Core Cognitive Impairments and their association with Symptomatology and Premorbid Adjustment in First-Episode psychosis

by

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Contributions of Authors

As the first author of both studies, I (Laura Béchard-Evans) made a significant contribution regarding the formulation of hypotheses, the research design, data collection, analysis as well as the writing of the project.

Dr. Ashok Malla has provided substantial contributions with regards to the research design, interpretation of findings and the structure of the manuscript contents and revisions.

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ABSTRACT

Background: The question whether certain cognitive domains in schizophrenia qualify as disproportionate/core impairments against a back-drop of generalized deficits remains unresolved. Investigating more homogeneous subgroups of patients may enhance our understanding of the exact nature of disproportionate deficits.

Method: One-hundred and twenty-one patients attending an early psychosis program completed a neuropsychological battery comprising of six cognitive domains and IQ. Symptom severity and pre-morbid adjustment were also assessed.

Results: Early psychosis patients with *high* levels of negative symptoms and "stable-poor" pre-morbid functioning have severe generalized cognitive impairment. Patients with *low* levels of negative symptoms and "stable-good" pre-morbid adjustment present with milder generalized impairments.

Conclusion: Contrary to our hypothesis, visual memory appears to be disproportionally impaired against a back-drop of severe generalized cognitive deficits in early psychosis patients. Patients who have a consistently poor (stable-poor) course pre-morbid adjustment and those with high levels of negative symptoms are more impaired.

RÉSUMÉ

Contexte: Les déficits cognitifs sont hétérogènes chez les schizophrènes. La question reliée à la présence de certains déficits cognitifs disproportionnés par rapport à un déficit généralisé reste non-résolue. L`étude de sous-groupes de patients plus homogènes au niveau de la sévérité des symptômes et du fonctionnement prémorbide pourrait éclairer notre compréhension entourant la nature exacte des déficits disproportionnés. **Méthode** : Cent-vingt et un patients suivis dans un programme de premier épisode psychotique ont complété une batterie neuropsychologique complète évaluant cinq domaines cognitifs et le QI global. La sévérité des symptômes et le fonctionnement prémorbide ont aussi été évalués. **Résultats :** Dans un échantillon hétérogène de premier épisode de psychose, les patients présentent des déficits cognitifs généralisés sévères. En classifiant les patients en sous-groupes, ceux avec de hauts niveaux de symptômes négatifs et un fonctionnement prémorbide «stable-pauvre » présentent des déficits cognitifs généralisés sévères. Les patients avec peu de symptômes négatifs et un fonctionnement prémorbide « stable-bon » démontrent des déficits généralisés plus modérés. **Conclusion:** Nos résultats indiquent la présence de sévères déficits cognitifs au niveau de la mémoire visuelle et de la vitesse de traitement de l`information chez les jeunes souffrant d`un premier épisode de psychose. De plus, il semble plus prononcés chez les patients avec un fonctionnement prémorbide «stable-pauvre ».

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CHAPTER 1

Background and Objectives

1.1. Neurocognition in Schizophrenia

Schizophrenia is a chronic and debilitating psychiatric illness with a median incidence of 15.2/100 000 persons (McGrath et al. 2008) and lifetime prevalence estimate of 3.3 per 1000 persons (Tandon et al. 2008). Diagnostic features of the illness consist primarily of symptoms such as hallucinations and delusions, also termed "positive" symptoms. In addition, individuals may experience "negative" symptoms which include loss of sense of pleasure, social withdrawal, impoverishment of thoughts and speech and flattening of affect. An eminent scientist by the name of Kraepelin (1919) (Kraepelin 1919) created the term *dementia praecox* (1896) to define the clinical manifestation of schizophrenia. When describing the disorder, Kraepelin emphasized the intellectual deterioration beginning in early adulthood that was linked to poor functional outcome in patients. In the early 20th century Bleuler coined the term *schizophrenia* (Bleuler 1911) to describe the illness. He agreed with Kraepelin that cognitive dysfunctions were an independent, core feature of the illness. Many years later these initial observations regarding cognitive impairments have become widely recognized leading to in depth investigations of this feature of the illness.

In the past 2 decades, research in the area of neuropsychology of schizophrenia has also been fuelled by findings implicating cognitive deficits as one of the important factors in determining outcome and quality of life (Green 1996, Green et al. 2000). In addition, the aim to "localize" impairments on neuropsychological tests to specific brain regions such as the frontal, temporal, hippocampal, parietal, striatal and cerebellar functions (Dickinson and Harvey 2009) has also stimulated research to understand the underlying characteristics of cognitive deficits.

Studies of neuropsychological impairments in schizophrenia have revealed that cognitive impairments are present during the first-episode (FEP) (Bilder et al. 2000, Mohamed et al. 1999) and remain stable throughout the course of the disorder (Heaton et al. 2001) supporting the model of cognitive deficits as primary and pathophysiologically related to schizophrenia (Bilder et al. 1992) and not secondary to acute psychotic symptoms.

Meta-analyses of cognitive impairments have generally shown that patients, both chronic and first-episode, are severely impaired and perform 1 to 2 standard deviations below healthy controls (Heinrichs and Zakzanis 1998, Mesholam-Gately et al. 2009). Furthermore, the cognitive profile of first-episode and chronic samples is characterized by substantial heterogeneity within a broad range of impairments including verbal memory, executive functions, attention and processing speed (Bilder et al. 2000, Hutton et al. 1998, Mohamed et al. 1999, Riley et al. 2000, Saykin et al. 1994). Nevertheless, the question whether certain "separable" core cognitive impairments can be differentiated from a diffuse/non-specific neuropsychological abnormality remains unresolved.

1.2. Generalized versus Disproportionate Cognitive Deficits in Schizophrenia

Some postulate that cognition in schizophrenia is characterized as a more generalized and diffuse deficit superimposed on smaller cognitive deficits that do not account for the larger deficit (Blanchard and Neale 1994, Braff et al. 1991, Dickinson et al. 2004, Goldberg et al. 1990, Hoff et al. 1992). In the largest quantitative review of cognitive impairments in schizophrenia up to date, Heinrichs & Zaksanis (1998) also concluded that "schizophrenia is characterized by a broadly based cognitive impairment, with varying degrees of deficit in all ability domains measured by standard clinical tests". In a more recent review of the literature, Reichenberg & Harvey (2007) concluded that "the impairment in general ability was as severe as that observed for more specific neuropsychological functions". Proponents of this view posit that between-groups performance deficit is better understood as a single, generalized deficit with smaller direct effects on selected cognitive domains. In addition, it is believed that the pattern of deficits reflects more diffuse dysfunctions in key systems rather than deterioration of specific brain regions.

Consistent with this view, a recent study by Dickinson et al. (2008) using a hierarchical six-factor model showed that approximately 63 % of the variance in overall cognitive performance was explained by one general factor. In addition, the analyses revealed direct diagnosis effects on verbal memory (14 % of the variance) and processing speed (9 % of the variance).

Taken together, these findings clearly reveal the existence of a generalized cognitive impairment in schizophrenia. However, some have suggested that cognition in schizophrenia is better characterized by the presence of as disproportionate cognitive impairment superimposed on a background of generalized impairment. To be qualified as disproportionate impairments, deficits need to be in excess of the averaged performance deficit across a range of other cognitive domains (Chapman and Chapman 1989). Indeed, establishing the selectivity of cognitive deficits

may facilitate the study of an association between specific cognitive impairments and brain regions implicated in schizophrenia (Toulopoulou et al. 2003).

The cognitive literature in schizophrenia has reported disproportionate impairments in almost all the cognitive processes with varying consistency and include verbal learning and memory (Albus et al. 1997, Censits et al. 1997, Saykin et al. 1991, Saykin et al. 1994), speeded visual-motor processing, attention/vigilance (Weickert et al. 2000), working memory (Gold et al. 1997) as well as executive functioning (Chan et al. 2006, Goldberg and Weinberger 1988, Hutton et al. 1998, Riley et al. 2000).

The inconsistencies regarding a generalized versus disproportionate cognitive deficits may, in part, be due to the interpretation of the findings by authors and to the lack of a reliable scheme for classifying deficits as "disproportionate". Nevertheless, the literature to date seems to point towards verbal learning/verbal memory (Cirillo and Seidman 2003, Heinrichs and Zakzanis 1998) and processing speed (Dickinson et al. 2004, Dickinson et al. 2007) as potentially the largest impairments which will be reviewed in the following sections (i.e. 1.3 and 1.4).

1.3. Verbal Memory as a Disproportionate Cognitive Impairment in Schizophrenia

In the beginning of the 20th century, the pioneers of schizophrenia research, Kraepelin (1919/1971) and Bleuler (1952), observed that memory was not affected in schizophrenia patients. Decades later, the use of standardized neuropsychological measurement has dramatically shifted this view and a large body of literature has revealed that verbal declarative memory is one of the largest impairment in medicated and non-medicated patients in chronic and first-episode samples (Aleman et al. 1999). More specifically, in a large meta-analysis of 70 studies investigating memory in schizophrenia, Aleman et al. (1999) found that the composite measure of long-term recall measures reflected the largest effect size (d = -1.21), although significant heterogeneity amongst studies was also observed. The authors concluded that the extent of the memory deficit was in accordance with a generalized rather than a disproportionate impairment. In Heinrichs & Zakzanis`s meta-analysis (1998) memory impairments were also the largest documented cognitive deficits amongst a broad range of neurocognitive impairments with an effect size of -1.41.

The severity of memory impairments has driven some to conclude that the deficits in schizophrenia resemble an amnesic syndrome (Paulsen et al. 1995). However, recent evidence has revealed that deficits are primarily found in encoding, which refers to the stage during which information is initially learned, rather than storage (Mohamed et al. 1999) thus refuting the hypothesis of amnesia (McKenna, 1990). Indeed, encoding deficits could be linked to other cognitive impairments such as processing speed. Brébion et al. (2007) (Brébion et al. 2007) found an association with cognitive speed slowing and effortful encoding processes in patients with schizophrenia

The specificity of verbal memory deficits in schizophrenia has also been reported consistently, including its presence even prior to onset of the illness in prodromal phase of schizophrenia

(Brewer et al. 2006, Lencz et al. 2006). More specifically, several studies have found that verbal memory impairments represent the largest deficit beyond a generalized deficit in at-risk individuals (Brewer et al. 2005, Eastvold et al. 2007, Hawkins et al. 2004). These findings have prompted some to conclude that verbal memory deficits are an important risk marker for the development of the illness and may indicate the presence of a prefrontal-hippocampal neuro-developmental abnormality (Lencz et al. 2006). These latter findings have led some to propose a genetic component to this deficit (Toulopoulou et al. 2003) and to investigate several candidate genes (Malhotra et al. 2002).

Despite these robust findings, some have proposed that memory impairments are secondary to other features such as attentional control processes or a consequence of slowing of processing speed rather than a primary feature of the illness (Brebion et al. 1997, Brebion et al. 1998).

Taken together, these findings clearly demonstrate that verbal memory impairments are perhaps the largest documented neurocognitive deficit in schizophrenia. Nevertheless, it remains difficult to conclude whether this deficit is disproportionate compared to other severely affected domains that may have received less attention from the neuropsychology literature such as processing speed.

1.4. Processing Speed as a Disproportionate Cognitive Impairment in Schizophrenia

Slowing of movements in schizophrenia was originally observed in the beginning of the 20th century and both Bleuler (1911) and Kraepelin (1919) described the phenomenon of psychomotor slowing. Although debate remains around the distinction between psychomotor slowing and processing speed, the latter term will be used herein and simply refers to speed with which different cognitive operations can be executed (Salthouse 1996). Indeed, evaluation of processing speed deficits results in an assessment of both cognitive and motor slowing and a clear distinction between the two may not be possible (Morrens et al. 2007). Others have categorized various measures of speed of information-processing into groups judged to reflect similar cognitive processes (Sheppard and Vernon 2008). In their large review of the literature examining the relationship between processing speed and intelligence in the general population, Sheppard et al. (2008) classified processing speed into the following groups: reaction time, general speed of information-processing, speed of short-term memory processing, speed of long-term memory retrieval tasks and inspection time tasks. Although their classification scheme was somewhat arbitrary, results revealed that diverse measures of mental speed were significantly correlated with intelligence measures while a trend was found for complex mental speed measures to be more highly correlated with intelligence. These results may indicate an overlap between these two processes which may be in part mediated by similar genetic factors.

In general, research on processing speed has been limited and scarce interest may have been, in part, due to the origins of processing speed which are based in distributed and complex neural network systems. In addition, the interest in finding cognition-enhancing drugs in schizophrenia has led research to focus on examining neuropsychological deficits resulting from specific brain structure abnormalities such as in the prefrontal and temporal brain regions. Finally, the difficulty

in linking processing speed deficits to specific brain systems and neural substrates may also have deterred research endeavours within this line of study (Antonova et al. 2004).

Nevertheless, the recent inclusion of processing speed as one of the 7 affected independent cognitive domains in schizophrenia by the National Institute of Mental Health initiative (Measurement and Treatment Research to Improve Cognition in Schizophrenia: MATRICS) has renewed interest in understanding the exact nature of this impairment. The MATRICS recognized processing speed as the first affected cognitive domain when ordering these domains from "relatively basic to higher level".

Neuropsychological tasks utilized to evaluate impairment in this domain include the Digit Symbol Coding Task (DST), a subtest of the Wechsler Adult Intelligence Scale (WAIS-III-R), the Trail Making Test-part A and the Stroop word and color naming conditions. Recent studies have focussed on investigating the performance on the Digit Symbol Coding Task, a simple 2-minute task involving scanning, matching, switching and writing operations, as performance is believed to represent a very general constraint on cognitive processing (Salthouse, 1996; Dickinson et al. 2007).

1.4.1. Studies investigating performance on the Digit Symbol Coding Task

In a recent meta-analysis investigating verbal fluency deficits, Henry & Crawford (2005) (Henry and Crawford 2005) found no evidence of this deficit being disproportionally impaired albeit effect sizes were in the moderate to large range according to Cohen`s (1988) criteria. Indeed, the effect size for the Digit Symbol was the largest effect size observed (g = -1.46) and the authors suggested that generalized deficits in schizophrenia may partially reflect cognitive slowing. A recent study by the Clinical Antipsychotic Trials of Intervention Effectiveness project (CATIE) found that performance on the Digit Symbol was the best predictor of overall performance accounting for 60 % of the variance in total scores from the larger cognitive test batteries (Keefe et al. 2005). However, patients in this trial were chronic with a mean of 14 years since first prescribed antipsychotic medication making difficult to exclude the possibility that neuroleptic use had a deleterious impact on task performance.

The large impairment on the Digit Symbol reported in previous studies and the fact that one of the most prominent reviews published to date in the field (Heinrichs & Zakzanis, 1998) did not include this task prompted Dickinson et al. (2007) to publish a meta-analysis on the magnitude of impairment on this coding task in schizophrenia. Findings revealed that the Digit-Symbol reflected the largest impairment documented in the schizophrenia neuropsychology literature with an effect size of -1.57. In addition, the effect was shown to be substantially larger than that of other processing speed tasks such as the Trail-Making part A (g = -0.88) and the Stroop word-reading condition (g = -0.97). Nevertheless, out of a total of 37 studies included in the meta-analysis less than 10 were conducted on first-episode psychosis samples thus preventing an adequate generalization of the results.

In a recent first-episode study by Rodriguez-Sanchez et al. (2007) (Rodriguez-Sanchez et al. 2007) examining processing speed, cognitive deficits found on a variety of measures disappeared

after controlling for the effect of performance on the Digit-Symbol. Again, important limitations such as the exclusion of patients with substance dependence and the inclusion of a considerable number of patients taking conventional anti-psychotic medications (33 %) impede the generalization of these findings to the first-episode psychosis population. Leeson et al. (2008) (Leeson et al. 2008) investigated performance on the Digit-Symbol in recent-onset schizophrenia and revealed that the Digit-Symbol was the only WAIS sub-test (out of 4 sub-tests) to significantly differ between patients and healthy controls. The authors, however, did not examine the disproportionate impairment on the Digit-Symbol relative to other measures of processing speed and cognitive domains which are shown to be highly impaired in schizophrenia.

Taken together, these findings clearly demonstrate that processing speed impairments as measured by the Digit-Symbol also reflects one of the largest deficits in schizophrenia and may even qualify as a cognitive endophenotype for the illness (Dickinson et al. 2007). In addition, the Digit Symbol has been regarded as one of the Wechsler`s least valid tests reflected by a consistently lower *g* loading compared to the other 10 Wechsler Adult Intelligence Scale-Revised (WAIS-R) subtests (Gignac and Vernon 2003). This appears to indicate that the Digit Symbol taps into distinct processes not assessed through a variety of other processing speed measures shown to be highly correlated with measures of intelligence (Sheppard et al. 2006). As such, more research is needed examining the deficit as measured by the Digit Symbol and whether this deficit qualifies as disproportionate processing speed impairment. Moreover, the heterogeneity of findings regarding disproportionate cognitive impairments raises the question whether impairments in excess of the averaged performance deficit across a range of other cognitive domains are only typical of certain subgroups of schizophrenia patients.

1.5. Disproportionate Impairments for a Sub-group of Patients?

A review of the literature indicates that cognitive dysfunctions in schizophrenia are heterogeneous in nature and vary substantially from one domain to another. Indeed, some neuropsychological functions in schizophrenia appear to be near-normal (Heinrichs and Awad 1993) while others seem disproportionally impaired (i.e. verbal memory, processing speed). Additionally, sample selection may explain a significant portion of the variance seen in cognitive deficits. For example, studies investigating the cognitive profiles of community-based first-episode samples such as the one used in the following two studies usually describe milder cognitive impairments (Townsend et al. 2001, Townsend and Norman 2004) compared to studies of consecutively admitted first-episode psychosis patients (Bilder et al. 2000, Hoff et al. 1992, Hutton et al. 1998, Mohamed et al. 1999). Indeed, it is expected that inpatient samples would present with a more severe course of illness compared to patients recruited as both outpatients (i.e. referred from family members, general practitioners, school psychologists, etc) and inpatients.

Nevertheless, several classification systems have been proposed to facilitate the study of cognitive impairments by defining more homogeneous subgroups of patients which in turn may lead to a more thorough understanding of the true nature of cognitive deficits. One of the most extensive categorization pertains to symptom profiles.

1.5.1. Symptom Profile and Cognitive Impairments

Although research has shown that cognitive impairments are not simply the result of symptomatology (Green et al. 2004), negative symptoms have been consistently associated with severity of cognitive deficits (Harvey et al. 2006) while positive symptoms have not (Brazo et al. 2002, Heydebrand et al. 2004, Malla et al. 2002).

Indeed, correlations between negative symptoms and cognitive deficits have generally been in the moderate range (i.e. r = 0.30) (Harvey *et al.* 2006). These findings seem consistent across age and course of illness, from the first-episode to a chronic state. This robust association has led some to suggest that the "negative" symptom profile in schizophrenia is in fact a cognitive impairment classification (Brazo et al. 2002, Mass et al. 2000). Conversely, others have concluded that the amount of variance explained is limited (Green and Walker 1985).

More in dept research investigating this relationship has shown associations between negative symptoms and specific neuropsychological deficits such as memory, attention, verbal fluency, psychomotor speed and executive function (Bilder et al. 1992, Heydebrand et al. 2004, Zakzanis 1998). A meta-analysis examining verbal memory in schizophrenia found that negative symptoms were the only significant variable affecting performance (Aleman et al. 1999). Another line of research has used various classification approaches to elucidate the cognitive heterogeneity seen in schizophrenia on the basis of predetermined symptom groups such as the deficit-non deficit dichotomization (Buchanan et al. 1994). The deficit syndrome is believed to represent a pathophysiologically distinct disease within schizophrenia characterized by enduring negative symptoms (Kirkpatrick et al. 2001). These patients are also thought to differ from non-deficit patients on various epidemiological, clinical and biological measures. Research shows that "deficit" patients perform more poorly than their "non-deficit" counterparts on most neuropsychological measures although findings are inconsistent regarding the existence of a

disproportionate cognitive impairment in the former group (Cohen et al. 2007). In their review of the neuropsychology of the deficit syndrome, Cohen et al. (2007) concluded that deficit patients did not "follow an obvious anatomically defined pattern of impairment".

Others have classified patients into distinct categories using a more dimensional perspective. Indeed, Liddle (1987) (Liddle 1987) proposed a three-syndrome classification model (i.e. psychomotor poverty, reality distortion and disorganisation) which is hypothesized to be related to functional deficits in specific areas of the brain (Liddle 1992). Studies investigating the heterogeneity of cognitive deficits in schizophrenia utilizing this dimensional approach to symptoms have shown that disorganization, in addition to negative symptoms, is significantly associated with neurocognitive impairments (Brazo et al. 2002, Goldstein et al. 1998). Conversely, others have failed to find support for this relationship but have found a link between reality distortion and neuropsychological functions (i.e. verbal memory) (Norman et al. 1997).

These findings point towards the unspecific nature of cognitive impairments within subclasses of patients with schizophrenia and demonstrate the need for more research investigating patterns of cognitive impairments across varying clinical profiles.

1.5.2. Premorbid Adjustment and Cognitive Impairments

Another approach to study the heterogeneity of schizophrenia is by identifying sub groups of patients based on course/progression of premorbid functioning expressed usually as "premorbid adjustment". Premorbid adjustment refers to functioning in a wide range of domains (i.e. school, work, relationship with peers) prior to the onset of psychosis in various life stages (i.e. childhood, early and late adolescence). Poorer pre-morbid adjustment during childhood and early adolescence has been linked to numerous clinical and demographic factors in both chronic and first-episode samples such as negative symptoms, male gender, earlier age of onset, lower remission rates and poorer response to treatment (Addington and Addington 1993, Gupta et al. 1995, Malla et al. 2002, Rund et al. 2004). A few studies have examined the relationship between pre-morbid adjustment and cognitive deficits but generally results seem to suggest an association between poorer pre-morbid adjustment and a wide range of cognitive impairments ranging from a generalized deficit (Rabinowitz et al. 2006) to more specific ones in attention/executive functions (Silverstein et al. 2002), verbal reasoning and concept formation (Addington & Addington, 1993), working memory (Larsen et al. 2004, Rund et al. 2004), verbal memory and fluency (Addington and Addington 2005) and visual memory span (Levitt et al. 1996).

Importantly, of the studies examining this association, very few have done so with first-episode psychosis samples (Addington & Addington, 2005; Larsen et al. 2004; Norman et al. 2005; Rabinowitz et al. 2006; Rund et al. 2004) thus preventing a “true” understanding of the relationship between pre-morbid adjustment and cognition. By applying the Haas & Sweeney method (1992) (Haas and Sweeney 1992) to categorize pre-morbid adjustment patterns (i.e. stable-poor, stable-good and deteriorating). Rabinowitz et al. (2006) examined performance on a global cognition measure across each of these subgroups in a large first-episode psychosis sample. Their results revealed that patients in the stable-poor group performed significantly

worse than patients in the stable-good group. In an FEP study by Addington & Addington (2005), results indicated that the only significant difference between the stable-good and deteriorating groups pertained to verbal memory and fluency. Scores on the other six cognitive domains (i.e. visual spatial ability, motor speed, visual memory, executive functions, attention and early information processing) did not significantly differ between groups and the authors concluded that cognition may not be one of the functions that clearly differentiate these patterns of pre-morbid functioning. The construct of pre-morbid adjustment has also been investigated in more detail using principal component analysis yielding two factors: one reflecting academic adjustment, the second reflecting social adjustment (Norman et al. 2005). Results revealed that patients in the stable-poor academic group demonstrated the worst cognitive functioning on most cognitive indices. When the classification was based on social adjustment, cognitive functioning did not differ across groups. Rund et al. (2004) also found that the general premorbid school functioning score was associated with IQ, a verbal learning measure and a working memory/fluency index while no association was found with premorbid social functioning.

The association between subgroups of premorbid adjustment and cognitive deficits in schizophrenia seems substantial; however, more research is needed to elucidate this relationship as findings appear quite non-specific. In addition, the question whether subgroups of patients with varying premorbid adjustment patterns present with a distinct cognitive profile remains unresolved. Indeed, all the studies examining this relationship included correlational analyses and analysis of variances (ANCOVA) which prevent a clear conclusion regarding the presence of a disproportionate cognitive impairment. Analyses using effect sizes are likely to provide a clearer picture regarding the magnitude of impairments across each cognitive domain.

1.6. Conceptual Bridge of Manuscript content

Taken together, previous research indicates that schizophrenia is characterized by a broad range of generalized cognitive impairments. Findings related to the existence of specific disproportionate impairments appear somewhat inconsistent although recent studies tend to demonstrate the largest effects on tests of verbal memory as well as executive functioning, attention and more recently, processing speed. More research is clearly needed to determine the exact nature of these core/disproportionate cognitive impairments. Indeed, the considerable heterogeneity of findings related to disproportionate cognitive deficits can stem from a variety of factors such as variation in clinical and sample characteristics. Consequently, the use of classification methods can shed light into understanding whether the occurrence of disproportionate cognitive impairments is a feature of the illness itself or an aspect of a more specific sub-group of patients.

1.7. Objectives

Previous research indisputably demonstrates the need for future studies to determine the exact nature of core/disproportionate cognitive impairments in schizophrenia. Furthermore, by creating more homogeneous sub groups of patients with distinct symptom and premorbid adjustment profiles, we may be able to facilitate the study of the disproportionate cognitive impairments that characterize the illness. The objectives of the present report are two-fold and will be addressed in two separate manuscripts:

(1) In the first study, we will attempt to replicate and extend previous studies indicating that performance on the Digit-Symbol is the most severely impaired task reflecting a central feature of the illness as suggested by a recent meta-analysis (Dickinson et al. 2007). In addition, we will examine whether the impairment found on the Digit-Symbol reflects a deficit that is disproportionate relative to other severely impaired neuropsychological functions such as verbal memory. Finally, we will also examine the pattern of disproportionate cognitive impairments in patients with varying symptom severity.

(2) In the second study, we will examine the cognitive profile of patients with a first-episode psychosis across distinct premorbid adjustment subtypes as defined by Haas & Sweeney (1992) (i.e. stable-poor, stable-good, deteriorating) as a means to understand heterogeneity for which there may be different underlying neurodevelopmental processes. More specifically, we will investigate whether disproportionate cognitive impairments are present within each subgroup and if so, we will examine the nature of these deficits.

Due to the disparity of findings related to the heterogeneity of cognitive functions in schizophrenia, several methodological and clinical confounders will also be addressed. First, this study will be conducted on a large community-based first-episode psychosis sample recruited

from a well-defined catchment area. Secondly, due to inconsistent findings regarding the effect of neuroleptic medications on cognitive functions our study sample will consists of stabilized patients with minimal life time pharmacological treatment prior to the neuropsychological testing.

CHAPTER 2:

METHOD

2.1. Treatment Setting:

Subjects for the following two studies were patients who present at a specialized early intervention service for a first-episode psychosis (FEP) in Montreal, Quebec (Prevention and Early Intervention Program for Psychoses-PEPP). There is no other first-episode program serving this catchment area and no alternative facilities are available privately in the Canadian system of mental health care.

2.2. Subjects:

Patients included in the following studies were accepted for treatment between 2003 and 2007 after having met the following inclusion criteria: 14–30 years old, diagnosis of a schizophrenia-spectrum disorder, previous antipsychotic therapy for no more than 1 month, and living within a specified catchment area. The exclusion criteria included: an IQ below 70, a history of organic mental disorder such as epilepsy, substance-induced psychosis, and an inability to speak either English or French. Healthy controls, recruited through advertising in the university and hospital grounds, were screened for neurological conditions as well as past and current psychiatric illnesses with the modified version of the Structured Clinical Interview for the DSM-IV (First 1995) for normal populations. Patients and controls signed an informed consent for participation after the nature of the evaluation protocol was explained to them. The study was approved by the human ethics committee for the Douglas Institute.

2.3. Assessments:

All clinical diagnostic assessments and symptom ratings were carried out by trained research staff and supervised by at least 2 senior psychiatrists. Neuropsychological assessments were conducted by trained research staff with supervision by an accredited neuropsychologist.

2.3.1. Diagnosis and Symptoms:

Diagnoses were determined using the Structured Clinical Interview for DSM-IV (First et al. 1995) soon after entry to the program and repeated at one year follow-up. Symptomatology assessments were performed at baseline, month 1, month 2, month 3 and month 6. Scores at baseline and closest to the time of the neuropsychological evaluation were used for analyses. Positive and Negative Syndrome Scale which assesses positive, negative and general psychopathology symptoms (PANSS) (Kay 1987) was used to rate symptoms.

2.3.2. Duration of Untreated Psychosis:

A semi-structured interview, the Circumstances of Onset and Relapse Schedule (CORS) which includes material adapted from the Interview for Retrospective Assessment of Onset of Schizophrenia (IRAOS), was conducted with the patient and the family member with the most contact with the patient. Additional information was obtained from case managers, health records and, whenever possible, school records (Malla et al. 2006).

Based on the CORS, duration of untreated psychosis (DUP) was calculated as the period (in weeks) between the date of onset of psychotic symptoms judged to have reached threshold for SCID-IV to the date of commencement of adequate treatment, defined as taking antipsychotic medication for a period of one month or until significant response was achieved (Malla et al. 2002). Inter-rater reliability was conducted on 20 randomly selected cases and rated separately by three raters. A relatively high degree of agreement was achieved on estimation of DUP (ICC varying from 0.86 to 0.98) (Bechard-Evans et al. 2007).

2.3.3. Medication:

All medication dosages were converted into chlorpromazine equivalencies (CPZE) based on widely used norms . The following equivalencies were used for 100 mg of chlorpromazine equivalent (CPZE): olanzapine = 6.25 mg; haloperidol = 1.88 mg; quetiapine = 125 mg; risperidone = 0.75 mg; loxapine = 10 mg and zuclopenthixol = 120 mg (injectable every month). For patients who were taking more than one anti-psychotic medication at time of testing (N = 8), CPZE were added to compute total dosages.

2.3.4. Neuropsychological assessment:

All patients accepting treatment at PEPP were approached to undergo a two-hour and a half session for administration of a battery of neuropsychological tests. The majority of patients and controls were tested using the English versions of the WAIS-R and the neuropsychological tests. Eleven commonly used tasks that are part of the neuropsychological battery performed at PEPP were selected to assess six widely studied neurocognitive domains (i.e. attention, verbal memory, visual memory, working memory, processing speed and reasoning/problem-solving) (Bodnar et al. 2008). A detailed description of the testing procedure and the neuropsychological battery are provided in the manuscripts.

2.4. Data Analysis:

SPSS for Window version 15.0 was used for statistical analysis. We first verified the distribution of the raw scores for each neuropsychological test. Data was normally distributed except for the scores on the following tests: Trail-Making part A and part B. Scores on these tasks were square-root transformed to correct for skewed distribution. Raw scores on each test were standardized (z-scores) based on the mean and standard deviations of a healthy control group. Data on neuropsychological tests where high scores indicated more impairment (i.e. Trail-Making Test-part A and part B, Tower of London-number of movements) were inversed. Finally, composite

scores for each cognitive domain were computed by averaging the z-scores for tasks underlying these domains.

To test for group differences on demographic variables between patient and controls, independent samples t-tests and Pearson Chi-squares were computed.

To test for group differences on all cognitive domains, analysis of covariance (ANCOVA) models were conducted with group (patient vs control) as the between-group factor and education as covariates. Since males showed poorer performance on the verbal memory domain compared to females ($t = -3.182$; $df = 117$; $p = 0.002$), gender was also entered as a covariate when testing for group differences on the verbal memory domain. All tests were two-tailed.

Since F values in the analysis of covariance are highly affected by sample size, which varied with each domain, effect sizes were computed using normal controls' SDs to measure the magnitude of the difference in performance between patients and controls on each domain (Mohamed *et al.* 1999).

To test for demographic and clinical differences between the "deteriorating", "stable-good" and "stable-poor" premorbid adjustment groups, chi-squares and analysis of variance with Bonferroni correction were employed. All tests were two-tailed. Effect sizes for each cognitive domains and IQ across premorbid adjustment groups were computed using normal controls' means and SDs.

CHAPTER 3:

Manuscript # 1:
Digit Symbol Coding Task and the role of negative symptoms relative to other cognitive impairments in First-Episode Psychosis

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3.1. Abstract

Background: There is evidence that impairments in a simple processing speed test, the Digit Symbol Coding Test are larger than the ones in other cognitive domains in schizophrenia. It is not clear whether these differences between domains can be identified during the first episode and if symptom severity is associated differentially with severity of impairments in different cognitive domains. **Method**: Patients (N=121) with diagnosis of a first-episode psychotic disorder completed a full cognitive battery at baseline. Test scores were converted into z-scores based on 32 healthy controls. Six cognitive domains were computed using the mean z-scores for relevant tasks (i.e. Verbal Memory, Visual Memory, Processing Speed, Working Memory, Attention, Reasoning/Problem-Solving) as well as an abbreviated Full IQ and a global neurocognition score. Performance on the DST was examined independently. **Results:** The patient sample (mean age 22.9; 70% male; education 11 years; median DUP 17.8 weeks) was significantly more impaired compared to healthy controls on most domains (except for the abbreviated Full IQ, Working Memory and Reasoning/Problem-Solving) and on the DST after adjusting for education. Impairments were most pronounced in the Visual Memory domain (ES=-2.33), the DST task (ES=-1.33) and the global score (ES=-1.16). Patients with high levels of negative symptoms showed more severe impairments across all cognitive domains compared to patients with low levels of negative symptoms and do not display a differential pattern of cognitive impairments. **Conclusion:** As early as the first episode, generalized cognitive impairments are present with more pronounced deficits in visual memory and the Digit-Symbol coding task.

3.2. Introduction

Processing speed in schizophrenia is often the first affected cognitive domain to show significant impairments in psychosis (Brebion et al. 1998, Jeste et al. 1996, Jogems-Kosterman et al. 2001, Mahurin et al. 1998, van Hoof et al. 1998). The domain of processing speed specifically refers to speed with which different cognitive operations can be executed and is generally represented by tasks such as the Digit Symbol Coding Task (DST), a subtest of the WAIS-III, the Trail-making Test-part A (TMT) and the Stroop Task (Salthouse et al. 1996).

A recent meta-analysis (Dickinson et al. 2007) found that the mean effect size across studies on the DST was significantly larger than effects for widely used measures of episodic memory, executive functioning and working memory and the ones reported for other commonly used measures of processing speed such as the Stroop word/color naming and the Trail Making-part A. Thus, these findings seem to suggest that performance on the DST reflects a disproportionate cognitive impairment (i.e. in excess of the averaged performance deficit across a range of other cognitive domains, Chapman & Chapman, 1989). However, of the 40 studies included in this meta-analysis, only 10 pertained to first-episode samples. As such, it is still unclear whether performance on the DST represents a core deficit within a first-episode psychosis sample. A recent paper by Rodriguez-Sanchez et al. (2007) comparing first-episode psychosis patients with healthy controls found that when the influence of processing speed as assessed by the DST was removed, the significant differences on all cognitive measures between the patient and healthy control disappeared. However, half the sample was taking conventional anti-psychotic medication at the time of neuropsychological testing, thus rendering it a less representative sample of first-episode psychosis patients.

In the present study, we attempt to replicate and extend the findings of previous studies in examining specific deficit in information processing speed, as assessed by the DST, relative to other widely studied cognitive impairments in a large sample of first-episode schizophrenia spectrum psychosis patients.

3.3. Method

Treatment Setting:

The present report is part of a larger prospective study of patients treated for a first-episode psychosis (FEP) in a specialized early intervention service, the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal, Quebec). There is no other first-episode program nor is there any other hospital based psychiatric service serving this catchment area. In addition, no alternative facilities are available privately within the Canadian system of mental health care.

Subjects:

Subjects for this study were consecutive patients accepted for treatment between 2003 and 2007 having met the following inclusion criteria (14–30 years old, diagnosis of a schizophrenia-spectrum disorder, previous antipsychotic therapy for no more than 1 month, and living within a specified catchment area) and exclusion criteria (IQ below 70, a history of organic mental disorder such as epilepsy, substance-induced psychosis, and an inability to speak either English or French). Healthy controls, recruited through advertising in local newspapers and on the university and hospital grounds, were screened for neurological conditions as well as past and current psychiatric illnesses with the modified version of the Structured Clinical Interview for the DSM-IV (First et al. 1995) for normal populations. Patients and controls signed an informed consent for participation after the nature of the evaluation protocol was explained to them. The study was approved by the human ethics committee for the Douglas Institute.

Assessments:

All assessments were carried out by trained research staff and supervised by at least 2 senior psychiatrists and a psychologist.

Diagnosis and Symptoms:

Diagnoses were determined using the Structured Clinical Interview for DSM-IV (First et al. 1995) soon after entry to the program and repeated at one year follow-up. Symptom assessments, using the 30-item Positive and Negative Syndrome Scale which assesses positive, negative and general psychopathology symptoms (PANSS) (Kay et al. 1987), were performed at baseline, month 1, month 2, month 3 and month 6. Scores at baseline and closest to the time of the neuropsychological evaluation were used for analyses (typically within two weeks of the assessment)

A semi-structured interview, the Circumstances of Onset and Relapse Schedule (CORS) which includes material adapted from the Interview for Retrospective Assessment of Onset of Schizophrenia (IRAOS), was conducted with the patient and the family member with the most contact with the patient. Additional information was obtained from case managers, health records and, whenever possible, school records (Malla et al. 2006).

Based on the CORS, duration of untreated psychosis (DUP) was calculated as the period (in weeks) between the date of onset of psychotic symptoms judged to have reached threshold for SCID-IV to the date of commencement of adequate treatment, defined as taking antipsychotic medication for a period of one month or until significant response was achieved (Malla et al. 2002). Inter-rater reliability was conducted on 20 randomly selected cases and rated separately by three raters. A relatively high degree of agreement was achieved on estimation of DUP (ICC varying from 0.86 to 0.98) (Béchard-Evans et al. 2007).

Medication:

All medication dosages were converted into chlorpromazine equivalencies (CPZE) based on widely used norms (Bezchlibnyk-Butler and Jeffries 2007). The following equivalencies were used for 100 mg of chlorpromazine equivalent (CPZE): olanzapine = 6.25 mg; haloperidol = 1.88

mg; quetiapine = 125 mg; risperidone = 0.75 mg; loxapine = 10 mg and zuclopenthixol = 120 mg (injectable every month). For patients who were taking more than one anti-psychotic medication at time of testing (N = 8), CPZE were added to compute total dosages.

Neuropsychological Assessment

All patients accepting treatment at PEPP were approached to undergo a two-hour and a half session for administration of a battery of neuropsychological tests. The assessment was conducted by trained research staff with supervision by an accredited neuropsychologist (M.L). Testing was completed in a single-day session within the first three months of entry in the program or in between the third and sixth month in a minority of cases (less than 4.1 %) to ensure clinical stabilization of acute psychotic symptoms (mean time from entry in the program to neuropsychological testing= 9.73 weeks; range: -1.57- 41 weeks). One patient was tested prior to acceptance into the program to rule out intellectual disability which resulted in a negative value.

Ten commonly used tasks that are part of the neuropsychological battery performed at PEPP were selected to assess six cognitive domains as suggested by the NIMH-Measurement and Treatment Research to improve Cognition in Schizophrenia (MATRICS) group (Nuerchterlein et al. 2004). The z-scores for each cognitive domain were computed using the mean and standard deviation of the healthy control group. An abbreviated full scale IQ was based on the short form of the *Wechsler Adult Intelligence Scale (WAIS-R)* (Wechsler, 1981) and used as an index of general intellectual functioning. In addition, due to recent findings which provide evidence showing that a single-cognitive factor model fits the data best, we also computed a global neurocognitive measure by using the mean standardized scores for each cognitive domain (Dickinson et al. 2006). Below is a listing of the six neurocognitive domains and a description of the tasks used to estimate these domains. To test our hypothesis of a larger impairment on the

Digit-Symbol coding task compared to other widely used cognitive tests, this task was evaluated separately from the Trail-Making test-part A which also reflects a form of processing speed.

Attention

D2 test (Brickenkamp, 1998) is a letter cancellation test composed of 14 lines of 47 letters each. Examinees are asked to slash out as many targets as they can among distracters in 4 minutes and 20 seconds. The final score used to assess performance is the total number of cancellations minus the total number of distracters wrongly slashed out.

Working Memory

Digit-Span Subtest of the Wechsler Adult Intelligence Scale III-Revised (WAIS-III-R) (Wechsler, 1981).

In this task, series of numbers are read aloud and the examinee is told to repeat the numbers in the same and reverse order for the backward digit-span. The final score refers to the number of correctly repeated sequences until the discontinue criterion (i.e. failure to reproduce two sequences of equal length) was met.

Spatial Span-Subtest of the Wechsler Memory Scale III (WMS-III) (Wechsler, 1997).

In this test of visual working memory, the examiner taps a series of three-dimensional blocks and the examinee is asked to tap the same blocks in the same and reverse order for the backward spatial span. The final score refers to the number of correctly tapped sequences of blocks until the discontinue criterion (i.e. failure to reproduce two sequences of equal length) was met.

Verbal Memory

Wechsler Logical Memory Scale III (WMS-III) (Wechsler, 1997). This instrument assesses both immediate and delayed recall of auditory material, specifically, two stories. The final score is the correct number of items successfully remembered.

Visual Memory

Wechsler Visual Reproduction Scale III (WMS-III) (Wechsler, 1997). This instrument assesses both immediate and delayed recall of visual material. The final score is the correct number of items successfully remembered.

Reasoning/Problem Solving

Trail-Making Test-Form B (Reitan, 1985). This task assesses set-shifting abilities where examinees have to correctly connect letters and numbers in an alternative order. Time for completion is used as the primary score.

Block Design subtest of the Wechsler Adult Intelligence Scale III-Revised (WAIS-III-R) (Wechsler, 1981). This task is timed and requires subjects to construct figures using 9 identical blocks.

Processing Speed

Trail-Making Test-Form A (Reitan, 1985) This task requires subjects to connect numbers in the correct chronological order. Time for completion was used as the primary score.

Digit-Symbol Coding Task (DST)

This task was not included in any cognitive domain as the main objective of this study was to investigate if it is disproportionally impaired in schizophrenia. It is a sub-test of the *Wechsler Adult Intelligence Scale III-Revised (WAIS-III-R)* (Wechsler, 1981) and requires subjects to correctly match as quickly as possible a set of symbols to numbers ranging from 1 to 9 during a 120 second time period.

Data Analysis

SPSS for Window version 15.0 was used for statistical analysis. All tests were two-tailed. Since sample sizes varied, effect sizes for each cognitive domains and IQ across pre-morbid adjustment groups were computed using normal controls' means and standard deviations (Mohamed, 1999).

To test for group differences on all cognitive domains, performance on the DST task and abbreviated IQ, analysis of covariance (ANCOVA) models were conducted with group (patient vs control) as the between-group factor and education as covariates. Gender was also entered as a covariate only when using verbal memory as a dependent variable since males showed poorer performance on the verbal memory domain compared to females ($t = -3.741$; $df = 122$; $p = 0.000$). All tests were two-tailed.

3.4. Results

One-hundred and twenty-nine (72%) of a total of 169 patients admitted to the program with a diagnosis in the schizophrenia-spectrum range (i.e. schizophrenia, schizophreniform, schizoaffective, delusional disorder and psychosis NOS) completed the full neuropsychological battery. The remaining patients who refused to complete the assessment did not differ from those who participated in the study on gender, age of onset, education, duration of untreated psychosis and symptoms at baseline but were different on ethnicity. Patients who completed the testing were more likely to be Caucasian (N=80, 66%) than Non-Caucasian (n=15, 45.5%) (86/43) compared to non-completers (15/18) (Fisher`s Exact Test; $p = 0.03$). Eight additional patients were deleted from further analyses as the neuropsychological assessment was performed after 6 months in the program thus yielding a final sample of one-hundred and twenty-one patients. Clinical and demographic characteristics of the patient and healthy comparison groups are provided in Table 1.

Main Findings

Figure 1 shows the mean neuropsychological profile for the patients relative to the healthy comparison group. In terms of effect sizes, the difference between patients and controls was greatest with to the Visual Memory domain (ES = -2.33), the DST task (ES = -1.33) followed by the Global Neurocognition Score (ES = -1.16).

The mean z-scores of the patient and healthy comparison groups on each cognitive domain and the DST task are presented in Table 2. Analysis of Covariance (ANCOVA) adjusting for education (and gender with the Verbal Memory domain) revealed that patients performed significantly worse than controls on most domains except for working memory, reasoning-problem solving and the abbreviated full IQ.

Effect of Clinical and Demographic Variables:

Given the large number of tests conducted, it was decided a-priori that only associations with a p-value below 0.01 would be interpreted as significant. Age at time of testing was not significantly associated with the abbreviated full IQ, scores on the DST and cognitive domain scores in both patients and healthy controls. In the patient sample, age at onset of psychosis and DUP (log-transformed due to a skewed distribution) were not correlated with the abbreviated full IQ, scores on the DST and cognitive domain scores. Finally, in the patient sample, males scored significantly lower compared to females on the Verbal Memory domain ($t = -3.182$; $p = 0.002$). To examine the association between level of symptoms and cognitive scores, Pearson bivariate correlations were conducted between PANSS positive, negative and general psychopathology factor scores and each cognitive domain, the abbreviated full IQ and scores on the DST (see Table 3). Results indicated that negative symptom levels as assessed by the PANSS were inversely correlated with performance on all cognitive measures. Correlation coefficients were generally in range defined by Cohen (1988) (Cohen 1988) as medium ($r = 0.3$). The general psychopathology factor was inversely correlated with the abbreviated Full IQ, Working Memory, Reasoning/Problem-Solving and Attention. The positive symptom factor was not correlated with any of the cognitive measures.

High versus Low negative symptoms subgroups and Neurocognition

We decided to further investigate the cognitive profile of patient by dividing our sample into two groups formed from a median split on the negative subscale of the PANSS (see Table 4). Analysis of covariance adjusting for education (and gender for the Verbal Memory domain) indicated that patients with *high* negative symptoms (scoring more than 13 on the negative subscale of the PANSS) (N = 57) were significantly more impaired on all cognitive domains, the abbreviated full IQ and performance on the DST compared to those with *low* negative symptoms. In addition, the severity of cognitive impairment as measured by effect sizes in this subgroup was larger on all cognitive domains compared to the subgroup with *low* levels of negative symptoms. In each subgroup, the visual memory domain reflected the largest impairment (Low negative symptom group: ES = -1.99; High negative symptom group: ES = -4.0). No specific pattern of cognitive deficits was found within each subgroup based on negative symptoms. The only difference seemed to relate to the severity of the cognitive impairments.

Impact of Medication Dosage:

We examined relationships between medication dosage at the time of testing (i.e., CPZE) and cognitive domain scores and the DST task score. The median CPZE dose was 200 mg per day (mean = 248, SD = 152, min-max = 13.3 - 673). Patients who were not taking anti-psychotic medication at the time of testing (n= 14) scored significantly higher on tasks assessing Processing Speed ($p = 0.011$), Attention ($p = 0.001$), Verbal Memory ($p = 0.01$), Global Neurocognition domain ($p = 0.015$) and abbreviated Full IQ ($p = 0.005$). These patients were excluded from further analyses. Pearson correlations conducted on the sample of patients taking antipsychotic medication at the time of testing revealed a significant negative correlation with the Verbal Memory domain only ($r = -0.243$; $p = 0.012$) but not with Working Memory ($r = -0.046$; $p = 0.645$), Reasoning/Problem-Solving ($r = 0.005$; $p = 0.959$), Processing Speed ($r = 0.025$; $p =$

0.0.796), Attention (r = -0.021; p = 0.0.841), DST (r = -0.093; p = 0.340), Abbreviated Full IQ (r = -0.093; p = 0.340), Visual Memory (r = -0.089; p = 0.398) and the global neurocognition score (r = -0.061; p = 0.571).

In addition, CPZE dose at the time of the neuropsychological evaluation was not correlated with symptomatology as assessed by the PANSS subscale and total scores.

3.5. Discussion

Impairments on the Digit-Symbol Coding Task

In this study, we sought to investigate whether a simple processing speed measure, the Digit Symbol, is more impaired compared to other widely studied cognitive domains in first-episode psychosis. Our results indicate that, after controlling for education, in patients compared to healthy controls with the exception of visual memory, DST was more impaired than attention, reasoning/problem-solving, working memory and other tasks measuring processing speed. These findings seem in line with several studies showing a large deficit in DST in schizophrenia patients (Dickinson et al., 2007; Keefe et al., 2006; Mohamed et al., 1999). Indeed, a recent study part of the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) showed that digit symbol was the best predictor of global cognitive performance, accounting for 60 % of the variance in total scores derived from larger cognitive assessment batteries (Keefe et al. 2006). In a recent meta-analysis investigating the Digit Symbol deficit, Dickinson et al. (2007) found that the effect size across studies was larger (g=-1.57) than effects for widely used measures of episodic memory, executive function, working memory and other tasks assessing processing speed such as the Stroop word reading (g=-0.97) and the Trail Making Test-part A (g = -0.88). Both these studies were generally based on samples of chronic patients (less than 10 first-episode psychosis studies were included in the meta-analysis). Thus, the current study extends upon previous ones by investigating the digit symbol deficit in a representative sample of first-episode

psychosis patients and shows that, indeed, the large impairment is present early on within the course of the illness and is a core feature of the illness.

Our results for the entire sample indicate that impairments on the DST are not disproportionate relative to the verbal episodic memory deficit. Indeed, our results indicate that the visual memory domain is the most impaired thus refuting our initial hypothesis as well as previous findings in chronic schizophrenia and first-episode psychosis (Censits et al. 1997, Hill et al. 2004, Saykin et al. 1991, Saykin et al. 1994) and a recent meta-analysis in early psychosis (Mesholam-Gately et al. 2009) suggesting that verbal memory impairments are the most severe. These unexpected findings are difficult to interpret as previous research investigating visual memory deficits in schizophrenia have been scarce (Brébion et al. 2009). However, potential explanations for these findings include a small sample size of healthy controls and the very low variance of scores on the visual memory tasks. The majority of the healthy control group scored within the top 10^{th} percentile on these tasks potentially explaining the large effect size for this domain. Indeed, Skelley et al. (2008) (Skelley et al. 2008) also found larger effect sizes on the Wechsler Reproduction Scale (Wechsler 1997) and postulated that the larger difference might be explained by the test`s poorer discriminating power. Their findings also revealed a higher accuracy levels (> 70% correct) for both controls and siblings of patients on the visual memory tasks compared to the verbal memory tests.

Additional explanations concern a relatively new line of research investigating the effects of processing speed on visual memory deficits (Brebion et al. 2009) showed that processing speed deficits as measured by the DST and the Trail-Making part A predicted visual-recognition efficiency in schizophrenia patients. Although we grouped together both the visual recall and recognition tasks together in one cognitive domain, the large impairment in visual memory found in this study may in part reflect impairments the large impairments in information processing

speed as assessed by the DST. Based on their results, Brebion et al. (2009) postulated that processing speed deficits may specifically impede the picture encoding part of visual memory tasks. This is in keeping with previous research suggesting that patients with schizophrenia have deficits in the encoding and not storage stage of the verbal memory process (Mohamed et al. 1999) and that processing speed tasks such as the DST also predict verbal encoding deficits (Brebion et al. 1998). Thus, patients with schizophrenia may have processing speed impairments that effect general encoding deficits for various types of stimuli including visual and verbal. On the other hand, tasks used to assess processing speed such as the DST may also tap into encoding processes partly explaining the overlap between the two. Indeed, Dickinson et al. (2008) (Dickinson and Gold 2008) raised the question whether the consistent findings of a large deficit on the DST were the result of the measurement properties of this instrument.

To clarify the exact nature of the underlying cognitive deficit assessed by the DST, research has attempted to delineate the various cognitive processes involved. Results appear to indicate that successful completion of the DST makes demands on several processes such as cognitive slowing, perception, working memory, sustained attention and visuo-motor coordination (Dickinson et al. 2007; Jeste et al. 1996; Brebion et al. 1998; Jogems-Kosterman et al. 2001; Mahurin et al. 1998; van Hoof et al. 1998). More specifically, a study conducted on a sample of healthy individuals revealed that performance on the DST was related to processing speed and visual scanning efficiency while memory (incidental learning) explained only 4 to 5 % of Digit-Symbol variance (Joy et al. 2003). Although in this study we did not investigate the actual processes involved in successfully completing the DST, our results indicated that another Processing Speed task, the Trail Making Test-part A, was less impaired when compared with the DST thus supporting the findings that the digit symbol taps into somewhat different cognitive processes than the ones assessed by the Trail Making Test-part A (Dickinson et al. 2007). Indeed,

it has been hypothesized that the latter task is operationally simpler and requires less coordination of complex assembly of elementary operations.

It is difficult to draw conclusions about the impact of antipsychotic medication on the present neurocognitive results. Indeed, patients who were not taking medication at the time of the testing seemed to have better results on most cognitive domains. This may simply reflect that these individuals were able to cope with symptoms of psychosis partly because of superior cognitive functions. Nevertheless, only fourteen patients were un-medicated making a definitive conclusion difficult. Furthermore, the correlations between dosage of medication and scores on the various cognitive domains were modest at best thus minimizing the effect of drug on performance. Finally, patients were taking low doses of novel antipsychotic medication for only a brief period prior to the neuropsychological testing (mean of 9.73 weeks from entry to the program). Previous findings also point towards inconsistencies regarding an association between these two measures. A recent study by Hill et al. (2004) on anti-psychotic naïve patients indicated that they performed significantly worse than healthy controls on verbal learning, short- and long-term memory while other studies (Keefe et al. 2005, Purdon 1999) have found an association between atypical neuroleptics and improved verbal memory performance.

Symptoms and neurocognition

Our findings generally showed moderate negative correlations as defined by Cohen (1988) ($r = 0.30$) between the negative symptom subscale of the PANSS and all cognitive domains including scores on the DST which is consistent with previous research conducted on first-episode psychosis (Heydebrand et al. 2004) but inconsistent with others (Rund et al. 2004).

Based on these findings, we decided to investigate whether disproportionate cognitive deficits on the Digit Symbol would be easily identifiable in more homogeneous subgroups of schizophrenia patients based on symptomatology. Thus, the relative impairment on the DST compared to other

cognitive domains in subgroups of patients with *high* and *low* negative symptoms was examined. Individuals with *high* levels of negative symptoms were significantly more impaired than patients with *low* levels of negative symptoms on all cognitive measures and effect sizes were large (≥ 0.8) in all domains. On the other hand, patients in the *low* negative symptoms subgroup at time of testing presented with less severe cognitive impairments. These findings seem to suggest that, although the pattern of cognitive impairment is similar in both groups, patients with *high* and *low* negative symptoms present with differential cognitive impairments on the DST and Visual Memory against a back-drop of generalized cognitive impairments although the overall cognitive profile of patients with *high* negative symptoms seems to be more severe.

Strengths of the current study include the use of a large, representative sample of recently treated first-episode psychosis patients. In addition, the CPZE dosages are substantially lower than the ones reported in some first-episode studies using inpatients (Bilder et al. 2000), but are in agreement with other FEP studies using unselected samples (Addington et al. 2002) thus reducing the potential confounds of medication. We also followed the consensus-based Measurement of Treatment Effects on Cognition in Schizophrenia (MATRICS) for devising our cognitive domains thus facilitating a comparison between the findings of the current study and previous as well as future studies in the field.

Several methodological limitations are noteworthy. The use of simple instructions on the DST task did not allow for a more thorough analysis of the various processes involved in successfully completing this task. Morrens et al. (2006) (Morrens et al. 2006) used a more sophisticated method by administering the DST on a digitizer tablet to allow for the computation of additional variables such as matching time and writing time. They found that although both these processes were impaired, they were unrelated in schizophrenia patients. Our results, however, do not allow us to separate these two processes. The sub-typing of patients based on symptoms was also

somewhat arbitrary and did not follow a previously published and reliable classification scheme. Heinrichs and Awad (1993) argued that this strategy is problematic as symptom ratings are subjective, fluctuate over time and may be difficult to understand in terms of neural mechanisms. Finally, the healthy control sample was small and included highly educated individuals working mainly in the hospital and university, thus caution is needed when interpreting the results.

In summary, our results suggest that performance on a simple processing speed measure, the DST, reflects a core deficit in first-episode schizophrenia spectrum psychosis sample (Albus et al. 1997; Censits et al. 1997; Riley et al. 2000; Rodriguez-Sanchez et al. 2007; Townsend et al. 2001; Saykin et al. 1994; Dickinson et al. 2007) although it does not seem to indicate that this deficit is disproportionate with respect to the generalized cognitive impairments found in a heterogeneous sample of first-episode psychosis patients. Nevertheless, the Digit Symbol task may have practical implications by allowing to characterize the broad cognitive impairment which is a central feature of the illness. Clearly, further studies are needed to investigate more specifically the neural mechanisms involved in the successful completion of the digit symbol task so as to guide interventions aimed to ameliorate this impairment. In addition, the use of more homogeneous subgroups of schizophrenia patients based on more reliable and valid classification schemes may facilitate our understanding of the exact nature of the deficit reflected in the DST.

Table 1. Sample Characteristics of healthy controls and first-episode patients

	Healthy Controls (N = 32)	First-Episode Patients (N=121)	Chi-square	t (df)
	N (%)	**N (%)**		
Gender Male	18 (56.3)	85 (70.2)	2.25	-
	Mean (SD)	**Mean (SD)**		
Age at cognitive testing	24.6 ± 3.5	22.9 ± 3.83	-	- 2.33 (142)*
Education (years)	14.4 ± 1.58	11.4 ± 2.39		- 6.17 (143)**
DUP-onset (weeks) (n=108)	-	55.9 (111.9) Median = 17.8	-	-
Total PANSS scores (n = 116)	-	59.2 ± 17.8		
Positive symptom subscale (n=121)	-	15.2 ± 7.12		
Negative symptom subscale (n=118)	-	15.0 ± 6.14		
General psychopathology subscale (n=118)	-	28.8 ± 8.38		
Type of Anti-psychotic at testing (N = 107)	-		-	-
Olanzapine (n=50)	-	10.78 ± 5.95		
Seroquel (n=13)	-	370 ± 188		
Risperdal (n=38)	-	2.20 ± 1.09		
Risperdal-Consta (n=4)	-	25 ± 0		
Haldol (n=1)	-	2 ± 0		
Loxapac (n=1)		75 ± 0		

Table 2. Comparison of FEP and controls at baseline assessment on neurocognitive domains and performance on the DST.

Domains	Patient Group (n=121)			Control Group (n=32)			Analysis
	Mean	SD	N	Mean	SD	N	F (df)
Digit-Symbol Coding WAIS subtest	66.2	14.9	120	85.6	14.5	32	29.22
Global z-scores	-1.33	1.03	120	0.0002	1.00	32	(1, 143)**
Processing Speed							
Trail Making A (completion time)	36.3	14.7	120	31.3	9.4	32	12.81
Global z-score	-0.93	1.12	119	0.000	0.859	32	(1, 142)*
Attention							
D2 test (concentration performance)	145.3	41.8	109	184	37	32	
Global z-score	-1.05	1.13	109	0.000	1.000	32	15.00 (1, 132)*
Reasoning/Problem-Solving							
Trail Making B (completion time)	79.4	35.9	117	60.5	15.9	32	
Block-Design WAIS subtest	42.7	12.5	120	51.9	8.55	32	
Global z-scores	-1.11	1.55	116	-0.0003	0.732	32	12.84 (1, 139)
Verbal Memory†							
Immediate recall	34.5	10.8	119	47.1	11.5	32	
Delayed recall	20.4	8.2	119	29.5	9	32	
Global z-scores	-1.05	0.90	119	-0.0001	0.979	32	25.97 (1, 142)**
Visual Memory							
Immediate recall	88.5	13.3	105	99.8	3.82	30	
Delayed recall	68.5	23.9	105	90.7	13.1	32	
Global z-scores	-2.33	2.42	105	0.059	0.817	30	17.1 (1, 127)**
Working Memory							
Digit Span WAIS subtest	15.6	4.2	121	17.3	4.03	32	
Spatial Span WMS subtest	15.9	3.6	119	17.8	3.33	32	
Global z-scores	-0.50	0.89	119	0.0005	0.796	32	16.85 (1, 142)
General Intelligence							
Abbreviated Full IQ	95	16	121	108	12.3	32	29.73 (1, 144)
Global Neurocognition							
Global z-scores	-1.16	1.04	102	0.078	0.569	30	25.11 (1, 124)**

All analyses of covariance were conducted with education as a covariate; †Analysis of Covariance with verbal memory were conducted with gender and education as covariates * $p \leq 0.05$; ** $p \leq 0.005$

Table 3. Pearson correlations of cognitive domains, scores on the DST and symptomatology in first-episode psychosis.

	Positive	Negative	General Psychopathology
Processing Speed	-0.077	***-0.232***	-0.174
Attention	-0.161	***-0.406***	***-0.218***
Reasoning/Problem-Solving	-0.139	***-0.356***	***-0.278***
Verbal Memory	-0.160	***-0.320***	-0.182
Visual Memory	-0.50	***-0.378***	-0.170
Working Memory	-0.137	***-0.421***	***-0.288***
General Intelligence Full IQ	-0.134	***-0.357***	-0.199
Digit Symbol Coding Task	-0.091	***-0.266***	-0.151
Global neurocognition Score	-0.198	***-0.425***	***-0.328***

Significant correlations (p < 0.01) are highlighted.

Table 4. Comparison of high versus low negative symptom subgroups of FEP and controls at baseline assessment on neurocognitive domains and performance on the DST.

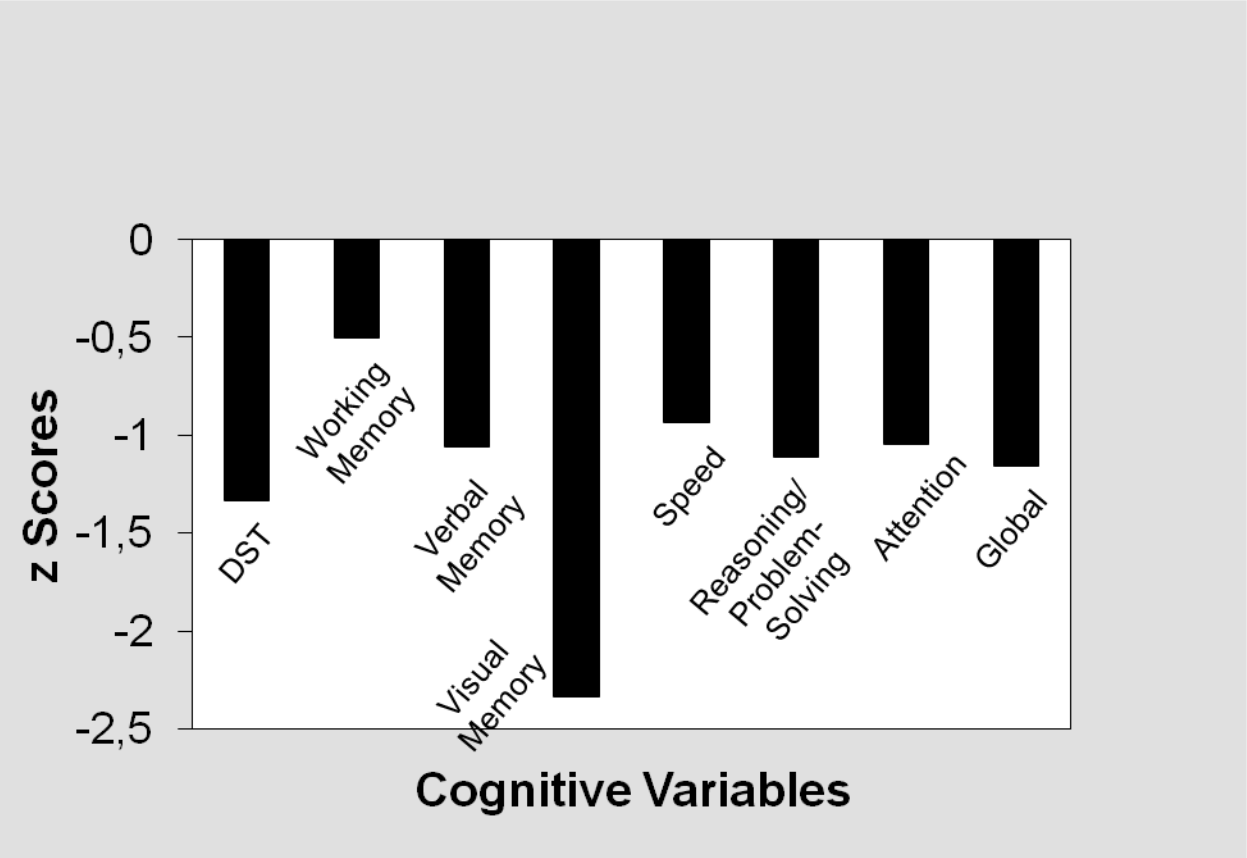
Domains	Patient Group (N = 121)		Control Group (N= 32)		Effect Size (ES)
	Mean	SD	Mean	SD	
Processing Speed					
PANSS negative score > 13	-1.07	1.19			-1.24
			0	0.86	
PANSS negative score < 13	-0.78	1.00			-0.91
Attention/Concentration					
PANSS negative score > 13	-1.43	1.13			-1.43
			0	1	
PANSS negative score < 13	-0.69	1.03			-0.69
Reasoning/Problem-solving					
PANSS negative score > 13	-1.07	1.19			-1.47
			-0.0003	0.73	
PANSS negative score < 13	-0.75	1.33			-1.03
Visual Memory					
PANSS negative score > 13	-3.22	2.67			-4
			0.06	0.82	
PANSS negative score < 13	-1.57	1.85			-1.99
Verbal Memory					
PANSS negative score > 13	-1.32	0.87			-1.34
			-0.0001	0.98	
PANSS negative score < 13	-0.82	0.88			-0.84
Working Memory					
PANSS negative score > 13	-0.84	0.77			-1.05
			0.0005	0.8	
PANSS negative score < 13	-0.18	0.90			-0.23
Digit Symbol Coding Task					
PANSS negative score > 13	-1.52	0.94			-1.52
			0.0002	1	
PANSS negative score < 13	-1.18	1.07			-1.18
Global neurocognition score					
PANSS negative score > 13	-1.58	1.02			-2.91
			0.08	0.57	
PANSS negative score < 13	-0.79	0.92			-1.53

All analyses of covariance were conducted with education as a covariate.

†Analyses of covariance with verbal memory were conducted with gender and education as covariates.

* $p < 0.05$; ** $p < 0.005$

Figure 1. Deficits in Scores on the DST and for Neuropsychological Functions of 121 Patients with First-Episode Psychosis†



† Relative to scores for health comparison subjects; by definition, the healthy comparison group had a mean score of zero on each scale. * Global Neurocognition domain excludes scores on the Digit Symbol Coding Task.

CHAPTER 4:

Manuscript # 2: Investigating cognitive deficits and symptomatology across premorbid adjustment patterns in First-Episode Psychosis.

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4.1. ABSTRACT

Background: Cognitive deficits in schizophrenia are well established and are known to be present during the first-episode of a psychotic disorder. In addition, consistent heterogeneity within these impairments remains unexplained. One potential source of variability may be the level of pre-morbid adjustment prior to the onset of the first-episode of a psychotic (FEP) disorder.

Methods: Ninety-four FEP patients and 32 healthy controls were assessed at baseline on several neuropsychological tests comprising of six cognitive domains (i.e. verbal memory, visual memory, working memory, processing speed, reasoning/problem-solving and attention) and an abbreviated version of the full IQ. A global neurocognitive domain was also computed. Pre-morbid adjustment patterns were divided into 3 groups according to the Haas & Sweeney method (1992).

Results: Based on the Cohen (1988) cut-off of 0.8 for effect size, the "stable-poor" pre-morbid adjustment group was significantly more impaired on most cognitive domains and full IQ compared to the "deteriorating" group who were more severely impaired on all measures compared to the "stable-good" group. The type of cognitive deficit within each subgroup did not differ and results indicated that a global neurognition measure may reliably reflect the severity of cognitive impairment within each subgroup.

Conclusion: Pre-morbid adjustment patterns prior to onset of psychosis are associated with severity but not type of cognitive impairment. Patients in the stable-poor group are generally more impaired compared to the deteriorating, who are in turn, more impaired than the stable-good group.

4.2. Introduction

Although marked cognitive deficits are present in both chronic and first-episode psychosis samples (Heinrichs and Zakzanis, 1998) considerable variability exists with regards to the exact nature and severity of these impairments (Addington et al. 2002; Bilder et al. 2000; Hill et al. 2004; Mohamed et al. 1999; Townsend et al. 2001; Riley et al. 2000). This may, in part, be attributable to the wide heterogeneity inherent in psychotic disorders.

One potential explanation for this heterogeneity is the variable level of functioning prior to the onset of the illness and numerous studies have addressed this aspect of development. Level of pre-morbid functioning in a wide range of domains (i.e. school, work, relationship with peers), especially its progression during childhood and adolescence, likely reflects a number of underlying processes, chief among them neuro-developmental. While poorer pre-morbid adjustment has been linked to male gender, earlier age of onset, negative symptoms, lower remission rates and poorer response to treatment (Addington and Addington, 1993; Gupta et al. 1995; Malla et al. 2002; Rund et al. 2004) it is also likely to be associated with variation in magnitude and/or pattern of cognitive deficits, suggesting variation in neurodevelopmental mechanisms underlying each pre-morbid adjustment pattern. The few studies that have investigated cognitive deficits within the context of pre-morbid adjustment have revealed inconsistent associations between poor pre-morbid functioning and a wide range of cognitive impairments such as attention and executive functions (Silverstein et al. 2002), working memory and verbal learning (Larsen et al. 2004; Rund et al. 2004), verbal reasoning and concept formation (Addington & Addington, 1993), verbal memory and fluency (Addington et al. 2005), poor visual memory span (Levitt et al. 1996) and a generalized cognitive dysfunction (Rabinowitz et al. 2006). In addition, these studies have significant limitations such as small

sample sizes (Addington et al. 1993), inclusion of patients with affective psychoses (Larsen et al. 2004), lack of healthy comparison groups (Addington et al. 2005; Larsen et al. 2004; Rund et al. 2004), use of chronic patients (Addington and Addington, 1993; Silverstein et al. 2002), exclusion of female patients (Levitt et al. 1996) and the exclusive use of a global neurocognitive measure (Rabinowitz et al. 2006).

Furthermore, these studies have not elucidated whether the relative severity of cognitive impairments varies with differences in the course and progression of pre-morbid functioning from childhood through adolescence. The course of pre-morbid functioning is likely reflective of whether the deficits or lack thereof, were present from childhood and stayed static or whether there was deterioration just prior to onset of psychosis during adolescence. These different patterns may represent different underlying mechanisms, such as early or late neurodevelopmental or neuroprogressive processes.

Thus, our aim was to address these limitations in the previous research on pre-morbid adjustment and neurocognitive functioning. Specifically, our main goal was to investigate the pattern and severity of cognitive impairments across three distinct pre-morbid adjustment course patterns as suggested by Haas & Sweeney (1992) (i.e stable-poor, stable-good and deteriorating course) using a large sample of first-episode psychosis patients newly admitted to an early-psychosis program. These three patterns refer to subgroups of patients with a distinct course of functioning prior to the onset of psychosis. In addition, we also sought to examine the demographic and clinical profiles of these three groups to enable a more thorough understanding of the cognitive deficits present within these groups. We hypothesized that number of cognitive domains affected and the severity of such deficits will be greatest in patients with “stable-poor” pre-morbid course followed by the “deteriorating” group and least in the “stable-good” group and that all groups will show cognitive deficits in comparison to matched healthy controls.

4.3. Method

Treatment Setting:

The present report is part of a larger prospective study of patients treated for a first-episode psychosis (FEP) in a specialized early intervention service, the Prevention and Early Intervention Program for Psychoses (PEPP-Montreal, Quebec). There is no other first-episode program serving this catchment area and no alternative facilities are available privately in the Canadian system of mental health care.

Subjects:

Subjects for this study were consecutive patients accepted for treatment between 2003 and 2007 having met the following inclusion criteria (14–30 years old, diagnosis of a schizophrenia-spectrum disorder, previous antipsychotic therapy for less than 1 month, and living within a specified catchment area) and exclusion criteria (IQ below 70, a history of organic mental disorder such as epilepsy, substance-induced psychosis, history of head injury resulting in unconsciousness and an inability to speak either English or French). Healthy controls, recruited through local newspapers ads and on the university and hospital grounds, were screened for neurological conditions as well as past and current psychiatric illnesses with the modified version of the Structured Clinical Interview for the DSM-IV ({First, 1995 #24}) for non-psychiatric populations. Patients and controls signed an informed consent for participation after the nature of the evaluation protocol was explained to them. The study was approved by the research ethics board at the Douglas Institute.

Assessments:

Diagnosis and Symptoms:

Diagnoses were determined using the Structured Clinical Interview for DSM-IV (First, 1995) soon after entry to the program and repeated at one year follow-up. Symptoms were assessed using the 30-item Positive and Negative Syndrome Scale (PANSS) (Kay 1987). Symptom ratings were conducted at two time points: (1) at study entry (during the acute phase of the episode); and (2) close to the time of the neuropsychological examination (typically within two weeks of the assessment). All assessments were carried out by trained research staff and supervised by at least 2 senior psychiatrists (AM and RJ).

Medication:

All medication dosages were converted into chlorpromazine equivalencies (CPZE) based on widely used norms (). The following equivalencies were used for 100 mg of chlorpromazine equivalent (CPZE): olanzapine = 6.25 mg; haloperidol = 1.88 mg; quetiapine = 125 mg; risperidone = 0.75 mg; loxapine = 10 mg and zuclopenthixol = 120 mg (injectable every month). For patients who were taking more than one anti-psychotic medication at time of testing (N = 7), CPZE were added to compute total dosages.

Pre-morbid Adjustment:

The Pre-morbid Adjustment Scale (PAS) (Cannon-Spoor et al. 1982) was used to rate pre-morbid functioning during four distinct age ranges: childhood (up to age 11); early adolescence (age 12–15); late adolescence (16-18) and adulthood (age 19 and above). Because the usual onset of schizophrenia spectrum disorders is in early adulthood, we did not include ratings for adulthood in any of our analyses. In addition, *pre-morbid* was defined as the period 6 months before the onset of the psychotic episode. Within each age range, information collected from the patient and from significant family members was used to make ratings on items regarding sociability and withdrawal, peer relationships, scholastic performance and adaptation to school.

For purposes of our analysis, a total score on items across age periods was calculated. Consistent with the usual scoring procedures for the PAS, the scores given within each age periods were divided by the maximum possible score resulting in an index varying between 0 and 1 with higher scores indicating poorer adjustment. Using the method suggested by (Haas and Sweeney 1992), we identified three groups – "deteriorating", "stable-good" and "stable-poor" on the basis of the course of scores across age periods. A "deteriorating" course was identified on the basis of a two-point change over relevant pre-morbid periods (i.e. from childhood to early and late adolescence). Patients were identified as having "stable-good" pre-morbid adjustment if they did not meet the criterion for deterioration and if their overall pre-morbid adjustment score was below the median for the sample and as having a "stable-poor" pre-morbid adjustment if their overall score was above the median.

Neuropsychological Assessment

All patients accepting treatment at PEPP were approached to undergo a two-hour and a half session for administration of a battery of neuropsychological tests. The assessment was conducted by trained research staff with supervision by an accredited neuropsychologist (M.L). Testing was completed in a single-day session within the first three months of entry in the program or in between the third and sixth month in a minority of cases (less than 4.1 %) to ensure clinical stabilization of acute psychotic symptoms (mean time from entry in the program to neuropsychological testing= 9.73 weeks; range: -1.57- 41 weeks). One patient was tested prior to acceptance into the program to rule out intellectual disability which resulted in a negative value.

Ten commonly used tasks that are part of the neuropsychological battery performed at PEPP were selected to assess six cognitive domains as suggested by the NIMH-Measurement and Treatment Research to improve Cognition in Schizophrenia (MATRICS) group (Nuechterlein et

al. 2004). The z-scores for each cognitive domain were computed using the mean and standard deviation of the healthy control group. An abbreviated full scale IQ was based on the short form of the *Wechsler Adult Intelligence Scale (WAIS-R)* (Wechsler 1981) and used as an index of general intellectual functioning. In addition, due to recent findings which provide evidence showing that a single-cognitive factor model fits the data best, we also computed a global neurocognitive measure by using the mean standardized scores for each cognitive domain (Dickinson et al. 2006). Below is a listing of the six neurocognitive domains and a description of the tasks used to estimate these domains:

Attention

D2 test (Brickenkamp 1998) is a letter cancellation test composed of 14 lines of 47 letters each. Examinees are asked to slash out as many targets as they can among distracters in 4 minutes and 20 seconds. The final score used to assess performance is the total number of cancellations minus the total number of distracters wrongly slashed out.

Working Memory

Digit-Span Subtest of the Wechsler Adult Intelligence Scale III-Revised (WAIS-III-R) (Wechsler 1981).

In this task, series of numbers are read aloud and the examinee is told to repeat the numbers in the same and reverse order for the backward digit-span. The final score refers to the number of correctly repeated sequences until the discontinue criterion (i.e. failure to reproduce two sequences of equal length) was met.

Spatial Span-Subtest of the Wechsler Memory Scale III (WMS-III) (Wechsler 1997).

In this test of visual working memory, the examiner taps a series of three-dimensional blocks and the examinee is asked to tap the same blocks in the same and reverse order for the backward

spatial span. The final score refers to the number of correctly tapped sequences of blocks until the discontinue criterion (i.e. failure to reproduce two sequences of equal length) was met.

Verbal Memory

Wechsler Logical Memory Scale III (WMS-III) (Wechsler 1997). This instrument assesses both immediate and delayed recall of auditory material, specifically, two stories. The final score is the correct number of items successfully remembered.

Visual Memory

Wechsler Visual Reproduction Scale III (WMS-III) (Wechsler 1997). This instrument assesses both immediate and delayed recall of visual material. The final score is the correct number of items successfully remembered.

Reasoning/Problem Solving

Trail-Making Test-Form B (Reitan 1985) This task assesses set-shifting abilities where examinees have to correctly connect letters and numbers in an alternative order. Time for completion is used as the primary score.

Block Design subtest of the Wechsler Adult Intelligence Scale III-Revised (WAIS-III-R) (Wechsler 1981). This task is timed and requires subjects to construct figures using 9 identical blocks.

Processing Speed

Trail-Making Test-Form A (Reitan 1985) This task requires subjects to connect numbers in the correct chronological order. Time for completion was used as the primary score.

Digit-Symbol Coding Task (DST). This task is a sub-test of the *Wechsler Adult Intelligence Scale III-Revised (WAIS-III-R)* (Wechsler 1981) and requires subjects to correctly match as quickly as possible a set of symbols to numbers ranging from 1 to 9 during a 120 second time period.

Data Analysis

SPSS for Window version 15.0 was used for statistical analysis. To test for demographic and clinical differences between the "deteriorating", "stable-good" and "stable-poor" pre-morbid adjustment groups, chi-squares and analysis of variance with Bonferroni corrections were employed. All tests were two-tailed. Since sample sizes varied, effect sizes for each cognitive domains and IQ across pre-morbid adjustment groups were computed using normal controls' means and standard deviations (Mohamed et al. 1999). To test for group differences on all cognitive domains and abbreviated IQ, analysis of covariance (ANCOVA) models were conducted with group (patient vs. control) as the between-group factor and education as covariates. Since males showed poorer performance on the verbal memory domain compared to females ($t = -3.741$; $df = 122$; $p = 0.000$), gender was also entered as a covariate when testing for group differences on the verbal memory domain.

4.4. Results

One-hundred and twenty-one out of 169 patients with a diagnosis in the schizophrenia-spectrum range (i.e. schizophrenia, schizophreniform, schizoaffective, delusional disorder and psychosis NOS) at baseline completed the full neuropsychological battery (completion rate of 72%). The remaining patients who refused to complete the assessment did not differ from those who participated in the study on gender, age of onset, education, duration of untreated psychosis and symptoms at baseline but were different on ethnicity. Caucasians (N=80, 66%) were more likely to have completed testing than Non-Caucasian (n=15, 45.5%) (Fisher`s Exact Test; $p = 0.03$). A total of 94 patients completed the Pre-morbid Adjustment Scale (PAS). These patients did not significantly differ from the ones who did not complete the assessment (N=27) with regards to gender, ethnicity, age of onset, education, duration of untreated psychosis and cognition. However, patients who did not complete the PAS had significantly higher baseline PANSS total

scores (t = 2.919; df = 114; p = 0.004). The following analyses are based on the 94 patients who completed both the neuropsychological evaluation and the PAS. Clinical and demographic characteristics of the patient (total sample and divided into three pre-morbid adjustment groups) and healthy comparison groups are provided in Table 1.

The raw scores for each cognitive test as well as the mean z-scores for patients and healthy controls are presented in Table 2. Analysis of Covariance (ANCOVA) revealed that patients performed significantly worse than controls on all cognitive domains and the abbreviated full IQ measure. However, the significant difference in working memory, reasoning/problem-solving and the abbreviated IQ measure disappeared after adjusting for education. Pearson correlations revealed that CPZE dosages were not correlated with any of our cognitive domains or full scale IQ. Due to the variety of antipsychotic medications used, we conducted an additional analysis examining the correlation between CPZE dosages for patients taking olanzapine (N=42) and risperidone (N=26) and our cognitive domains. Results indicated that verbal memory was the only domain negatively correlated with CPZE dosages (person r = -0.297; p = 0.016).

Demographic Variables across Premorbid Adjustment groups (Table 3)

Based on the Haas & Sweeney method (Haas and Sweeney 1992), 39.4 % of patients were categorized as having "stable-poor" functioning, 30.9 % as having a "deteriorating" premorbid adjustment and 29.8 % as having "stable-good" functioning. One-way analysis of variances (ANOVA) and chi-squares were calculated to determine the differences between these three groups in symptoms, education, age of onset, CPZE dosages at the time of neuropsychological testing and gender. *Post-hoc* tests with Bonferonni corrections were used to determine the groups between which the differences occurred. Results show that the three pre-morbid adjustment patterns did not significantly differ with regards to age of onset, CPZE dosages and gender.

Patients in the "stable-good" group had significantly more years of education compared to the "deteriorating" group ($F = 8.17$; $p < 0.05$).

Clinical Variables across Pre-morbid Adjustment groups (Table 3)

Baseline Symptoms during acute phase

During the acute phase of the illness (baseline assessment), the "stable-good" group scored significantly higher on the PANSS positive scale at baseline compared to the "deteriorating" group ($F = 6.375$; $p < 0.005$). In addition, the "deteriorating" group presented with higher symptoms on the PANSS negative scale compared to the "stable-good" group ($F = 3.377$; $p < 0.05$). Patients did not differ with regards to the PANSS total and general psychopathology scales at baseline.

Symptoms at time of neuropsychological testing during stabilized phase

Analyses of symptoms at the time of neuropsychological testing (when patients were stabilized) revealed that the groups significantly differed with regards to only the severity of negative symptoms. The "deteriorating" group presented with higher scores on the PANSS negative scale compared to the "stable-good" group ($F = 4.914$; $p < 0.05$).

Cognition across Pre-morbid Adjustment groups (Table 4):

Effect sizes were computed for each cognitive domain and full scale IQ separately for the three pre-morbid adjustment groups (Table 3). Figure 1 presents the z-scores for each cognitive domain and full scale IQ across the three pre-morbid adjustment groups. For most domains (except for Working Memory and Processing Speed), the "stable-poor" group showed larger impairments compared to the "deteriorating" group which in turn was more impaired than the "stable-good"

group. For the Working Memory domain, the "deteriorating" group presented with the largest impairments followed by the "stable-poor" and "stable-good" groups. Severity of impairments on the Processing Speed tasks was similar between the "stable-poor" and "deteriorating" pre-morbid adjustment groups. Effect size estimates for each domain ranged from -0.32 to -2.16 in the "stable-good" group, -0.8 to -2.67 in the "deteriorating" group and -0.51 to -2.98 in the "stable-poor" group. The most impaired cognitive domains did not vary within each premorbid adjustment group. Indeed, all three groups presented with the largest impairments on Visual Memory, Reasoning/Problem-Solving and the Global composite score.

4.5. Discussion

This study examined the neuropsychological and clinical profile of a community sample of first-episode psychosis across three pre-morbid adjustment patterns as defined by Haas & Sweeney (1992). Our findings indicate that these subtypes are useful and may represent patients with varying neurocognitive profiles, suggesting distinct underlying neurodevelopmental processes. Although our results seem to differ slightly from previous studies with regards to percentage of patients in each pre-morbid adjustment subtype, three groups were easily identifiable. The majority of our patients fell within the "stable-poor" group (39%) and similar proportions of patients were in the "deteriorating" (31%) and "stable-good" (30%) groups. Other studies investigating pre-morbid adjustment patterns in both chronic and first-episode samples have found slightly different proportions in the "stable-poor" and "deteriorating" groups while the proportion of patients who fall in the "stable-good" group seems to be similar to one reported here (Haas and Sweeney 1992, Larsen et al. 1996, Rabinowitz et al. 2006). In addition, these groups varied with regards to cognitive and clinical correlates, thus suggesting concurrent validity of these subtypes.

Cognitive Impairments across Premorbid Adjustment Patterns

Our central findings are similar to other studies with regards to the general association between poorer pre-morbid functioning and cognitive dysfunction. Based on effect size estimates, the "stable-poor" group was significantly more impaired on *five* out of seven of our cognitive domains (i.e. Visual and Verbal Memory, Reasoning/Problem-Solving, Attention, "abbreviated" full IQ and the global neurocognition measure) compared to the "deteriorating" functioning group and on all measures compared to the "stable-good" group. Similarly, the "deteriorating" group was more impaired on all cognitive domains compared to the "stable-good" group.

Based on a cut-off of 0.8 (Cohen, 1988) for large effect sizes, a closer examination of our findings reveal that the "stable-poor" group are severely impaired on *seven* of our cognitive measures, the "deteriorating" group on *eight* cognitive measures and the "stable-good" group on *five* cognitive measures. Our results clearly illustrate that pre-morbid patterns are reliable, quantifiable factors which explain a portion of the heterogeneity pertaining to cognitive impairments in first-episode psychosis patients. In addition, our findings support the concept of a continuum of neurocognitive function in schizophrenia and allow the differentiation between subgroups of patients who show milder dysfunction and others presenting more severe impairments. Although our cognitive battery was large it was not completely comprehensive and as a result it remains difficult to conclude whether a specific cognitive domain enables the differentiation between sub-groups of pre-morbid adjustment. Indeed, pre-morbid adjustment appears to have better prognostic validity with regards to severity than the type of cognitive dysfunction during the first-episode of psychosis.

Premorbid Adjustment Patterns: Demographic and Clinical Correlates

No significant difference between pre-morbid adjustment patterns with regards to gender, age of onset, and ethnicity was found. Some reports with chronic and first-episode samples have found a gender difference whereby males exhibit poorer pre-morbid functioning than their female

counterparts (Addington and Addington 1993, Childers and Harding 1990, Larsen et al. 1996). Other studies have not replicated these findings and it seems reasonable to conclude that gender differences in pre-morbid functioning may not be significant in a representative sample of FEP patients (Fennig et al. 1995, Larsen et al. 2004).

Our general findings regarding symptomatology and pre-morbid adjustment groups are in line with several studies showing an association between negative but not positive symptoms and pre-morbid adjustment in both chronic and first-episode samples (Bilder et al. 2000, Buchanan et al. 1990, Gupta et al. 1995, Kelley et al. 1992). Patients with a "deteriorating" course had significantly more negative symptoms compared to the "stable-good" group at the time of baseline assessment when patients were acutely ill and at time of neuropsychological testing when patients were stabilized. Thus, it seems that the association between pre-morbid functioning and the presence of negative symptoms later in the illness course is stronger for individuals who present deterioration in functioning during adolescence. These findings are in line with other studies (Buchanan et al. 1990, Kelley et al. 1992, Mukherjee 1991). Indeed, Kelley et al. (1992) postulated that this deterioration was due to late maturation, altered myelination processes during late adolescence and faulty synaptic pruning during adolescence. Our findings also revealed that patients in the "stable-poor" group showed a trend towards higher negative symptoms compared to the "stable-good" group and lower negative symptoms compared to the "deteriorating" group, although these associations did not reach statistical significance. Importantly, most previous reports have investigated this relationship using correlational analyses which may mask the specific links between subgroups of patients with distinct pre-morbid functioning and symptomatology. The current study allowed a more thorough examination of the relationship between symptoms and pre-morbid adjustment using meaningful subtypes. Interestingly, although the "stable-poor" pre-morbid adjustment group present with more severe cognitive

deficits, the negative symptom profile seems to be somewhat less severe. This may indicate that, although overlapping, negative symptoms and cognitive deficits are not inextricably linked. More research is needed to fully understand the nature of the neurodevelopmental abnormalities that come into play during adolescence and their role in establishing the course of pre-morbid adjustment.

Furthermore, our study is the first to reveal that severity of positive symptoms during the acute phase of the illness, in addition to being unrelated to poorer pre-morbid functioning, is linked to better pre-morbid adjustment, implying an acute onset in the latter group. Severity of positive symptoms after stabilization (at the time of neuropsychological testing) was not associated with subgroups of pre-morbid adjustment. Similarly, Amminger et al. (1997) (Amminger et al. 1997) found that patients with complete remission of positive symptoms after eight weeks of therapy had experienced better pre-morbid adjustment in early adolescence and childhood. Perhaps patients with a good pre-morbid functioning have positive symptoms whose origin differs from those with a "deteriorating" and a "stable-poor" course. In addition, these individuals may experience more severe positive symptoms and lower levels of negative symptoms during the acute phase as well as quicker stabilization and/or remission of positive symptoms. These findings clearly illustrate the need for more research targeted at investigating patients with a "stable-good" pre-morbid adjustment. More specifically, it needs to be clarified whether and what kind of cognitive impairments and neurodevelopmental abnormalities are present during the pre-morbid phase of the illness in this subgroup and if such abnormalities have a meaningful impact on functioning despite being relatively mild. Future studies should also investigate the progression of these cognitive deficits within each premorbid adjustment group. Perhaps patients with a "stable-good" course merely represent a subgroup with a right-shifted neurodevelopmental trajectory where the disturbances start later and progress for a longer period of time before

culminating into noticeable cognitive impairments or alternately they may have had minimal if any neurodevelopmental abnormality accounting for a more favourable course.

In conclusion, our findings related to the association between poor pre-morbid functioning, cognitive deficits and negative symptoms during the acute and stabilization phases of the illness may indicate that poor premorbid functioning (either with a deteriorating or a stable-poor course) is the result of a more gradual, insidious onset of a deficit type of schizophrenia (Carpenter et al. 1988). The poor social and academic functioning of these individuals during the teen years may reflect the slow onset of schizophrenia characterized by stable negative symptoms even during the first-episode. More research is needed, perhaps using neuroimaging techniques, to clarify the link between functioning and negative symptoms as well as its implication with neuropsychological functions. Our study also reveals that individuals with a "stable-poor" and "deteriorating" course represent distinct groups who differ with regards to their cognitive and symptom profile, although the distinction with regards to cognition is related to severity rather than type of deficit. This may imply the need for a different approach to study clinical neuropsychology using more sophisticated and specific measures. Our study is the first report to show that patients with good premorbid adjustment present with higher positive symptoms during the acute phase of the illness, lower negative symptoms during the acute and stabilization phases and milder cognitive deficits.

Several limitations of this study warrant consideration. First, the use of summary scores for each cognitive measure may prevent a thorough understanding of the various processes involved in each general cognitive domain. However, the goal of the current study was to examine the general cognitive deficits present within each subgroup of premorbid adjustment. In addition, we cannot rule out the possibility that neuroleptic medications had a deleterious effect on neuropsychological functions even though analyses did not reveal significant correlations.

The use of a retrospective tool to assess premorbid functioning also has its inherent limitations. Scores are based on the recollection of patients and their families pertaining to functioning dating back several years and thus, memory biases may occur. Further, the small sample sizes in each subgroups of premorbid adjustment functioning may have reduced statistical power thus potentially increasing the occurrence of type II errors. Finally, the healthy control sample was small and included highly educated individuals working mainly in the hospital and university, thus caution is needed when interpreting the results.

Despite these methodological limitations, the current study has provided several improvements on previous research such as the use of a large representative sample of first-episode psychosis taking low doses of atypical neuroleptic medication; the inclusion of several neuropsychological tasks assessing various cognitive domains as well as symptom assessments during the acute and stabilized phases of the illness.

Table 1.Demographic and Clinical Characteristics of First-Episode Psychosis and Healthy Control Subjects

Domains	Healthy Controls (N = 32)	TOTAL SAMPLE First-Episode Patients (N=94)	Chi-square	t (df)	Deteriorating Premorbid Adjustment (N=29)	Stable-good Premorbid Adjustment (N=28)	Stable-poor Premorbid Adjustment (N=37)	Chi-Square	F (df)
	N (%)	N (%)			N (%)	N (%)	N (%)		
Gender Male	18 (56.3)	65 (69.1)	1.767		19 (65.5)	17 (60.7)	29 (78.4)	2.59	-
	Mean (SD)	Mean (SD)			Mean (SD)	Mean (SD)	Mean (SD)		
Age at cognitive testing	24.6 (3.5)	23.1 (3.71)		-2.052 (116)**	22.9 (3.68)	24 (3.27)	22.5 (4)		1.338 (2)
Age of onset	-	22.1 (3.98)			21.8 (4.17)	23.19 (3.59)	21.58 (4.06)	-	1.456 (2)
Education	14.4 (1.58)	11.5 (2.49)		-7.291 (59.6)	11.2 (2.65)	12.9 (1.97)	10.6 (2.28)	-	8.166 (2)**
DUP-onset (weeks)	-	45.4 (64.6) Median= 17.4			66.2 (83.4)	38.5 (47.9)	34.9 (56.9)		1.325 (2)
Total PANSS scores-Baseline	-	76.3 (14.7)			74.7 (15.4)	73.1 (15.4)	79.9 (13.1)	-	1.886(2)
Positive symptom subscale	-	23.5 (5.39)			20.9 (4.81)	25.6 (5.66)	23.9 (4.89)	-	6.375(2)*
Negative symptom subscale	-	16.8 (6.38)			18.3 (7.23)	14.2 (4.99)	14.2 (4.99)	-	3.377(2)*
General subscale	-	35.8 (8.33)			35.5 (8.36)	33.3 (8.58)	38 (7.73)	-	2.694(2)
Total PANSS scores-At time testing	-	57.7 (16.5)			61.3 (17.7)	53.3 (15.9)	57.9 (15.6)	-	1.630(2)
Positive symptom subscale	-	14.6 (6.63)			14.3 (6.2)	14.8 (7.59)	14.6 (6.36)	-	0.049(2)
Negative symptom subscale	-	14.3 (5.81)			16.5 (7.16)	11.8 (3.89)	14.4 (5.13)	-	4.914(2)*
General subscale	-	28.4 (8.05)			30.6 (8.53)	25.6 (7.22)	28.7 (7.88)	-	2.804(2)

Type of Anti-psychotic at testing (N = 82)	- - - -						
Olanzapine (n=42)	- -	10.6 (5.54)	9.38 (3.86)	9.46 (5.21)	12.5 (6.58)		
Quetiapine (n=10)		336 (157)	300 (81.7)	500 (0)	332 (207)		
Risperdone (n=26)		2.13 (1.07)	1.92 (.99)	2.86 (1.28)	1.81 (0.77)		
Risperdone-Consta (n=2)		25 (0)	-	25 (0)	25(0)		
Haloperidol (n=1)		2 (0)	-	-	2 (0)		
Loxapine (n=1)		75 (0)	-	-	75 (0)		
CPZE Dosages			204.9 (105.9)	266.1 (164.9)	244.7 (158.9)	-	1.127 (2)

* $p < 0.05$; ** $p < 0.005$

Table 2. Comparison of first-episode subjects (FE) and healthy control group at baseline assessment on neurocognitive domains.

Domains	Patient Group			Control Group			Analysis
	Mean	SD	N	Mean	SD	N	F (df)
Processing Speed							
Trail Making A (completion time)	36.5	14.3	92	31.3	9.4	32	
Digit-Symbol Coding WAIS subtest	67.5	14.8	93	85.6	14.5	32	
Global z-score	-0.9006	1.08	92	0.000	0.859	32	14.11 (1, 115)*
Attention							
D2 test (concentration performance)	147.9	42.1	86	184	37	32	
Global z-score	-0.9773	1.138	86	0.000	1.000	32	11.18 (1, 109)*
Reasoning/Problem-Solving							
Trail Making B (completion time)	78	34.9	92	60.5	15.9	32	
Block-Design WAIS subtest	42.9	12.1	93	51.9	8.55	32	
Global z-scores	-1.019	1.486	91	-0.0003	0.732	32	14.31 (1, 114)
Verbal Memory†							
Immediate recall	35.02	10.8	92	47.1	11.5	32	
Delayed recall	20.5	8.4	92	29.5	9	32	
Global z-scores	-1.027	0.902	92	-0.0001	0.979	32	22.43 (1,115)**
Visual Memory							
Immediate recall	89.9	12.8	81	99.8	3.82	30	
Delayed recall	69.9	23.9	81	90.7	13.1	32	
Global z-scores	-2.09	2.34	81	0.059	0.817	30	18.93 (1, 103)*
Working Memory							
Digit Span WAIS subtest	16.03	4.16	94	17.3	4.03	32	
Spatial Span WMS subtest	16	3.62	92	17.8	3.33	32	
Global z-scores	-0.435	0.88	92	0.0005	0.796	32	16.57 (1, 115)
General Intelligence							
Abbreviated Full IQ	96	16	94	108	12.3	32	26.1 (1, 117)
Global Neurocognition							
Global z-scores	-1.071	1.026	80	0.078	0.569	30	25.73 (1, 102)*

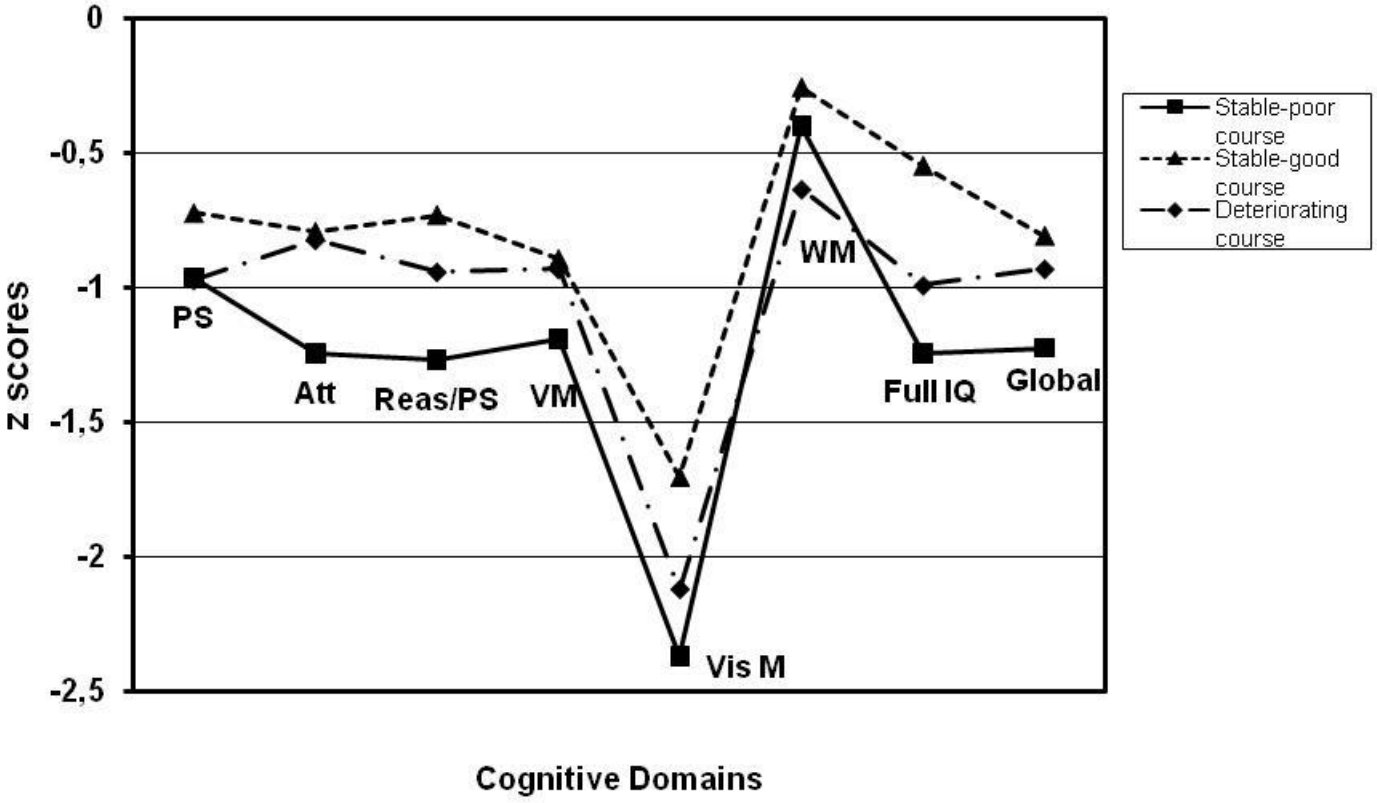
All analyses of covariance were conducted with education as a covariate.
†Analysis of Covariance with verbal memory were conducted with gender and education as covariates; * $p < 0.05$;
** $p < 0.005$

Table 3. Effect sizes of different cognitive domains across premorbid adjustment patterns.

Domains	Deteriorating Premorbid Adjustment		Stable-good Premorbid Adjustment		Stable-poor Premorbid Adjustment	
	Mean (SD)	ES	Mean (SD)	ES	Mean (SD)	ES
Processing Speed						
Trail Making A (completion time)	38.7 (16.9)		36.5 (12.7)		34.6 (13.2)	
Digit-Symbol Coding WAIS subtest	66.7 (14)		72.6 (16.8)		62.7 (12.7)	
Global z-score	-0.975 (1.229)	-1.13	-0.725 (1.115)	-0.84	-0.966 (0.94)	-1.12
Attention						
D2 test (concentration performance)	153.5 (51.7)		154.6 (37.8)		137.9 (35.5)	
Global z-score	-0.825 (1.397)	-0.83	-0.795 (1.022)	-0.8	-1.246 (0.959)	-1.25
Reasoning/Problem -Solving						
Trail Making B (completion time)	76.3 (31.5)		74.3 (38.4)		82 (35.4)	
Block-Design WAIS subtest	44.2 (12.9)		43.2 (11.9)		41.8 (11.8)	
Global z-score	-0.945 (1.512)	-1.29	-0.732 (1.175)	-1	-1.27 (1.642)	-1.73
Verbal Memory†						
Immediate recall	35.6 (10.9)		36.5 (11.1)		33.5 (10.4)	
Delayed recall	21.7 (8.9)		21.7 (9.02)		18.7 (7.4)	
Global z-score	-0.932 (0.946)	-0.95	-0.896 (0.945)	-0.92	-1.194 (0.832)	-1.22
Visual Memory						
Immediate recall	90.6 (13.6)		91.5 (10.8)		88.2 (13.7)	
Delayed recall	66.8 (25.2)		74.6 (23.8)		68.5 (23.2)	
Global z-score	-2.125 (2.56)	-2.67	-1.707 (2.004)	-2.16	-2.37 (2.445)	-2.98

Working Memory						
Digit Span WAIS subtest	15 (4.28)		16.6 (3.61)		16.4 (4.41)	
Spatial Span WMS subtest	15.4 (4.05)		16.7 (3.76)		15.8 (3.13)	
Global z-score	-0.636 (1.0322)	-0.80	-0.257 (0.781)	-0.32	-0.403 (0.815)	-0.51
General Intelligence Abbreviated Full IQ	95.6 (16.7)	-0.99	101 (14.5)	-0.55	92.5 (16.1)	-1.25
Global Neurocognition Global z-scores	-1.129 (1.199)	-2.12	-0.81 (0.933)	-1.56	-1.225 (0.934)	-2.29

Figure 1. Cognitive impairments across domains for each premorbid adjustment course patterns.



PS: Processing Speed; Att: Attention; Reas/PS: Reasoning/Problem-solving; VM: Verbal Memory; Vis M: Visual Memory; WM: Working Memory; Full IQ: Abbreviated full scale IQ; Global: Composite Neurocognitive Score.

CHAPTER 5:

DISCUSSION AND CONCLUSIONS

The presence of a generalized cognitive impairment in chronic as well as first-episode schizophrenia patients is indisputable. Such deficits are viewed as a central underlying feature of the illness. In addition, studies reveal that specific and relatively more severe cognitive impairments are superimposed onto a diffuse cognitive dysfunction. These impairments, regarded as disproportionate (Dickinson et al. 2006), usually involve verbal memory, executive functions, attention and processing speed. However, inconsistent findings frequently arise from studies investigating these impairments in schizophrenia. Indeed, some have argued that verbal memory deficits represent a cognitive endophenotype for the illness, while others regard executive dysfunctions to be a central feature. Conversely, there has been a burgeoning interest into processing speed impairments and more specifically, on a simple measure called the Digit Symbol, leading some to suggest that this impairment represents a core feature that may mediate a broader diversity of cognitive disturbances.

The heterogeneity of the illness itself may directly contribute to the variety of results pertaining to the nature of disproportionate cognitive impairments. Indeed, several attempts have been made to devise more homogeneous subgroups of patients characterized by similar clinical profiles to elucidate cognition in schizophrenia.

Enhancing our understanding of this feature of the illness may guide treatment schemes geared towards improving the cognitive performance of patients. These interventions could, in turn, lead to better occupational and social outcomes.

The present report attempted to shed some light on the previously mentioned inconsistencies in findings with regards to cognitive heterogeneity in schizophrenia. More specifically, in the present report we attempted to answer the following questions:

1) Whether the deficit on a simple processing speed task called the Digit-Symbol reflects the largest impairment in a first-episode psychosis sample and whether it qualifies for a disproportionate cognitive impairment in schizophrenia.
2) In addition, we attempted to verify whether the heterogeneity of cognitive impairments may be, in part, explained by varying levels of premorbid functioning as defined by distinct course patterns (i.e. stable-poor, deteriorating, stable-good) (Haas & Sweeney, 1992).

First, our results of study 1 (Chapter 3) suggest that first-episode psychosis patients present with severe cognitive impairments in most cognitive domains with slightly larger impairments on tasks assessing Visual Memory and on the Digit Symbol thus refuting our initial hypothesis regarding Verbal Memory being a disproportionate cognitive impairment in schizophrenia. Nevertheless, although the first study did not support our hypothesis, the interpretation of our results should be viewed with caution for reasons that will be described further on. On the other hand, our hypothesis regarding the Digit Symbol task appears to have been confirmed and results revealed that patients were more impaired compared to other widely used processing speed measures (i.e. the Trail Making-part A) potentially reflecting a fundamental differences of the tasks and/or the cognitive processes assessed. These findings are in line with others (Dickinson et al. 2007; Heinrichs & Zakzanis, 1998) and may guide future studies investigating the genetic basis of cognitive performance in schizophrenia (Dickinson et al. 2008). Indeed, most genetic studies in the field have focused primarily on potentially localizable cognitive processes. Results have been inconsistent with some studies finding an association between the val*108/158* met

polymorphism of the COMT gene (involved in dopamine transmission and activity) and working memory (Donohoe et al. 2007, Woodward et al. 2007) and attention (Bilder et al. 2002). Others have suggested a link between the *val* allele and general cognitive decline in schizophrenia but not with specific cognitive impairments (Mata et al. 2006). Thus, while these studies may offer targets for future genetic studies, the failure to replicate in this field can elicit future research to focus on the link between potential genetic markers and the consistent finding of a severe impairment on the DST task.

5.1 High versus Low Negative symptoms: Existence of disproportionate cognitive impairments?

We investigated the occurrence of distinct cognitive profiles within subgroups of patients with varying symptom severity. When we classified patients into *high* versus *low* levels of negative symptoms, our findings revealed a somewhat different pattern of cognitive impairments. Consistent with the literature pertaining to an association between negative symptoms and cognitive deficits, the patient group with high levels of negative symptoms group presented with larger/more severe cognitive deficits across all cognitive domains compared to the patients with lower levels. These results are in line with the view that "negative and cognitive symptoms may be separable, if not conceptually independent, domains of the illness" (Harvey et al. 2006).

These findings have significant implications for the prognosis of patients especially when considering previous results revealing that Digit Symbol is the only WAIS-III index associated with everyday functioning (Dickinson and Coursey 2002). Indeed, much research has focused on a sub-group of patients with a combination of severe negative symptoms and cognitive impairments due to its association with poor outcome (Hawkins et al. 1997, Pogue-Geile and Harrow 1985). However, our results suggest that patients with *low* levels of negative symptoms,

although generally less cognitively impaired, still present with disproportionate severe impairments in specific cognitive processes.

5.2 Premorbid Adjustment Patterns: Existence of disproportionate cognitive impairments?

Our results of study 2 (Chapter 4) with regards to premorbid adjustment patterns clearly demonstrate that patients with a "stable-poor" functioning generally present with more severe cognitive impairments compared to the "deteriorating" group which, in turn, are more impaired than the "stable-good" group. This classification method (Haas & Sweeney, 1992) seems to indicate that differentiation between these sub-groups is possible on the basis of severity rather than type of cognitive dysfunction. Thus, we did not find evidence of disproportionate cognitive impairments in a subgroup of schizophrenia based on the pattern of premorbid adjustment. Nevertheless, our general findings add to previous literature which shows that premorbid adjustment has good prognostic value for a variety of clinical characteristics such as, age of onset and severity of negative symptoms and outcomes such as treatment response and remission status (Addington and Addington, 1993; Gupta et al. 1995; Malla et al. 2002; Rund et al. 2004). Importantly, we did not investigate the possible association of substance use with premorbid adjustment and poor outcome in schizophrenia. Indeed, since both substance use and premorbid adjustment are independent predictors of long-term poor outcome in schizophrenia (Malla and Payne 2005) it is quite likely that both factors interact with each other in ways that remain unclear.

In addition, our findings may suggest that individuals with a "stable-good" premorbid adjustment simply have additional protective factors, either neurobiological or environmental which enable them to circumvent the deleterious effects of impaired verbal memory and to a lesser extent slower information processing speed on academic and social functioning.

Our results must be interpreted with caution as they may reflect the properties of psychometric measures used to assess cognitive functions. This common critique stems from the findings of a generalized cognitive impairment in schizophrenia (Jonides and Nee 2005). It may be that neuropsychological tasks are not refined enough to tap into specific cognitive deficits and thus, assess a wide range of cognitive processes. In a sample of healthy subjects, Joy et al. (2003) investigated the relative contribution of speed, memory and visual scanning in determining scores on the Digit Symbol. They concluded that speed and visual scanning efficiency accounted for a similar proportion of the variance in Digit Symbol performance while memory (using incidental learning tests) played a smaller secondary role when partialling out the variance accounted for by speed. Thus, although the authors did not specifically investigate the role of verbal memory, we cannot entirely rule out the possibility that poor performance on the Digit Symbol in our sample was due to cognitive processes other than processing speed. Conversely, the severe visual memory impairments found in our sample may also be, in part, due to processing speed inefficiencies. In another recent study by Morrens et al. (2008) (Morrens et al. 2008) in schizophrenia patients, results indicated that the Digit Symbol assesses both cognitive and psychomotor slowing but concluded that this latter aspect was not as properly assessed. These findings clearly indicate that more research is needed to delineate the various processes involved in successfully completing the Digit Symbol in order to clearly conclude that this task reliably assesses processing speed.

Taken together, our findings clearly support the view of a generalized cognitive impairment which is fundamental to psychotic disorders. However, our studies also provide some considerable advances with regards to the inconsistencies of disproportionate cognitive impairments (i.e. in excess of the averaged performance deficit across a range of other cognitive domains). Perhaps the variability of the findings pertaining to this line of research is, in part, due

to sample characteristics. For example, samples of first-episode psychosis consisting of individuals with more severe negative symptoms may "dilute" the findings of disproportionate cognitive impairments and demonstrate a broad range of severe impairments across all cognitive domains. Similarly, samples including poorly functioning patients who presented with a more insidious onset of the illness may also prevent a clear distinction between the magnitudes of impairments across domains. Indeed, our results strengthen the view that, in order to understand the complex nature of schizophrenia, samples need to include the majority of potential incidence cases for psychotic disorders. In conclusion, our findings are broadly in line with the pathophysiological models of schizophrenia suggesting widespread abnormalities among cortico-subcortical connections in a hetereogeneous groups of schizophrenia patients with distinct levels of symptoms and premorbid adjustment (Andreasen et al. 1999). On the other hand, more severely ill patients (i.e. higher levels of negative symptoms and poorer premorbid adjustment) may present with more widespread abnormalities which translate in additional cognitive deficits in other domains such as executive functions. Thus, in these individuals, specific neurobiological factors such as reduced dopaminergic or serotenergic transmission in specific brain regions may explain the additional severe cognitive impairments.

5.3. Bibliography

1. McGrath J, Saha S, Chant D, Welham J: Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev 2008; 30:67-76.

2. Tandon R, Keshavan MS, Nasrallah HA: Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. Schizophr Res 2008; 102(1-3):1-18.

3. Kraepelin E. Manic-Depressive Insanity and Paranoia. Edinburg, UK: Livingstone; 1919.

4. Bleuler E. Dementia Praecox or the Group of Schizophrenias. Zinkin J, editor. New York: International Univ. Press; 1911.

5. Green MF: What are the functional consequences of neurocognitive deficits in schizophrenia? Am J Psychiatry 1996; 153(3):321-30.

6. Green MF, Kern RS, Braff DL, Mintz J: Neurocognitive deficits and functional outcome in schizophrenia: are we measuring the "right stuff"? Schizophr Bull 2000; 26(1):119-36.

7. Dickinson D, Harvey PD: Systemic hypotheses for generalized cognitive deficits in schizophrenia: a new take on an old problem. Schizophr Bull 2009; 35(2):403-14.

8. Bilder RM, Goldman RS, Robinson D, Reiter G, Bell L, Bates JA, Pappadopulos E, Willson DF, Alvir JM, Woerner MG, Geisler S, Kane JM, Lieberman JA: Neuropsychology of first-episode schizophrenia: initial characterization and clinical correlates. Am J Psychiatry 2000; 157(4):549-59.

9. Mohamed S, Paulsen JS, O'Leary D, Arndt S, Andreasen N: Generalized cognitive deficits in schizophrenia: a study of first-episode patients. Arch Gen Psychiatry 1999; 56(8):749-54.

10. Heaton RK, Gladsjo JA, Palmer BW, Kuck J, Marcotte TD, Jeste DV: Stability and course of neuropsychological deficits in schizophrenia. Arch Gen Psychiatry 2001; 58(1):24-32.

11. Bilder RM, Lipschutz-Broch L, Reiter G, Geisler SH, Mayerhoff DI, Lieberman JA: Intellectual deficits in first-episode schizophrenia: evidence for progressive deterioration. Schizophr Bull 1992; 18(3):437-48.

12. Heinrichs RW, Zakzanis KK: Neurocognitive deficit in schizophrenia: a quantitative review of the evidence. Neuropsychology 1998; 12(3):426-45.

13. Mesholam-Gately R, Giuliano AJ, Goff KP, Faraone SV, LJ. S: Neuropsychology in first-episode schizophrenia: A meta-analytic review. Neuropsychology 2009:315-36.

14. Hutton SB, Puri BK, Duncan LJ, Robbins TW, Barnes TR, Joyce EM: Executive function in first-episode schizophrenia. Psychol Med 1998; 28(2):463-73.

15. Riley EM, McGovern D, Mockler D, Doku VC, S OC, Fannon DG, Tennakoon L, Santamaria M, Soni W, Morris RG, Sharma T: Neuropsychological functioning in first-episode psychosis--evidence of specific deficits. Schizophr Res 2000; 43(1):47-55.

16. Saykin AJ, Shtasel DL, Gur RE, Kester DB, Mozley LH, Stafiniak P, Gur RC: Neuropsychological deficits in neuroleptic naive patients with first-episode schizophrenia. Arch Gen Psychiatry 1994; 51(2):124-31.

17. Blanchard JJ, Neale JM: The neuropsychological signature of schizophrenia: generalized or differential deficit? Am J Psychiatry 1994; 151(1):40-8.

18. Braff DL, Heaton R, Kuck J, Cullum M, Moranville J, Grant I, Zisook S: The generalized pattern of neuropsychological deficits in outpatients with chronic schizophrenia with heterogeneous Wisconsin Card Sorting Test results. Arch Gen Psychiatry 1991; 48(10):891-8.

19. Dickinson D, Iannone VN, Wilk CM, Gold JM: General and specific cognitive deficits in schizophrenia. Biol Psychiatry 2004; 55(8):826-33.

20. Goldberg TE, Saint-Cyr JA, Weinberger DR: Assessment of procedural learning and problem solving in schizophrenic patients by Tower of Hanoi type tasks. J Neuropsychiatry Clin Neurosci 1990; 2(2):165-73.

21. Hoff AL, Riordan H, O'Donnell DW, Morris L, DeLisi LE: Neuropsychological functioning of first-episode schizophreniform patients. Am J Psychiatry 1992; 149(7):898-903.

22. Chapman LJ, Chapman JP: Strategies for resolving the heterogeneity of schizophrenics and their relatives using cognitive measures. J Abnorm Psychol 1989; 98(4):357-66.

23. Toulopoulou T, Morris RG, Rabe-Hesketh S, RM. M: Selectivity of verbal memory deficit in schizophrenic patients and their relatives. Am J Med Genet B Neuropsychiatr Genet 2003; 116B(1):1-7.

24. Albus M, Hubmann W, Mohr F, Scherer J, Sobizack N, Franz U, Hecht S, Borrmann M, Wahlheim C: Are there gender differences in neuropsychological performance in patients with first-episode schizophrenia? Schizophr Res 1997; 28(1):39-50.

25. Censits DM, Ragland JD, Gur RC, Gur RE: Neuropsychological evidence supporting a neurodevelopmental model of schizophrenia: a longitudinal study. Schizophr Res 1997; 24(3):289-98.

26. Saykin AJ, Gur RC, Gur RE, Mozley PD, Mozley LH, Resnick SM, Kester DB, Stafiniak P: Neuropsychological function in schizophrenia. Selective impairment in memory and learning. Arch Gen Psychiatry 1991; 48(7):618-24.

27. Weickert TW, Goldberg TE, Gold JM, Bigelow LB, Egan MF, Weinberger DR: Cognitive impairments in patients with schizophrenia displaying preserved and compromised intellect. Arch Gen Psychiatry 2000; 57(9):907-13.

28. Gold JM, Carpenter C, Randolph C, Goldberg TE, Weinberger DR: Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. Arch Gen Psychiatry 1997; 54(2):159-65.

29. Chan RC, Chen EY, Law CW: Specific executive dysfunction in patients with first-episode medication-naive schizophrenia. Schizophr Res 2006; 82(1):51-64.

30. Goldberg TE, Weinberger DR: Probing prefrontal function in schizophrenia with neuropsychological paradigms. Schizophr Bull 1988; 14(2):179-83.

31. Cirillo MA, Seidman LJ: Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. Neuropsychol Rev 2003; 13(2):43-77.

32. Dickinson D, Ramsey ME, Gold JM: Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. Arch Gen Psychiatry 2007; 64(5):532-42.

33. Aleman A, Hijman R, de Haan EH, Kahn RS: Memory impairment in schizophrenia: a meta-analysis. Am J Psychiatry 1999; 156(9):1358-66.

34. Paulsen JS, Heaton RK, Sadek JR, Perry W, Delis DC, Braff D, Kuck J, Zisook S, Jeste DV: The nature of learning and memory impairments in schizophrenia. J Int Neuropsychol Soc 1995; 1(1):88-99.

35. Brébion G, David AS, Bressan RA, LS. P: Role of processing speed and depressed mood on encoding, storage, and retrieval memory functions in patients diagnosed with schizophrenia. J Int Neuropsychol Soc 2007; 13(1):99-107.

36. Brewer WJ, Wood SJ, Phillips LJ, Francey SM, Pantelis C, Yung AR, Cornblatt B, McGorry PD: Generalized and specific cognitive performance in clinical high-risk cohorts: a review highlighting potential vulnerability markers for psychosis. Schizophr Bull 2006; 32(3):538-55.

37. Lencz T, Smith CW, McLaughlin D, Auther A, Nakayama E, Hovey L, Cornblatt BA: Generalized and specific neurocognitive deficits in prodromal schizophrenia. Biol Psychiatry 2006; 59(9):863-71.

38. Brewer WJ, Francey SM, Wood SJ, Jackson HJ, Pantelis C, Phillips LJ, Yung AR, Anderson VA, McGorry PD: Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. Am J Psychiatry 2005; 162(1):71-8.

39. Eastvold AD, Heaton RK, Cadenhead KS: Neurocognitive deficits in the (putative) prodrome and first episode of psychosis. Schizophr Res 2007; 93(1-3):266-77.

40. Hawkins KA, Addington J, Keefe RS, Christensen B, Perkins DO, Zipurksy R, Woods SW, Miller TJ, Marquez E, Breier A, McGlashan TH: Neuropsychological status of subjects at high risk for a first episode of psychosis. Schizophr Res 2004; 67(2-3):115-22.

41. Malhotra AK, Bates JA, Jaeger J, Petrides G, Robinson DG, Bilder RM, Nassauer KW: No evidence for phenotypic variation between probands in case-control versus family-based association studies of schizophrenia. Am J Med Genet 2002; 114(5):509-11.

42. Brebion G, Amador X, Smith MJ, Gorman JM: Mechanisms underlying memory impairment in schizophrenia. Psychol Med 1997; 27(2):383-93.

43. Brebion G, Amador X, Smith MJ, Gorman JM: Memory impairment and schizophrenia: the role of processing speed. Schizophr Res 1998; 30(1):31-9.

44. Salthouse TA: The processing-speed theory of adult age differences in cognition. Psychol Rev 1996; 103(3):403-28.

45. Morrens M, Hulstijn W, Sabbe B: Psychomotor slowing in schizophrenia. Schizophr Bull 2007; 33(4):1038-53.

46. Sheppard L, Vernon P: Intelligence and speed of information-processing: A review of 50 years of research. Personality and Individual Differences 2008; 44:535-51.

47. Antonova E, Sharma T, Morris R, Kumari V: The relationship between brain structure and neurocognition in schizophrenia: a selective review. Schizophr Res 2004; 70(2-3):117-45.

48. Henry JD, Crawford JR: A meta-analytic review of verbal fluency deficits in schizophrenia relative to other neurocognitive deficits. Cogn Neuropsychiatry 2005; 10(1):1-33.

49. Keefe RS, Eesley CE, Poe MP: Defining a cognitive function decrement in schizophrenia. Biol Psychiatry 2005; 57(6):688-91.

50. Rodriguez-Sanchez JM, Crespo-Facorro B, Gonzalez-Blanch C, Perez-Iglesias R, Vazquez-Barquero JL: Cognitive dysfunction in first-episode psychosis: the processing speed hypothesis. Br J Psychiatry Suppl 2007; 51:s107-10.

51. Leeson VC, Barnes TR, Harrison M, Matheson E, Harrison I, Mutsatsa SH, Ron MA, Joyce EM: The Relationship Between IQ, Memory, Executive Function, and Processing Speed in Recent-Onset Psychosis: 1-Year Stability and Clinical Outcome. Schizophr Bull 2008.

52. Gignac G, Vernon P: Digit Symbol Rotation: A more g-loaded version of the tradional Digit Symbol subtest. Intelligence 2003; 31:1-8.

53. Heinrichs RW, Awad AG: Neurocognitive subtypes of chronic schizophrenia. Schizophr Res 1993; 9(1):49-58.

54. Townsend LA, Malla AK, Norman RM: Cognitive functioning in stabilized first-episode psychosis patients. Psychiatry Res 2001; 104(2):119-31.

55. Townsend LA, Norman RM: Course of cognitive functioning in first episode schizophrenia spectrum disorders. Expert Rev Neurother 2004; 4(1):61-8.

56. Green AI, Tohen MF, Hamer RM, Strakowski SM, Lieberman JA, Glick I, Clark WS: First episode schizophrenia-related psychosis and substance use disorders: acute response to olanzapine and haloperidol. Schizophr Res 2004; 66(2-3):125-35.

57. Harvey PD, Koren D, Reichenberg A, Bowie CR: Negative symptoms and cognitive deficits: what is the nature of their relationship? Schizophr Bull 2006; 32(2):250-8.

58. Brazo P, Marie RM, Halbecq I, Benali K, Segard L, Delamillieure P, Langlois-Thery S, Van Der Elst A, Thibaut F, Petit M, Dollfus S: Cognitive patterns in subtypes of schizophrenia. Eur Psychiatry 2002; 17(3):155-62.

59. Heydebrand G, Weiser M, Rabinowitz J, Hoff AL, DeLisi LE, Csernansky JG: Correlates of cognitive deficits in first episode schizophrenia. Schizophr Res 2004; 68(1):1-9.

60. Malla AK, Norman RM, Manchanda R, Townsend L: Symptoms, cognition, treatment adherence and functional outcome in first-episode psychosis. Psychol Med 2002; 32(6):1109-19.

61. Mass R, Schoemig T, Hitschfeld K, Wall E, Haasen C: Psychopathological syndromes of schizophrenia: evaluation of the dimensional structure of the positive and negative syndrome scale. Schizophr Bull 2000; 26(1):167-77.

62. Green M, Walker E: Neuropsychological performance and positive and negative symptoms in schizophrenia. J Abnorm Psychol 1985; 94(4):460-9.

63. Zakzanis KK: Neuropsychological correlates of positive vs. negative schizophrenic symptomatology. Schizophr Res 1998; 29(3):227-33.

64. Buchanan RW, Strauss ME, Kirkpatrick B, Holstein C, Breier A, Carpenter WT, Jr.: Neuropsychological impairments in deficit vs nondeficit forms of schizophrenia. Arch Gen Psychiatry 1994; 51(10):804-11.

65. Kirkpatrick B, Buchanan RW, Ross DE, Carpenter WT, Jr.: A separate disease within the syndrome of schizophrenia. Arch Gen Psychiatry 2001; 58(2):165-71.

66. Cohen AS, Saperstein AM, Gold JM, Kirkpatrick B, Carpenter WT, Jr., Buchanan RW: Neuropsychology of the deficit syndrome: new data and meta-analysis of findings to date. Schizophr Bull 2007; 33(5):1201-12.

67. Liddle PF: Schizophrenic syndromes, cognitive performance and neurological dysfunction. Psychol Med 1987; 17(1):49-57.

68. Liddle PF: Regional brain abnormalities associated with specific syndromes of persistent schizophrenic symptoms. Clin Neuropharmacol 1992; 15 Suppl 1 Pt A:401A-2A.

69. Goldstein G, Allen DN, Seaton BE: A comparison of clustering solutions for cognitive heterogeneity in schizophrenia. J Int Neuropsychol Soc 1998; 4(4):353-62.

70. Norman R, Malla AK, Morrison-Stewart SL, Helmes E, Williamson PC, Thomas J, L. C: Neuropsychological correlates of syndromes in schizophrenia. Br J Psychiatry 1997; 170:134-9.

71. Addington J, Addington D: Premorbid functioning, cognitive functioning, symptoms and outcome in schizophrenia. J Psychiatry Neurosci 1993; 18(1):18-23.

72. Gupta S, Rajaprabhakaran R, Arndt S, Flaum M, Andreasen NC: Premorbid adjustment as a predictor of phenomenological and neurobiological indices in schizophrenia. Schizophr Res 1995; 16(3):189-97.

73. Rund BR, Melle I, Friis S, Larsen TK, Midboe LJ, Opjordsmoen S, Simonsen E, Vaglum P, McGlashan T: Neurocognitive dysfunction in first-episode psychosis: correlates with symptoms, premorbid adjustment, and duration of untreated psychosis. Am J Psychiatry 2004; 161(3):466-72.

74. Rabinowitz J, Harvey PD, Eerdekens M, Davidson M: Premorbid functioning and treatment response in recent-onset schizophrenia. Br J Psychiatry 2006; 189:31-5.

75. Silverstein ML, Mavrolefteros G, Close D: Premorbid adjustment and neuropsychological performance in schizophrenia. Schizophr Bull 2002; 28(1):157-65.

76. Larsen TK, Friis S, Haahr U, Johannessen JO, Melle I, Opjordsmoen S, Rund BR, Simonsen E, Vaglum PV, McGlashan TH: Premorbid adjustment in first-episode non-affective psychosis: distinct patterns of pre-onset course. Br J Psychiatry 2004; 185:108-15.

77. Addington J, Addington D: Patterns of premorbid functioning in first episode psychosis: relationship to 2-year outcome. Acta Psychiatr Scand 2005; 112(1):40-6.

78. Levitt JJ, O'Donnell BF, McCarley RW, Nestor PG, Shenton ME: Correlations of premorbid adjustment in schizophrenia with auditory event-related potential and neuropsychological abnormalities. Am J Psychiatry 1996; 153(10):1347-9.

79. Haas GL, Sweeney JA: Premorbid and onset features of first-episode schizophrenia. Schizophr Bull 1992; 18(3):373-86.

80. Norman RM, Malla AK, Manchanda R, Townsend L: Premorbid adjustment in first episode schizophrenia and schizoaffective disorders: a comparison of social and academic domains. Acta Psychiatr Scand 2005; 112(1):30-9.

81. First M, Spitzer, RL, MG, Williams, JBW. Structured Clinical Interview for DSM-IV Axis 1 Disorders. Research. B, editor.: New York State Psychiatric Institute; 1995.

82. Kay SR, Fiszbein, A. & Opler, L.A. : The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia Bulletin 1987; 13:261-76.

83. Malla A, Norman R, Schmitz N, Manchanda R, Bechard-Evans L, Takhar J, Haricharan R: Predictors of rate and time to remission in first-episode psychosis: a two-year outcome study. Psychol Med 2006; 36(5):649-58.

84. Bechard-Evans L, Schmitz N, Abadi S, Joober R, King S, Malla A: Determinants of help-seeking and system related components of delay in the treatment of first-episode psychosis. Schizophr Res 2007; 96(1-3):206-14.

85. Bezchlibnyk-Butler KZ, Jeffries JJ: Clinical Handbook of Psychotropic Drugs. 2007.

86. Jeste DV, Heaton SC, Paulsen JS, Ercoli L, Harris J, Heaton RK: Clinical and neuropsychological comparison of psychotic depression with nonpsychotic depression and schizophrenia. Am J Psychiatry 1996; 153(4):490-6.

87. Jogems-Kosterman BJ, Zitman FG, Van Hoof JJ, Hulstijn W: Psychomotor slowing and planning deficits in schizophrenia. Schizophr Res 2001; 48(2-3):317-33.

88. Mahurin RK, Velligan DI, Miller AL: Executive-frontal lobe cognitive dysfunction in schizophrenia: a symptom subtype analysis. Psychiatry Res 1998; 79(2):139-49.

89. van Hoof JJ, Jogems-Kosterman BJ, Sabbe BG, Zitman FG, Hulstijn W: Differentiation of cognitive and motor slowing in the Digit Symbol Test (DST): differences between depression and schizophrenia. J Psychiatr Res 1998; 32(2):99-103.

90. Nuerchterlein K, Barch D, Gold J: Identification of separable cognitive factors in schizophrenia Schizophr Res 2004; 72:29-39.

91. Dickinson D, Ragland JD, Calkins ME, Gold JM, Gur RC: A comparison of cognitive structure in schizophrenia patients and healthy controls using confirmatory factor analysis. Schizophr Res 2006; 85(1-3):20-9.

92. Cohen J. Statistical Power for the Behavioral Sciences. Hillsdale, NJ: Laurence A Erlbaum Associates; 1988.

93. Hill SK, Schuepbach D, Herbener ES, Keshavan MS, Sweeney JA: Pretreatment and longitudinal studies of neuropsychological deficits in antipsychotic-naive patients with schizophrenia. Schizophr Res 2004; 68(1):49-63.

94. Brébion G, Bressan RA, David AS, LS. P: Role of processing speed and premorbid IQ on visual recognition in patients with schizophrenia.
. J Clin Exp Neuropsychol 2009; 31(3):302-11.

95. Skelley S, Goldberg TE, Egan MF, Weinberger DR, JM. G: Verbal and visual memory: characterizing the clinical and intermediate phenotype in schizophrenia.
. Schizophr Res 2008; 105(1-3):78-85.

96. Wechsler D. Wechsler Memory Scale-Revised. Corporation P, editor. New York; 1997.

97. Dickinson D, Gold JM: Less unique variance than meets the eye: overlap among traditional neuropsychological dimensions in schizophrenia. Schizophr Bull 2008; 34(3):423-34.

98. Joy S, Fein D, Kaplan E: Decoding digit symbol: speed, memory, and visual scanning. Assessment 2003; 10(1):56-65.

99. Purdon SE: Cognitive improvement in schizophrenia with novel antipsychotic medications. Schizophr Res 1999; 35 Suppl:S51-60.

100. Morrens M, Hulstijn W, Van Hecke J, Peuskens J, Sabbe BG: Sensorimotor and cognitive slowing in schizophrenia as measured by the Symbol Digit Substitution Test. J Psychiatr Res 2006; 40(3):200-6.

101. Cannon-Spoor HE, Potkin SG, Wyatt RJ: Measurement of premorbid adjustment in chronic schizophrenia. Schizophr Bull 1982; 8(3):470-84.

102. Wechsler D. Wechsler Adult Intelligence Scale Revised (WAIS-R), Manual. Corporation TP, editor. Cleveland, OH; 1981.

103. Brickenkamp R. Test D. Gottingen: Aufmerksamkeits-Belastung-Test
1998.

104. Reitan RM. The Halstead-Reitan Neuropsychological Test Battery. Tucson, AZ: Neuropsychology Press; 1985.

105. Larsen TK, McGlashan TH, Johannessen JO, Vibe-Hansen L: First-episode schizophrenia: II. Premorbid patterns by gender. Schizophr Bull 1996; 22(2):257-69.

106. Childers SE, Harding CM: Gender, premorbid social functioning, and long-term outcome in DSM-III schizophrenia. Schizophr Bull 1990; 16(2):309-18.

107. Fennig S, Putnam K, Bromet EJ, Galambos N: Gender, premorbid characteristics and negative symptoms in schizophrenia. Acta Psychiatr Scand 1995; 92(3):173-7.

108. Buchanan RW, Kirkpatrick B, Heinrichs DW, Carpenter WT, Jr.: Clinical correlates of the deficit syndrome of schizophrenia. Am J Psychiatry 1990; 147(3):290-4.

109. Kelley ME, Gilbertson M, Mouton A, van Kammen DP: Deterioration in premorbid functioning in schizophrenia: a developmental model of negative symptoms in drug-free patients. Am J Psychiatry 1992; 149(11):1543-8.

110. Mukherjee S: Schizophrenia: more than two disease processes? Am J Psychiatry 1991; 148(12):1756-7.

111. Amminger GP, Resch F, Mutschlechner R, Friedrich MH, Ernst E: Premorbid adjustment and remission of positive symptoms in first-episode psychosis. Eur Child Adolesc Psychiatry 1997; 6(4):212-8.

112. Carpenter WT, Jr., Heinrichs DW, Wagman AM: Deficit and nondeficit forms of schizophrenia: the concept. Am J Psychiatry 1988; 145(5):578-83.

113. Donohoe G, Morris DW, Robertson IH, Clarke S, McGhee KA, Schwaiger S, Nangle JM, Gill M, A. C: Variance in facial recognition performance associated with BDNF in schizophrenia. Am J Med Genet B Neuropsychiatr Genet 2007; 144(B)(4):578-9.

114. Woodward N, Jayathilake K, HY. M: COMT val108/158met genotype, cognitive function, and cognitive improvement with clozapine in schizophrenia. Schizophr Res 2007; 90(1-3):86-96.

115. Bilder R, Volavka J, Czobor P, Malhotra AK, Kennedy JL, Ni X, Goldman RS, Hoptman MJ, Sheitman B, Lindenmayer JP, Citrome L, McEvoy JP, Kunz M, Chakos M, Cooper TB, JA. L: Neurocognitive correlates of the COMT Val(158)Met polymorphism in chronic schizophrenia. . Biol Psychiatry 2002; 52(7):701-7.

116. Mata I, Arranz MJ, Staddon S, Lopez-Ilundain JM, Tabares-Seisdedos R, RM. M: The high-activity Val allele of the catechol-O-methyltransferase gene predicts greater cognitive deterioration in patients with psychosis. Psychiatr Genet 2006; 16(5):213-6.

117. Dickinson D, Coursey RD: Independence and overlap among neurocognitive correlates of community functioning in schizophrenia. Schizophr Res 2002; 56(1-2):161-70.

118. Hawkins KA, Hoffman RE, Quinlan DM, Rakfeldt J, Docherty NM, Sledge WH: Cognition, negative symptoms, and diagnosis: a comparison of schizophrenic, bipolar, and control samples. J Neuropsychiatry Clin Neurosci 1997; 9(1):81-9.

119. Pogue-Geile MF, Harrow M: Negative symptoms in schizophrenia: their longitudinal course and prognostic importance. Schizophr Bull 1985; 11(3):427-39.

120. Malla A, Payne J: First-episode psychosis: psychopathology, quality of life, and functional outcome. Schizophr Bull 2005; 31(3):650-71.

121. Jonides J, Nee DE: Assessing dysfunction using refined cognitive methods. Schizophr Bull 2005; 31(4):823-9.

122. Morrens M, Hulstijn W, Sabbe B: The effects of atypical and conventional antipsychotics on reduced processing speed and psychomotor slowing in schizophrenia: a cross-sectional exploratory study. Clin Ther 2008; 30(4):684-92.

123. Andreasen NC, Nopoulos P, O'Leary DS, Miller DD, Wassink T, Flaum M: Defining the phenotype of schizophrenia: cognitive dysmetria and its neural mechanisms. Biol Psychiatry 1999; 46(7):908-20.