and that patients with good form perception (XA% and WDA%) had more severe positve symptoms. Statistically it is possible that a third unknown variable had a shared variance, or that the PANSS positive factor reflects a heterogeneity of symptoms that potentially could contribute to differential correlations, which were not accounted for in our analysis. Of the PANSS positive factor derived items, only P1 (delusions) and P3 (hallucinations) can directly be translated into impaired reality testing. The other PANSS positive factor items reflect distortions in thought content (unusual, suspiciousness, grandiosity, lack of insight) and not so much distortions on a visual-perceptual level.

Another possible explanation is offered by previous Rorschach research, which indicated that high Lambda (ratio of pure form

responses compared to all responses) is a defensive compensatory mechanism often found in psychosis. This may mask the severity of thought and perceptual disturbances (Dao & Prevatt, 2006). However, no studies could be traced that measured Lambda longitudinally after FEP. We found that Lambda was raised at baseline with a mean of 2.28(±3.23) but after 6 months Lambda increased significantly to a mean of 3.44±5.05. Between month 6 and month 12 Lambda remained relatively stable. These findings suggest that defensive compensation against psychosis is manifest early after FEP and that further consolidation of defensiveness takes place in temporal association with clinical improvement. Furthermore, although Lambda was increased, we found more perceptual and thought disturbances at baseline as measured by the Rorschach PTI. Our results therefore do not support the notion that raised Lambda in acute psychosis will obscure the essential features of psychosis.

The results of our study support the findings of previous studies indicating a temporal association between perceptual accuracy (form perception) and neurocognitive impairment. Improvement in symptoms co-varied with improvement in neurocognition and thought and perceptual disturbance, with neurocognitive impairment and perceptual inaccuracy remaining relatively stable following treatment, which is independent from symptomatic improvement. This finding is consistent with previous studies indicating stability of neurocognitive impairment and perceptual inaccuracy (Ilonen *et al.*, 2010; Barder *et*

al., 2013). Perceptual inaccuracy, as measured by poor form perception on the Rorschach PTI, appears to reflect an underlying neurocognitive impairment, more specifically executive deficits (WM and speed of processing) and impaired visual learning. The association between thought disorder, visual scanning deficits and executive impairments have also been documented elsewhere (Minassian *et al.*, 2005; Stirling *et al.*, 2010). Our study investigated only visual perception as measured by the Rorschach PTI, but the multi-sensory model proposed by De Jong *et al.* (2013) deserves mentioning here in terms of its implication for future research. In this model schizophrenia is viewed as a severe form of disintegration between sensory input and neurocognitive processing. This opens the avenue for novel future studies.

The significance of perceptual accuracy *per se* needs to be qualified in our study since the inter-rater reliability for WSum6 (thought disorder) variables was fair (ICC=.55). This is in contrast to form perception which was good for F-(ICC=.74) to excellent for F+ (ICC=.80). This could affect the interpretation of results since the degree of thought disturbance, as measured by the Rorschach PTI, could be higher or lower than the documented findings in our study. Nevertheless, a clear trend was established with perceptual inaccuracy being relatively more stable than thought disturbances, regardless the degree thereof.

PREDICTORS OF OUTCOME

It is generally accepted that neurocognitive impairment and thought disorder in schizophrenia are related to functional and social outcomes (Bowie & Harvey, 2008; Nielsen, 2011). In particular, neurocognitive deficits in social cognition (Savla *et al.*, 2012; Combs *et al.*, 2011), working memory and executive function (O'Connor *et al.*, 2013; González-Ortega *et al.*, 2013), speed of processing (Kern *et al.*, 2011) and verbal memory (Bodnar *et al.*, 2008) have been associated with these outcomes. Furthermore, the persistence of thought disorder after FEP (Bearden *et al.*, 2011) and visual-perceptual deficits (Kimhy *et al.*, 2007) in schizophrenia patients have been found to be a robust predictor of poor outcomes.

In our study we found that only HLOE (beta= -0.54, $p<0.01$) predicted PANSS total score at month 12, when entering baseline measures and demographic variables into regression analysis. Longitudinally we found that HLOE and improvement from baseline to month 6 in Sum2 (severe deviant verbalizations and illogical thinking), PANSS excited factor and WDA% (good form perception) explained 78.3% of the variance in PANSS total score at month 12. In terms of clinical outcome we therefore conclude that higher educational level, degree of improvement in thought disorder, form perception and excited symptoms, are associated with better symptomatic response. A higher level of educational attainment is generally associated with

higher IQ, which potentially may serve as a neuroprotective factor in facilitating better treatment response.

In terms of functional and social outcomes we found that HLOE and change scores (improvement between baseline and month 6) for cognitive, perceptual and thought disorder measures were better predictors of outome. The amount of improvement in PANSS total and excited symptoms, working memory and attention/vigilance accounted for 82.3% of the variance in SOFAS at month 12.

Regression coefficients remained the same for WHOQoL at month 12, when entering the amount of improvement in symptoms, improvement in neurocognition and improvement in Rorschach PTI variables from baseline to month 6. This is probably due to the WHOQoL answers which reflect the patient's self assessment on aspects pertaining to physical, environmental, psychological and social health. We found little improvement over time on WHOQoL answers, which may be indicative of the broader societal constraints. The living conditions of the patients in the catchment area reflected the broader socio-economic landscape of South Africa, which is marked by conditions of inequality, poverty, unemployment, limited access to health services, etc. For this reason we believe the SOFAS to be a more robust measure of social and functional outcomes in schizophrenia. Future research could incorporate more appropriate

and sensitive outcome measures relevant to the South African context.

We also investigated predictors of remission status as defined by the Remission in Schizophrenia Working Group (Andreasen *et al.*, 2005). We found that DUP ($F=5.40$, $p<0.05$) and FAB2 ($F=5.96$, $p<0.05$) predicted remission status when entering baseline measures and demographic variables into regression analysis. The effect of predicting remission status was strengthened significantly when using

- the amount of improvement in PANSS total score from baseline to month 6 ($F=31.67$, $p<0.01$),
- improvement in excited symptoms from baseline to month 6 ($F=11.01$, $p<0.01$),
- improvement in attention/vigilance from baseline to month 6 ($F=6.28$, $p<0.05$)
- and age ($F=6.53$, $p<0.05$), as predictors.

Overall, we found evidence that the amount of improvement in neurocognitive, thought and perceptual disorder between baseline and month 6, were related to social and functional outcomes in FEP schizophrenia. Baseline neurocognitive deficits, thought or

perceptual disturbances did not predict symptomatic improvement at month 12.

Interestingly we found that the amount of improvement in symptoms from baseline to month 6, more specifically in PANSS total and excited symptoms, predicted outcomes in terms of social and occupational functioning as well as symptomatic improvement. Of note is the significance of excited symptoms *per se* (hostility, poor impulse control, excitement, uncooperativeness) and their relation to symptomatic and functional outcome. Similar associations have been documented elsewhere (Emsley *et al.*, 2006; Jerrell & Hrisko, 2013), but research to date investigating excited symptoms is scarce. Future studies could investigate the underpinnings of excited symptoms in schizophrenia and their relation to various outcome measures.

We furthermore found that improvement in neurocognition from baseline to month 6, in particular in attention/vigilance, was invariably related to social and occupational functioning and remission status. The same applied for WM and remission status. It is possible that attentional impairment is a function of increased excitability during the acute phase of FEP schizophrenia, hence the shared relation to outcome. Further studies are needed to investigate this relationship and its effect on treatment outcome correlates.

STRENGTHS AND LIMITATIONS

Most studies assessing neurocognition and thought disorder in schizophrenia have used cross-sectional designs with stabilized and chronic patient samples. This study offered the advantage of

- assessing FEP patients who were largely treatment naive at baseline,
- tracking changes over a course of 12 months after treatment with a low-dose single antipsychotic depot, thereby
- assuring treatment adherence and avoiding the confounding variables associated with chronicity and polypharmacy.

The use of standardized assessment instruments is an added advantage when documenting findings that are comparable to other studies and can be replicated in future research.

This is the first study to assess neurocognitive deficits and disturbances in thought and form perception longitudinally, in close temporal association, using the MCCB and Rorschach PTI in a FEP schizophrenia cohort. Assessing patients before treatment when they were floridly psychotic offered the opportunity to gage the salient neurocognitive, thought, perceptual and clinical features associated with acute illness.

Although careful planning was executed to ensure scientific rigor, several limitations were inherently part of this study:

1. The sample size was small (N=42), and was further diminished by a relatively high attrition rate. This reduced the statistical power and limited the statistical analyses of sub-units. This limitation was evident especially for identifying outcome predictors; very small numbers were encountered in some groups, e.g., number of females, non-remitters, etc.
2. We did not include a healthy control group. However, the MCCB and RCS are adequately normed on large European and American samples, albeit normative data in South Africa is still lacking. Furthermore, we do not know to what degree a practice effect could account for improvement in MCCB scores, over and above the minimal effect sizes documented in the MCCB standardization study. The inclusion of a control group would make analysis of a practice effect possible in comparable statistical units.
3. The inclusion of patients who were actively using illegal substances may have acted as a confounder. Yet, we found substance use had no effect and the number of patients who were using substances was very small.
4. The inclusion of a comparator group, either receiving a higher dose, or else oral flupenthixol, or a second generation antipsychotic would have strengthened our findings.

5. The duration of our study was sufficient to document longitudinal changes in FEP schizophrenia, yet extending the study over a 2-year period would have added support to our findings indicating relative stability of neurocognitive and perceptual disturbances.
6. Although the cross-cultural applications of the MCCB and RCS have been researched and found to be valid across cultures, more research on these instruments are needed on South African samples, to determine the effect of possible cultural bias.
7. We found that the MCCB was relatively insensitive to the measurement of social cognition in our cohort. The need exists to use more appropriate and culturally relevant instruments to assess aspects of social cognition. Similarly, the use of a self-report measure to assess quality of life may not accurately reflect social and functional outcomes.
8. The recruitment of patients from the spectrum of schizophrenia disorders encompasses a broad diagnostic entity that allows for important sub-group differences, which may have been missed in our study.
9. The use of the Rorschach PTI as a measure of thought disorder is debateable given it's low correlation with other measures of thought disorder, it's modest interrater reliability coefficients (refer to page 206) and the incongruent fit between thought processes and spoken language.

Despite these limitations, we believe that the findings of this study are significant and clinically relevant. We hope that the dissemination of our results will prompt future research to further investigate the relationships between thought and perceptual disorder, neurocognition and symptom expression in schizophrenia.

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CHAPTER 11:

CONCLUSION

Neurocognitive deficits and thought disorder have long been regarded as hallmark features in schizophrenia. Their relative stability has been widely accepted, but their response to treatment remains controversial. The development of more sensitive, standardized instruments such as the MCCB and Rorschach PTI have led to numerous studies in schizophrenia over the past two decades. The literature on schizophrenia has often been characterized by a division between neurocognitive science and "Rorschach science". The protagonists of the latter have generally relied on Rorschach nomenclature and interpretation without regard for the neurocognitive underpinnings of Rorschach measurement. In this study we examined the relatedness between neurocognitive deficits and disturbances in thought and form perception, using the MCCB and Rorschach PTI as primary co-measures. A cohort of FEP schizophrenia patients offered us the ideal opportunity to tap into the salient features of neurocognitive and thought and perceptual disturbances: their significance in FEP, their association, and trajectory over the course of treatment, and their significance as predictors of outcome.

In our study we found a significant degree of neurocognitive impairment across domains, thought and perceptual disturbances, and the observation of concordant elevation in symptoms in schizophrenia patients during pre-treatment. Improvement in thought disorder and improvement across neurocognitive domains occurred during the first 6 months after treatment, with improvement in form perception occurring later from month 6 to month 12. Improvement in symptoms had a positive influence on neurocognitive, thought and perceptual disturbances, but by month 12 residual neurocognitive and perceptual disturbances were still evident when symptom levels were approaching normal limits. We concluded that poor form perception may reflect an underlying neurocognitive deficit, and that symptoms and neurocognitive and perceptual deficits, although closely related, are separate in terms of treatment response. We confirmed the relative stability of neurocognitive and thought and perceptual disturbances, the correlation between neurocognitive and negative / disorganization symptoms, and the correlation between form perception and positive symptoms. We have also identified HLOE, improvement in form perception, improvement in neurocognition and improvement in excited symptoms as stronger predictors of outcome measures.

This study should hopefully stimulate further research into multimodal sensory-perceptual processes prior to, during and after onset of schizophrenia and its association with clinical, neurocognitive,

neurological and functional correlates. The use of the MCCB and Rorschach PTI were challenging in terms of it's administrability and tolerability during the acute stage of schizophrenia when patients were floridly psychotic. In some cases testing had to be stopped or postponed until the patient has 'settled' enough to be testable. During acute psychosis patients characteristically are more excitable with higher scores on hostility, poor impulse control and uncooperativeness. This may have had a negative impact on the test situation, level of motivation, and test performance.

With the advance of the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative (National Institutes of Health, 2013) we can hopefully move forward with the promise of more sensitive and accurate neurotechnologies that will assist us in deciphering some of the intricacies of brain function and disease expression in schizophrenia.

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Appendix A

Table 1 : Summary table for demographic variables

	Mean	Range	SD	P* MCCB	PTI	PANSS
Age, years	24	16-45	6.9	0.05	0.29	0.13
Gender						
Male, n (%)	34 (81%)			0.71	0.91	0.18
Females, n (%)	8 (19%)					
Ethnicity, n (%)						
Mixed	28 (67%)			0.51	0.82	0.41
African	11 (26%)					
Caucasian	3 (7%)					
Education, years	10.7	7-15	2.1	0.16	0.95	0.24
Diagnosis, n (%)						
Schizophreniform	22 (53%)					
Schizophrenia	19 (45%)					
Schizoaffective	1 (2%)					
DUP, days	237	8-1307	269	0.1	0.35	0.24
Substance use, n (%)	4 (9%)			0.73	0.68	0.11

P* = paired t-tests for continuous variables and Chi square tests for categorical variables
MCCB = MATRICS Cognitive Consensus Battery
PTI = Perceptual Thinking Index
PANSS = Positive and Negative Syndrome Scale

Table 2 : LSD means at each time point for MCCB, PTI and PANSS scores

	Baseline	Month 6	Month 12	P*	P**
MCCB Composite	15.5	27.3	26.3	<0.0001	0.7
A/V	26.3	35.5	36.7	<0.0001	0.5
SoP	22.7	31.8	31.2	<0.0001	0.9
VerbLrng	36.2	41.4	38.7	<0.01	0.7
VisLrng	32.5	39.8	38.2	<0.01	0.9
WM	25.8	37.0	36.5	<0.0001	0.8
RPS	33.6	40.2	39.6	<0.001	0.9
SC	26.8	31.3	31.9	0.05	0.4
PTI Total	2.2	1.7	1.3	<0.05	0.4
Lambda	2.2	3.4	3.5	<0.01	0.9
WSum6	59.8	36.2	14.9	<0.01	0.1
FAB2	0.48	0.00	0.11	<0.05	0.6
Sum2	6.2	2.5	1.5	<0.01	0.8
M-	2.5	1.0	1.2	0.07	0.9
XA	60.0	62.4	68.5	0.22	<0.05
WDA	62.6	64.7	69.1	0.19	0.2
X-	38.3	33.2	28.6	0.06	0.1
PANSS Total	89.1	48.2	44.2	<0.0001	0.2
PANSS P	23.1	7.6	5.0	<0.0001	<0.05
PANSS N	22.3	10.6	7.9	<0.0001	<0.05
PANSS D	21.3	8.9	6.5	<0.0001	<0.05
PANSS E	7.4	3.1	2.6	<0.0001	0.3
PANSS A/D	11.2	4.9	3.8	<0.0001	0.1

P* = p values for differences between baseline and month 6 scores
P** = p values for differences between month 6 and month 12 scores
MCCB = MATRICS Cognitive Consensus Battery
A/V = Attention / Vigilance
SoP = Speed of Processing
VerbLrng = Verbal Learning
Vis Lrng = Visual Learning
WM = Working Memory
RPS = Reasoning and Problem Solving
SC = Social Cognition
PTI = Perceptual Thinking Index
Lambda = ratio of pure form responses compared to all responses
WSum6 = sum of 6 weighted scores for Unusual Thinking and Illogical Combinations
FAB2 = Fabulized Thinking and Implausible Combinations
Sum2 = Deviant Verbalizations and Illogical Thinking
M- = Poor Human Form perception
XA = Good Form perception
WDA = Good Form perception to Whole and Large Detail
X- = Poor Form perception

PANSS = Positive and Negative Syndrome Scale
P = Positive factor
N = Negative factor
D = Disorganization factor
E = Excited factor
A/D = Anxiety / Depression factor

Acronyms

AIDS	Acquired Immunodeficiency Syndrome
BRAIN	Brain Research through Advancing Innovative Neurotechnologies
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CDI	Coping Deficit Index
CPT	Continuous Performance Tests
CSF	Cerebrospinal Fluid
DA	Dopamine
DEPI	Depression Index
DLPFC	Dorsolateral Prefrontal Cortex
DUP	Duration of Untreated Psychosis
EII	Ego Impairment Index
EPSE	Extraparydamil side effects
EUFEST	European First Episode Schizophrenia Trial
FD	Flupenthixol Depot
FEP	First Episode Psychosis
FGA	First Generation Agent
HIV	Human Immunodeficiency Virus
HLOE	Highest Level of Education
HPA	Hypothalamic-pituitary-adrenal axis
HRV	Human Representational variable
HVI	Hypervigilance Index
ICC	Intraclass Correlation Coefficients
ICV	Intracranial Volume
LNS	Letter-number-span test

MATRICS	Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB	MATRICS Consensus Cognitive Battery
MDN	Mediodorsal thalamic nucleus
MLD	Metachromatic leucodystrophy
MMPI	Minnesota Multiphasic Personality Index
NAA	N-acetylaspartate
NIMH	National Institute of Mental Health of the USA
OBS	Obsessive Style Index
OC	Observed Cases
OFC	Orbitofrontal Cortex
PANSS	Positive and Negative Syndrome Scale
PET	Positron Emission Tomography
PPI	Prepulse inhibition
PTI	Perceptual Thinking Index
rCBF	regional Cerebral Blood Flow
RCS	Rorschach Comprehensive System

Coding on the RCS

1. Location: W= whole response; D= common detail; Dd= infrequent detail S= use of white space response.
2. Determinants: F= pure form; M= human movement; FM= animal movement; m= inanimate movement; C= pure chromatic colour; CF= chromatic colour-form; FC= chromatic form-colour; Cn= chromatic colour naming; C'= pure achromatic colour; C'F= achromatic colour-form; FC'= achromatic form-colour; T= pure texture; TF= texture-form; FT= form-texture; V=pure vista; VF= vista-form; FV= form-vista; Y= pure diffuse shading; YF= undifferentiated shading-form; FY= undifferentiated form-shading; FD= form dimension; rF= reflection-form; Fr= form-reflection.

RCS Indices

1. Perceptual Thinking Index (PTI),
2. Depression Index (DEPI),
3. Coping Deficit Index (CDI),
4. Suicide Constellation (SCON),
5. Hypervigilance Index (HVI), and
6. Obsessive Style Index (OBS)

RIAP5	Rorschach Interpretation Assistance Program
RIM	Rorschach Inkblot Method
SCID-P	Structured Clinical Interview for DSM-IV disorders
SCON	Suicide Constellation
SCZI	Schizophrenia Index
SD	Standard Deviation
SGA	Second-generation agents
SOFAS	Social and Occupational Functioning Scale
STG	Superior temporal gyrus
TDI	Thought Disorder Index
TLC	The Scale for the Assessment of Thought, Language and Communication
TOL	Tower of London test
TMTA	Trail-making Test A
VBM	Voxel-based morphometry
VCFS	Velocardiofacial syndrome
WAIS	Wechsler Adult Intelligence Scale
WBV	Whole Brain Volume
WCST	Wisconsin Card Sorting Test
WHOQOL	World Health Organization Quality of Life
WM	Working Memory