FACULTY OF SOCIAL SCIENCES
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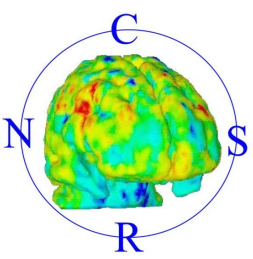
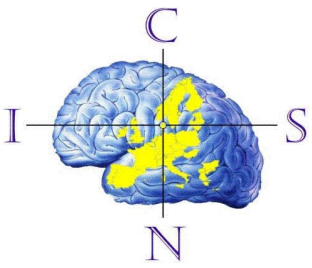
PhD thesis

Rune Andersen

Cognition in First Episode Schizophrenia:

Core Deficits and Effects of Antipsychotics





PhD Thesis

Cognition in First Episode Schizophrenia: Core Deficits and Effects of Antipsychotics

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TABLE OF CONTENTS

APPENDICES

PREFACE

This PhD project was carried out at the Center for Neuropsychiatric Schizophrenia Research (CNSR) and from 2009 at the Lundbeck Foundation Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS). CNSR and CINS are hosted by the Capital Region of Denmark, Mental Health Services and since 2006 located at the Psychiatric University Center in Glostrup (CINS from 2009). The project is based on a clinical study in which a cohort of antipsychotic-naïve, first-episode schizophrenia patients was cognitively assessed before and after six months of treatment with the second generation antipsychotic quetiapine.

The thesis consists of two introductory chapters on the relevant theoretical background concerning cognitive deficits in schizophrenia (Chapters 1 and 2). The methodology and empirical data concerning the cognitive profile of first-episode antipsychotic-naïve schizophrenic patients and effects of quetiapine are presented and discussed separately. Chapter 3 thus presents data from a large cohort of first-episode antipsychotic-naïve schizophrenic patients, and Chapter 4 presents data from the six months of treatment with quetiapine. Chapter 5 is a conclusion of the thesis, and Chapter 6 suggests future directions in research.

ACKNOWLEDGEMENTS

I first became part of the Center for Neuropsychiatric Schizophrenia Research (CNSR) in 2003 when I, as still a student, assisted on a study about cholinergic augmentation of cognitive deficits in schizophrenia. After graduating I stayed on to work towards my PhD about the cognitive function in schizophrenia.

My closest collaborators and fellow PhD students have been Hans Rasmussen, Bjørn Ebdrup, Bodil Aggernæs, and Trine Hammer, whom I thank for support during the process of planning, recruiting and testing the patients, their relatives and matched healthy controls. I am grateful to my principal supervisor Anders Gade for his support and guidance throughout, and for introducing me to cognition research in schizophrenia. Many thanks to my project supervisor Birte Glenthøj for initiating and helping to fund the studies described in this thesis as well as for advice on neuropsychiatric research and general support on issues and challenges I have provided her with. Thanks to my co-supervisor Bob Oranje for unwavering support and competent advice on statistics and research methodology. Sincere thanks to Birgitte Fagerlund for continuous support and guidance in the long process of completing my thesis. Thanks to Henrik Lublin for useful sessions on issues of psychopharmacology and psychopathology, and thanks to Lisbeth Jensen for help with most things practical. Thanks to all of my past and present colleagues at the CNSR for your professional feedback and support. Patients, their relatives, and healthy controls, are especially thanked for their contribution of time and efforts. Without their cooperation, my work would not have been possible.

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Thanks to my family - my parents and my brother - and close friends for providing needed distractions from the issues and challenges of finalizing the thesis. And finally, a very special thanks to my exceptional wife Yu-Min for her endless support and for providing the most needed distractions.

LIST OF ARTICLES

The thesis is based on the following research articles, which are presented in the appendices:

Andersen, R., Fagerlund, B., Oranje, B., Gade, A., Rasmussen, H., Ebdrup, B.H., Aggernaes, B & Glenthoj, B.Y. (in preparation). The Influence of Impaired Processing Speed on Cognition in First-Episode Antipsychotic-Naïve Schizophrenic Patients.

Andersen, R., Fagerlund, B., Oranje, B., Gade, G., Rasmussen, H., Ebdrup, B.H., Aggernaes, B & Glenthoj, B.Y. (submitted). Cognitive Effects of Six Months Treatment with Quetiapine in Antipsychotic-Naïve First-Episode Schizophrenia.

LIST OF ABBREVIATIONS

ANCOVA = Analysis of Covariance
ANOVA = Analysis of Variance
CAFÉ = Comparison of Atypicals in First Episode of Psychosis
CANTAB = Cambridge Neuropsychological Test Automated Battery
CATIE = Clinical Antipsychotic Trials of Intervention Effectiveness
CINS = Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research
CNB = Penn Computerized Neurocognitive Battery
CNSR = Center for Neuropsychiatric Schizophrenia Research
CNTRICS = Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia
COGS = Consortium on the Genetics of Schizophrenia
CPT = Continuous Performance Test
DART = Danish Adult Reading Test
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders
EUFEST = European First Episode Schizophrenia Trial
ICD-10 = International Classification of Diseases (World Health Organization)
IED = Intra- and Extradimensional set shifting
IQ = Intelligence Quotient
MATRICS = Measurement and Treatment Research to Improve Cognition in Schizophrenia
MCCB = MATRICS Consensus Cognitive Battery
NART = National Adult Reading Test
PANSS = Positive and Negative Syndrome Scale
RCFT = Rey-Osterrieth Complex Figure Test
RTI = Reaction and Movement Time
RVIP = Rapid Visual Information Processing
SCAN = Schedules for Clinical Assessment in Neuropsychiatry Version 2.1
SCOLP = Speed and Comprehension of Language Processing
SD = Standard deviation
SDMT = Symbol Digit Modalities Test
SOC = Stockings of Cambridge
SPSS = Statistical Package for the Social Sciences
SSP = Spatial Span
SWM = Spatial Working Memory
SOC = Stockings of Cambridge
ToM = Theory of Mind
WAIS = Wechsler Adult Intelligence Scale
WCST = Wisconsin Card Sorting Test

DANSK RESUMÉ (DANISH SUMMARY)

Kognition ved debuterende skizofreni: Kerneforstyrrelser og effekten af antipsykotika

Et af de centrale træk ved skizofreni er forstyrret kognition. Dog er grad og karakter af kognitive forstyrrelser hos debuterende antipsykotika-naive skizofrene patienter, og virkningerne af antipsykotika på disse forstyrrelser, stadig noget uklar, bl.a. fordi tidligere undersøgelser ofte har inkluderet relativt små og heterogene forsøgsgrupper.

De primære mål med denne ph.d.-afhandling var at karakterisere den grundlæggende kognitive profil hos debuterende og hidtil ubehandlede skizofreni patienter, at undersøge den generelle effekt af langsom forarbejdningshastighed på kognition, og at undersøge effekten på kognition af seks måneders antipsykotisk monoterapi med quetiapin. Inklusionen af en relativt homogen gruppe af antipsykotika-naive debuterende skizofreni patienter skulle sikre, at potentielle problemer såsom virkninger af kronicitet eller antipsykotisk medicin undgås.

Afhandlingen er baseret på et klinisk forskningsstudie udført på Center for Neuropsychiatric Schizophrenia Research, hvor en kohorte af antipsykotika-naive, debuterende skizofreni patienter blev undersøgt med et omfattende neuropsykologisk testbatteri før og efter seks måneders behandling med det andet generations antipsykotikum quetiapin. For pålideligt at kunne undersøge omfanget af kognitive forstyrrelser og test-retest effekten på neuropsykologiske test blev en rask kontrolgruppe også testet ved baseline og efter seks måneder.

Otteogfyrre patienter og 48 raske kontrolpersoner blev undersøgt med et omfattende neuropsykologisk testbatteri ved baseline, der målte forskellige kognitive funktioner, såsom verbal intelligens, forarbejdningshastighed, vedvarende opmærksomhed, arbejdshukommelse, tænkning og problemløsning, verbal indlæring og hukommelse, visuel indlæring og hukommelse, reaktionstid, og eksekutiv forarbejdninghastighed. Efter at patienterne var blevet behandlet med quetiapin i seks måneder, blev både patienter og matchede kontroller testet igen. I alt 24 patienter gennemførte undersøgelsesforløbet.

Resultaterne fra baseline studiet viste, at antipsykotika-naive debuterende patienter med skizofreni har moderat til svære forstyrrelser i alle de kognitive domæner, der blev undersøgt, sammenlignet med raske kontrolpersoner. Efter at have kontrolleret for forarbejdningshastighed, forsvandt alle signifikante forskelle mellem patienter og raske kontrolpersoner på de kognitive domæner.

Resultaterne fra follow-up studiet, hvor patienterne efter de indledende undersøgelser gennemgik seks måneder behandling med quetiapin, og hvor en ubehandlet kontrolgruppe gennemgik samme undersøgelser, gav ikke bevis for, at quetiapin generelt forbedrede de kognitive funktioner.

Overordnet peger resultaterne på at langsom forarbejdningshastighed kan være en væsentlig årsag til kognitive forstyrrelser hos skizofreni patienter, og at der er et behov for nye behandlingsstrategier rettet mod de kognitive forstyrrelser ved skizofreni.

ENGLISH SUMMARY

One of the core features of schizophrenia is impaired cognition. However, the severity and pattern of cognitive deficits in antipsychotic-naïve patients with first-episode schizophrenia, and the effects of antipsychotics on these deficits, still remain somewhat unclear, because previous studies have often employed relatively small and heterogeneous samples.

The primary objectives of the present PhD thesis were to characterize the basic cognitive structure and profile of antipsychotic-naïve first-episode schizophrenia patients, investigate the contribution of impaired processing speed on cognition, and to examine the effects on cognition of six months of quetiapine monotherapy. The inclusion of a relatively homogeneous group of first-episode, antipsychotic-naïve schizophrenia patients should entail that potentially confounding issues such as effects of chronicity or medication would not be present.

The thesis is based on a clinical longitudinal study carried out at the Center for Neuropsychiatric Schizophrenia Research in which a cohort of antipsychotic-naïve, first-episode schizophrenia patients was assessed with a comprehensive neuropsychological test battery before and after six months of treatment with the second generation antipsychotic quetiapine. In order to examine the magnitude of cognitive deficits and the test-retest effects of neuropsychological tests, a matched healthy control group was also tested at baseline and after six months.

Forty-eight patients and 48 healthy controls were tested with a comprehensive neuropsychological test battery at baseline that assessed domains of verbal intelligence, processing speed, sustained attention, working memory, reasoning and problem solving, verbal learning and memory, visual learning and memory, reaction time, and speed of executive processing. Following this, the patients were treated with quetiapine for a period of six months, after which both patients and matched controls were retested. A total of 24 patients completed the study.

The results of the baseline study revealed that first-episode, antipsychotic-naïve patients with schizophrenia show moderate to severe deficits in all the major cognitive domains that were assessed, when compared to healthy controls. After controlling for speed of processing as an

additional covariate, all significant differences between patients and healthy controls on cognitive domains disappeared.

The results from the follow-up study, in which the patients after the initial baseline assessments were treated for 6 months with quetiapine while the controls received no treatments, did not indicate evidence of a general cognition enhancing effects of quetiapine.

In conclusion, the main results indicate that impaired processing speed may be a substantial general component behind cognitive deficits in schizophrenia patients, and that better treatment strategies are warranted to ameliorate the cognitive deficits in schizophrenia.

CHAPTER 1 - INTRODUCTION

Schizophrenia is a chronic, severe, and disabling disorder that affects an estimated one person in a hundred (McGrath et al., 2009). The symptoms of schizophrenia vary greatly in type and intensity from person to person (Tandon, Nasrallah & Keshavan, 2009). Psychotic episodes with "positive" symptoms of delusions, hallucinations, disorganized speech and behaviour are often alternated or intermingled with periods in which "negative" deficit symptoms, such as poverty of speech, flattening of affect, lack of initiative and social withdrawal, are prominent. These varied and insidious symptoms generally begin in late adolescence or early adulthood and usually progress throughout life.

Considerable evidence suggests that schizophrenia is fundamentally a disorder of subtle aberrations of brain development and plasticity, which manifests itself in cognitive impairment (Jindal & Keshavan, 2008a). The profile of cognitive deficits is broad, severe, and is likely present in most if not all patients (Dickinson et al., 2007). Marked cognitive deficits can be detected at the time of the first psychotic episode (Mesholam-Gately et al., 2009) or even earlier than the onset of clinical symptoms (Bilder et al., 2006; Woodberry et al., 2008). There may be a (further) decline in cognitive function just prior to or during onset of illness (Rund, 2009), also in patients performing seemingly normal on neuropsychological tests (Palmer et al., 1997). The cognitive deficits stay relatively stable throughout the course of illness (Rund, 1998), independent of symptom change (Heaton et al., 2001), and have considerable detrimental effects on social and vocational outcomes (Green, 1996; Green et al., 2000), as well as for treatment success and rehabilitation (Silverstein et al., 1998).

Cognitive enhancement has been recognized as an important treatment target in schizophrenia (Harvey, 2009). Results of current studies (Mishara & Goldberg, 2004; Keefe et al., 2007a, 2007b; Goldberg et al., 2007; Davidson et al., 2009) examining the impact of antipsychotic medication on cognition have been largely disappointing, ranging from small improvements to worsening. Early clinical studies (Keefe et al., 1999; Meltzer & McGurk, 1999; Harvey & Keefe, 2001; Woodward et al., 2005) suggested that there may be a modest advantage for second generation over first generation antipsychotics due to a different profile of receptor actions that have additional and less adverse effects.

To test the effects of second generation antipsychotics on cognitive function in patients with schizophrenia, it is optimal to include only first episode patients in a study (Salimi, Jarskog & Lieberman, 2009; Hill et al., 2010). This is to avoid potentially confounding effects of chronicity, long-term medication and institutionalization. First episode patients also respond in high rates to antipsychotic medication at doses roughly half of those required for chronic patients.

A delineation of the cognitive deficits in first episode patients and the changes brought about by an antipsychotic medication with a specific receptor profile would provide valuable information about the neurobiology of schizophrenia (Thaker, 2007; Jindal & Keshavan, 2008b). Cognitive deficits might thus be potent indicators of specific genetic traits that represent susceptibility for schizophrenia, and the antipsychotic medication might identify putative molecular targets active in modulating cognition.

To reliably identify subtypes of schizophrenia with distinct deficit and treatment profiles, it is important to include a broad neuropsychological test battery that is sensitive and specific enough to detect all the separate domains of cognitive functioning (Nuechterlein et al., 2004; Silverstein, 2008; Kertzman et al., 2008). For several reasons, it is also important to let a matched group of healthy subjects undergo the same neuropsychological testing as the patients, mainly to compare performance and detect deficits in patients, but also to detect improvement from treatment (Fagerlund et al., 2004; Goldberg et al., 2007; Szöke et al., 2008; Crespo-Facorro et al., 2009; Hill et al., 2010). Otherwise the changes in patient performance may simply be due to effects of learning or practice and not reflect genuine improvement.

The controlled study of cognitive deficits in first episode patients has relevance for understanding the neurobiological basis of schizophrenia (Gur et al., 2007). It could contribute to a more reliable diagnosis of the schizophrenic psychoses and help to differentiate subtypes (Green & Nuechterlein, 1999; Lewis, 2004; Keefe & Fenton, 2007; Szöke et al., 2008). This might even help to identify individuals with increased risk of schizophrenia and thus contribute to early diagnosis and intervention (Brewer et al., 2006; Niendam et al., 2009). Knowledge gained from studying effects of antipsychotic medication on patients with different cognitive and symptom profiles could also contribute to more individualised treatment strategies (Salimi, Jarskog & Lieberman, 2009).

CHAPTER 2 - COGNITIVE DEFICITS IN SCHIZOPHRENIA

A core feature of schizophrenia is cognitive impairment. Patients generally perform an average of 0.5 to 1.5 standard deviations below healthy control means on neuropsychological tests, a performance consistent with mild to moderate cognitive impairment (Fioravanti et al., 2005; Mesholam-Gately et al., 2009; Kravariti et al., 2009). Although some patients perform within age-adjusted norms, their performance is worse than predicted based on estimated levels of cognitive functioning before illness and parental education (Keefe, Eesley & Poe, 2005). The most prominent cognitive deficits occur in the domains of memory, attention, working memory, executive function, speed of processing, and social cognition (Nuechterlein et al., 2004; Fioravanti et al., 2005; Gur et al., 2007). These deficits often appear in milder form before the onset of clinical symptoms, having been demonstrated in adolescents at risk for schizophrenia and individuals in prodromal states (Bilder et al., 2006; Woodberry et al., 2008; Pantelis et al., 2009b). Attenuated but significant deficits are also present in clinically unaffected first-degree relatives of patients with schizophrenia (Sitskoorn et al., 2004; Snitz et al., 2006), demonstrating that cognitive impairment is at least partially heritable and thus possibly intrinsic to schizophrenia (Gur et al., 2007; Toulopoulou et al., 2007). The cognitive deficits in schizophrenia persist and remain relatively stable throughout the patient's life regardless of remission of psychosis (Rund, 1998; Heaton et al., 2001), and have substantial influence on psychosocial functioning and social integration (Green, 1996; Green et al., 2000). Treatment with antipsychotic medication only has little, if any, effect on cognitive deficits (Keefe et al., 2007a, 2007b; Goldberg et al., 2007; Szöke et al., 2008; Davidson et al., 2009).

The crucial aspects

The cognitive deficits in schizophrenia are profound and clinically relevant (Palmer, Dawes & Heaton, 2009). The study of these deficits has generated numerous publications and defies comprehensive review in the current thesis. Therefore, the approach of this chapter is deliberately selective, and emphasizes only robust findings from the most clinically relevant areas for schizophrenia. These areas include cognitive deficits as biological risk markers, general and specific deficits in different cognitive domains, the stability and course of cognitive impairment, the

relationship between clinical symptoms and cognition, the importance of cognition for functional outcome, the impact of current pharmacological treatment on cognitive functions, and conceptual and methodological issues in the use of cognition as an outcome measure. In addition, this chapter will focus on characterizing the basic cognitive structure and profile of patients with first episode schizophrenia.

Cognitive endophenotypes

The liability to schizophrenia is highly heritable, as shown through the patterns of risk in first-degree relatives (Gottesman & Gould, 2003). However, robust susceptibility genes for schizophrenia have remained elusive. This may be because it is not schizophrenia itself that is heritable, but neurobiological traits associated with vulnerability to schizophrenia. These traits are called endophenotypes and refer to measurable phenotypes that lie intermediate between genetic infrastructure and clinical presentation. An endophenotype may thus be any neurobiological measure that can be related to the underlying molecular genetics of the illness (Braff et al., 2007). The key criteria for endophenotypic vulnerability measures include association with illness, state independence, heritability, findings of higher rates in relatives of probands than in the general population, and cosegregation within families (Gottesman & Gould, 2003). Measures of cognitive impairment in schizophrenia more than meet these criteria for endophenotypes (Gur et al., 2007).

General and specific cognitive deficits

Impairment in cognitive function has been indicated as a potential endophenotypic marker of schizophrenia (Gur et al., 2007). This is because significant impairment is present in first-episode schizophrenia, remains relatively stable throughout the course of illness, cannot be explained by the effect of symptoms or medication, appears to be present before the onset of the disorder, and is even found among some healthy relatives of patients with schizophrenia (Palmer, Dawes & Heaton, 2009). However, there is considerable variability in the profile and magnitude of cognitive

impairment associated with schizophrenia. Even first-episode patients that might represent the characteristics of schizophrenia more definitively have variation in the extent of impairment across domains (Fioravanti et al., 2005; Mesholam-Gately et al., 2009; Kravariti et al., 2009). Some show impairment in only a few domains relative to healthy subjects, while others show a range of deficits in most or all domains, but still with considerable variability in the extent of impairment, from medium to large effect sizes (approximately 0.5 to 1.5 standard deviations). Whether this heterogeneity reflects specific brain dysfunctions within distinct genetic subtypes or individual variation in the effects of a general underlying pathophysiology is not properly understood (Gur et al., 2007; Palmer, Dawes & Heaton, 2009; Dickinson & Harvey, 2009).

It might be possible to parsimoniously account for large parts of the heterogeneous cognitive deficits of schizophrenia by considering only a single underlying deficit or a small number of core deficits (Dickinson, Iannone, Wilk & Gold, 2004; Dickinson & Gold, 2008; Dickinson, Ragland, Gold & Gur, 2008; Dickinson & Harvey, 2009). Instead of a diverse array of multiple independent deficits, there may be a largely generalized cognitive deficit. This single-factor model of cognitive deficits in schizophrenia has been demonstrated by, among others, the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) trial that included an unprecedented number of patients and found them to be characterized at baseline by a broad cognitive deficit rather than domain specific deficits (Keefe, Bilder & Harvey, 2006). The cause of such a generalized deficit could be abnormalities in connections among widespread brain regions or narrower mechanisms with potentially widespread effects. Evidence to support such neurobiological underpinnings in schizophrenia (Dickinson & Harvey, 2009) include widespread reductions in gray matter and neuronal arborisation, diminished myelin density and white matter coherence, poor signal integration at the level of the neuron and neural network, and abnormalities associated with excitatory and inhibitory neurotransmitters. Another possibility is that a relatively specific aberration in dopamine-mediated frontal-striatal loops could create an information-processing bottleneck broadly affecting cognitive performance (Robbins, 1990; Kapur, 2003). Yet another possibility is that performance on different cognitive measures is similarly impaired in schizophrenia because the measures tap into an overlapping set of specific localized impairments in frontal, temporal, hippocampal, parietal, striatal, and cerebellar functions (Dickinson, Ramsey & Gold, 2007; Dickinson, Ragland, Gold & Gur, 2008). This would explain why cognitive performance deficits in schizophrenia have been identified in almost every measurable cognitive

domain, from basic sensory and perceptual functions through preconscious information processing and early attention to higher order cognition, including selective and sustained attention, working memory, episodic memory in verbal and nonverbal domains, processing speed, and problem solving. Should any measure show disproportionate impairment then it does so because it simultaneously assays a larger set of these discrete deficits than other measures. The largest of such differences in effect size between schizophrenia patients and healthy comparison subjects are on measures of verbal episodic memory and processing speed (Heinrichs & Zakzanis, 1998; Dickinson, Ramsey & Gold, 2007). This supports the idea of only a general or limited number of underlying deficits in schizophrenia, and not a multitude of "differential" or "separate" domains. Alternatively, however, it can not be excluded that disproportionate effects are the result of the measurement properties of different instruments (Chapman & Chapman, 1973; Miller, Chapman, Chapman & Collins, 1995), because verbal memory and processing speed may simply just be measured more reliably than other capacities, or be simultaneously sensitive to a greater number of somewhat differentially impaired abilities. Thus there may still be specific "core" deficits, but these are not credibly reflected in the multifactorial character of the neuropsychological measures used to assess cognition (MacDonald & Carter, 2002; Jonides & Nee, 2005). Most standard neuropsychological tests do in fact not measure specific, identifiable cognitive processes. Often they assess more than one process or domain of functioning, and therefore do not fit neatly into the "construct" they indicate to measure. Many tests thus involve attention, working memory, and decision making components in addition to the specific process purportedly being measured (Silverstein, 2008). Multiple cognitive "domains" would appear impaired if any one of these underlying key components were compromised. For example, a prominent deficit in working memory would be expected to impact language comprehension, arithmetic skills, and problem solving (among many others), given the critical role of transient information storage in these cognitive operations (Goldman-Rakic, 1994). This does not mean that there are no separable and independent ability domains, but only that they are small in numbers and have a broad impact without being differentially noticeable.

Deficits in fundamental or "core" cognitive domains could potentially be measures of endophenotypic vulnerability markers for schizophrenia, and refer to the distinct causes or neural substrates of this illness. There are several examples of how cognitive endophenotypes can act as genetically mediated neurobiological components of the risk for developing schizophrenia (Gur et

al., 2007). One is how impaired working memory and associated abnormalities of prefrontal cortex reflect the mechanism of a common functional polymorphism. The catechol-O-methyltransferase (COMT) gene regulates prefrontal dopamine, which modulates the response of prefrontal neurons during working memory (Weinberger et al., 2001). A functional polymorphism (val158met) of the COMT gene increases prefrontal dopamine catabolism, impairs prefrontal cognition and physiology, and by this mechanism slightly increases the risk for schizophrenia. This genetically related deficit in cognition has been shown in a subpopulation of schizophrenia patients and their relatives (Egan et al., 2001), which suggests that the group of heterogeneous schizophrenic disorders can be reduced by identifying homogeneous subgroups of cognitively impaired patients (Gur et al., 2007). However, there are severe limitations to detecting different cognitive endophenotypes for schizophrenia as they may be influenced by the same genes, because they measure part of the same construct or because the underlying genes have a broad impact on the brain, which, in turn, affects multiple functions (Aukes et al., 2009).

To apply viable cognitive measures as endophenotypes in genetic studies of schizophrenia, the Consortium on the Genetics of Schizophrenia (COGS) - a multisite collaboration (Calkins et al., 2007) that examines the genetic architecture of quantitative endophenotypes in families with schizophrenia - has selected attention, verbal memory, and working memory as candidate endophenotypes (Gur et al., 2007). In addition to these endophenotypic measures, the COGS included measures from the Penn Computerized Neurocognitive Battery (CNB) to characterize the cognitive functioning of participants in domains of abstraction and mental flexibility, attention and working memory, face memory, spatial memory, spatial processing, sensorimotor dexterity, and emotion processing. Initial analyses (Greenwood et al., 2007) of the endophenotypes and the CNB measures show them all to be significantly heritable. A study (Toulopoulou et al., 2007) on genetic modelling in twins also found substantial overlap between cognition and schizophrenia. The study estimated the heritabilities of intelligence, working memory, processing speed, perceptual organization, and verbal comprehension, and quantified the genetic relationship between each of these and schizophrenia. The most heritable were intelligence and working memory. Significant but lesser portions of covariance between the other cognitive domains and schizophrenia were also found to be genetically shared.

There have been substantial advances in endophenotyping schizophrenia with cognitive measures, however, the neuropsychological tests used to measure specific, identifiable cognitive domains may not do so very accurately. To reliably capture the severity and pattern of cognitive deficits in schizophrenia, there must be a conceptual consensus on how to cluster tests into distinct domains. A fundamental step in identifying the major separable cognitive impairments in schizophrenia was initiated with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) programme. This initiative (Nuechterlein et al., 2004; Kern et al., 2007) emphasized factor analytic studies to evaluate the empirical evidence for cognitive performance dimensions in schizophrenia. The main goal was to develop a reliable and valid consensus cognitive battery for use in clinical trials that would standardize the evaluation of pharmacological treatment targeting cognitive deficits in schizophrenia. The MATRICS Consensus Cognitive Battery (MCCB) came to favor the inclusion of ten well-known neuropsychological tests and their partition into seven separable cognitive dimensions. However, although these dimensions may be distinguishable at the statistical or analytic level, they may not reveal the degree of separateness among them or among the neuropsychological measures used to measure them (Dickinson & Gold, 2008). The cognitive dimensions (and underlying measures) may share substantial common variance and therefore not be independent of one another to be suitable for assaying discrete and catalytic neural systems. Thus, the MCCB may be an insufficient tool for unravelling the complex neurobiology of schizophrenia and is unlikely to allow precise testing of novel pharmacological agents targeting specific brain mechanisms. But although the MCCB may not be able to separate "neurocognitive" domains as clearly as it ideally might have done, it is still a pronounced improvement in distinguishing relatively specific and independent features of cognitive impairment in schizophrenia.

The cognitive domains identified by MATRICS are speed of processing, attention and vigilance, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, and social cognition (Nuechterlein et al. 2004). An overview of these separable cognitive domains and (verbal) intelligence - an index of general cognitive ability that was initially considered for inclusion in MATRICS, but was left out due to lack of responsiveness to treatment - as well as their impairments in schizophrenia, is provided next.

Intelligence

It is well established that schizophrenia is often associated with a global impairment in cognitive functioning (Aylward, Walker & Bettes, 1984). This is reflected by a significantly lower Intelligence Quotient (IQ) in patients than in healthy comparison subjects. An IQ is a combined average score derived from several different standardized tests designed to assess general intelligence. The different tests in a battery also assess the multiple components of cognitive functioning, but the component functions tend to correlate (although there can be specificity), perhaps because general intelligence derives from a specific frontal system that direct most cognitive processes (Duncan et al., 2000). The most well known and well-validated battery of tests operationalized to measure IQ is the Wechsler Adult Intelligence Scale (WAIS), which is currently composed of 10 core subtests and 5 supplemental subtests, with the 10 core subtests comprising full scale IQ (Wechsler, 2008). The median full scale IQ is centered at 100, with a standard deviation of 15. The WAIS can also be indexed into 4 scores representing major components of intelligence, i.e. verbal comprehension, perceptual reasoning, working memory and processing speed. A test with high correlation to WAIS is the National Adult Reading Test (NART; Nelson, 1982) - named the Danish Adult Reading Test (DART; Dalsgaard, 1998) in its Danish version - which provides a valid estimate of premorbid intelligence, retrospectively. In this test a subject has to read out loud a list with 50 irregularly spelled words. The ability to pronounce these words correctly relies on consolidated knowledge and not on current cognitive capacity.

Low intelligence is a risk factor for schizophrenia (Zammit et al., 2004; Burdick et al., 2009). This association does not appear to be a consequence of the pathological process of symptomatic disease onset (Reichenberg et al., 2006), although there is evidence for a slight reduction in intelligence around and immediately after illness onset (Nelson et al., 1990; Frith et al., 1991). The intellectual decline does not additionally progress beyond the first years of illness, and intellectual function in schizophrenia does not otherwise seem subject to a deteriorating or dementia-like process (Byrne et al., 1999; Cosway et al., 2000).

Impaired IQ in schizophrenia may be construed as a premorbid, lifelong characteristic with some degree of aetiological significance for the illness (Russell et al., 1999; Aukes et al., 2009). Years before the onset of psychotic symptoms individuals with schizophrenia, as a group, demonstrate

mean IQ scores approximately one-half of a standard deviation below that of healthy comparison subjects (a difference in IQ by a magnitude of one standard deviation corresponds to 15 IQ points). This estimate of premorbid IQ has been attained through several study designs, including follow-back studies of school-, conscript-, or clinic-based testing, longitudinal birth or conscript cohort studies, and studies of samples at genetic risk for schizophrenia (Woodberry et al., 2008). Poor IQ performance can distinguish at an early age those high-risk individuals who later develop schizophrenia from those who do not (Sørensen et al., 2006). Furthermore, low intelligence is a risk-factor for an early onset of schizophrenia and a severe course of illness (David et al., 1997; Gilvarry et al., 2000; Kremen et al., 2001). Children and adolescents with early onset also appear to stagnate in cognitive development, indicated by stable IQ raw scores and a lack of age-related improvements (Bedwell et al., 1999; Jepsen et al., 2009). This may implicate low intelligence as an outward marker of poor neurodevelopment that could eventually influence the onset and trajectory of psychotic symptoms (Zammit et al., 2004), a hypothesis that is supported by evidence of an association between low premorbid IQ and small whole brain and gray matter volumes in schizophrenia patients (Antonova et al., 2005), as well as by evidence of an association between the severity of intellectual decline in schizophrenia and genetic variation in the dysbindin-1 (DTNBP1) genotype (Burdick et al., 2007).

While low intelligence is a (genetic) risk factor for early-onset and severe schizophrenia, a high premorbid IQ is considered a protective factor predictive of later onset and a milder illness profile (David et al., 1997; Gilvarry et al., 2000; Kremen et al., 2001), or even for eliminating the risk altogether (Barnett et al., 2006; Koenen et al., 2009). High cognitive reserve promotes resilience to psychosis by influencing interpretation of stimuli and events more accurately (Frith, 1987; Strauss, 1993; Garety & Freeman, 1999; Broome et al., 2007). Through the superior ability to dispel, reinterpret or rationalize odd experiences, there is less risk of developing delusional beliefs. There is thus also less risk of attributing internal perceptual events to an external source, which is occasionally common in the general population, as people of higher cognitive capacity are less biased towards endorsing a deviant interpretation of this type of psychotic-like experience (Baker & Morrison, 1998; Johns & van Os, 2001; Krabbendam et al., 2004; Johns, 2005).

High IQ may be important not only in decreasing the risk of succumbing to schizophrenia, but also in predicting outcome after its onset (Munro et al., 2002). High general cognitive ability, as

measured by IQ, is thus a sensitive and reliable predictor of better social and clinical outcome in first-episode schizophrenia, even more than high scores on measures of specific ability (Leeson et al., 2009). Patients with schizophrenia who have high premorbid and childhood IQ also have better long-term outcomes, although symptom severity may be similar to patients with low premorbid and childhood IQ (Munro et al., 2002).

Speed of processing

Cognitive measures loading highly on this index of processing efficiency emphasize the speed with which digit/symbol pairings can be completed, target symbols can be located, number or number/letter sequences on a page can be identified and connected, and colours can be named (Nuechterlein et al., 2004). Verbal fluency, often measured by the number of words starting with a given letter that can be generated in a brief time period, also loads as a measure of processing speed, although it is not traditionally thought of as such (Keefe et al., 2004b). The cognitive processes tapped by tests loading on this domain are relatively simple, often involve perceptual and motor components, and always emphasize speed of performance (Tulsky & Price, 2003). Reaction time can thus also be indexed in the speed of processing domain (Jensen, 2006), although it could be useful to view reaction time as separate, because it may reflect speed of information processing at more basic levels. The measure of reaction time is the elapsed time between the presentation of a sensory stimulus and the subsequent behavioural response, typically a button press but can also be an eye movement, a vocal response, or some other observable behaviour.

Speed of information processing may be considered a core cognitive deficit in schizophrenia and might be mediating a broader diversity of cognitive disturbances. In a study by Rodriguez-Sanchez et al. (2007) all significant differences between first-episode patients and healthy control subjects in cognitive functioning disappeared when the result of the WAIS-III digit symbol substitution test was included as an additional covariate. A meta-analytic comparison (Dickinson, Ramsey & Gold, 2007) of digit symbol coding tasks and other cognitive measures in schizophrenia concluded that the largest single impairment in schizophrenia was on such tasks. Studies (Schatz, 1998; Gale & Holzman, 2000; Krieger, Lis & Gallhofer, 2001; Demetriou et al., 2008; Kertzman et al., 2008) of

reaction time deficits in schizophrenia have shown a systematic association with intelligence and many cognitive processes, such as executive functions, working memory, and inferential processes.

Cognitive deficits in schizophrenia may be fundamentally determined by a slow speed of information processing (Rodriguez-Sanchez et al., 2007). This fundamental deficit may also account for the broad diversity of symptoms and reduced functional capacity in schizophrenia, because the underlying neurobiological systems might be the same (Dickinson & Harvey, 2009). A systemic disruption in the circuitry connecting the thalamus, frontal cortex and cerebellum might, for example, produce difficulty in prioritizing, processing, coordinating, and responding to information, the very hallmarks of schizophrenia (Andreasen et al., 1998). This disruption in neural activation transmission might be rooted in broadly reduced prefrontal and temporal gray matter volumes (Sanfilipo et al., 2002). It might also be rooted in white matter alteration, because processing speed is heavily dependent on the integrity of white matter and this is presented with abnormalities in schizophrenia (Dwork et al., 2007). White matter integrity is also highly relevant to the development of psychosis (Witthaus et al., 2008) and predictive of functional outcome (Mitelman & Buchsbaum, 2007).

Performance on processing speed tasks has been proved related to social, clinical, and functional outcomes in schizophrenia (Ojeda et al., 2008; Sánchez et al., 2009), as well as distinguishing risk of developing the illness (Niendam et al., 2003). There has been found specific correlates between aspects of performance and clinical symptoms (Ngan & Liddle, 2000). These correlates were also found to be modulated by how persistent and fluctuating the illness has presented itself. The more persistent the illness, the more negative the impact on measures of processing speed has been. This "neurotoxic" effect (McGlashan, 2006) has also been demonstrated in a study by Eberhard et al. (2003) that found deficits in processing speed to deteriorate linearly with the number of psychotic episodes.

Vigilance and attention

Attentional dysfunctions have long been considered core features of schizophrenia (Braff, 1993; Bredgaard & Glenthøj, 2000; Gur et al., 2007). The impairments include different constructs of attentional functioning such as the ability to detect relevant stimuli, and to focus attention on certain relevant stimuli, while suppressing or ignoring irrelevant stimuli at the same time, as well as to maintain attention on a stimulus until it is processed.

Attentional deficits in schizophrenia mainly include problems with sustained attention (Cornblatt & Keilp, 1994), selective attention (Nestor et al., 2001), and cognitive control of attention (Cohen, Braver & O'Reilly, 1996). But while cognitive control of attention and selective attention perhaps have too strong conceptual relationships to working memory and executive function to distinguish between, sustained attention - or vigilance, as it is more often called - is indicated to be separable from other cognitive factors (Nuechterlein et al., 2004).

The most prominent measures loading highly on sustained attention are versions of the Continuous Performance Test (CPT) that evaluate the ability to maintain a focused readiness to detect and respond to selected target stimuli over a prolonged time period (Nuechterlein, 1983; Cornblatt et al., 1988; van Zomeren & Spikman, 2003; Lezak, 2004). This typically involves tachistoscopic presentations of a quasirandom series of stimuli at a rapid fixed rate over 5-15 minutes with instructions to respond to a predestinated stimulus or sequence of stimuli (Nuechterlein et al., 1994). The individual stimuli are usually single visual letters or digits, but visual numbers with several digits and visual shapes, auditory stimuli, and degraded stimuli have been used as well (Cornblatt et al., 1988; Seidman et al., 1998). An example of a CPT is the computerized Rapid Visual Information Processing (RVIP) test (Sahakian & Owen, 1992; Levaux et al., 2007), where subjects are required to monitor a continuous stream of digits at a rate of 100 digits per minute, for specified three-digit strings (e.g. 3-5-7 in consecutive order). The digit strings are displayed to the right side of the stimuli throughout the test, to reduce demands on working memory.

Performance measures in most versions of the CPT usually include the number of correct detections, the number of false alarms (commission errors), and reaction times for correct detections. Correct detections and false alarms may be converted into two other measures,

perceptual sensitivity, which reflects the ability to discriminate between signal (targets) and noise (non-targets), and response bias, which measures the tendency to respond regardless of whether a target is present, and reflects constructs other than sensitivity, such as fatigue and motivation (Green & Swets, 1966; Nuechterlein, 1983; Nuechterlein et al., 1983).

Performance on the CPT has been consistently found impaired in patients with schizophrenia - primarily in target detection rates and signal/noise discrimination measures (Nuechterlein et al., 1991) - independent of clinical state and across various stages of the illness (Addington & Addington, 1997; Kurtz et al., 2001; Liu et al., 2002). Even prior to the first psychotic episode and by the time patients experience their first episode of psychosis, poor ability to maintain attention is typically present (Cornblatt et al., 1985; Caspi et al., 2003). There is further evidence for a progressively deteriorating course of deficits, from moderate impairment in first episode to severe impairment in chronic phases of the illness, although there is considerable heterogeneity (Liu et al., 2006). Poor performance has also been found in first-degree relatives of patients with schizophrenia, including the children, siblings, and parents of patients with schizophrenia, as well as in non-clinical subjects with high schizotypy scores (Kurtz et al., 2001; Liu et al., 2002). Based on these findings, it has been suggested that the deficit in sustained attention represents a stable trait in patients with schizophrenia, independent of fluctuations in symptomatology and, as such, a vulnerability marker predictive of illness (Chen & Faraone, 2000; Sarfati & Hardy-Baylé, 2002; Gur et al., 2007).

A deficit in sustained attention might serve as a possible cognitive endophenotype for schizophrenia and therefore be a useful tool in understanding the neurobiological and genetic underpinnings of the illness (Gur et al., 2007). The neurobiological substrate of CPT performance has been investigated using functional neuroimaging (Siegel et al., 1993). Schizophrenia patients show abnormally low relative glucose metabolic rate in medial frontal cortex, cingulate gyrus, medial temporal lobe, and ventral caudate during activation of a degraded stimulus version of CPT. This version involves the continuous target detection of blurred, degraded stimuli and has high perceptual or working memory loads (Nuechterlein, 1991; Cornblatt & Keilp , 1994; Nuechterlein & Asarnow, 1999), which appears relevant to successful use of CPT as an endophenotype (Nuechterlein & Dawson, 1984). Poor performance on the degraded stimulus version of CPT has thus been found related to the estimated risk for the later development of schizophrenia and is noticeably more marked in

siblings and parents of schizophrenia patients than in most other CPT versions (Grove et al., 1991; Cornblatt et al., 1999; Snitz, Macdonald & Carter, 2006). Poor performance has also been related to specific genes and subtypes of schizophrenia (van Amelsvoort et al., 2004; Hallmayer et al., 2005).

Deficits in sustained attention can result in difficulty following social conversations and an inability to follow important instructions regarding treatment, therapy, or work functions, simple activities such as reading or watching television become labored or impossible. Deficits in patients with schizophrenia are significant predictors of outcome, including social deficits, community functioning, and skills acquisition (Green, 1996; Green et al., 2000; González-Blanch et al., 2009).

Working memory

The concept of working memory is far from unitary and considered either an immediate memory held "on-line" for a brief period or a manipulation of a limited amount of information (Perry et al., 2001; Barch, 2005). The cognitive functions that comprise working memory have been proposed by Baddeley (1986) to include limited capacity storage buffers and a central executive control system that guides the manipulation of information held within the subsidiary storage buffers. An example of a task that assesses transient, on-line maintenance functions that do not involve manipulation of the stored information is the digit forward repetition task. An example of a task that assesses executive-functioning working memory, where storage, manipulation, and retrieval of information are required, is the reversed digit repetition task.

Schizophrenia patients have demonstrated deficits on a variety of verbal and spatial working memory tasks (Goldman-Rakic, 1994; Barch, 2005). Verbal working memory impairments are quite common and often moderate to severe in magnitude (Gold et al., 1997; McGurk et al., 2004). Moreover, these deficits are not simply an artifact of an inability to encode the information, as observed in attentional impairments (Stone et al., 1998). Spatial working memory deficits are also commonly found in schizophrenia. Tasks to measure these deficits often require the subject to maintain spatial location of visual information while performing interference tasks. Even minimal demands beyond attentional capacity result in deficiencies in schizophrenia patients (Seidman et al.,

1994). Working memory performance deficits in general often appear to be more severe on tasks that involve maintenance plus complex manipulation functions than those observed in maintenance-only tasks (Gold et al., 1997; Barch, 2005).

The working memory deficits in schizophrenia patients show associations with clinically important features of the illness. For example, impairments on working memory tasks show substantial relationships with measures of more complex cognitive processes such as problem solving, language comprehension, and planning (Gold et al., 1997; Hutton et al., 1998). Difficulty in encoding and then arranging information can make it difficult for schizophrenia patients to handle social and interpersonal situations that require attention to multiple streams of information. Working memory impairments show consistent relationships with various aspects of poor functional outcome, including poor social and vocational functioning and less benefit from rehabilitation interventions (Green et al., 2000; Smith et al., 2002; Kopelowicz et al., 2005). Impairments are similarly shown to cause less goal-oriented behaviour, disorganized cognitions, and failure of self-monitoring (Silver, 2003).

Working memory deficits appear to reflect traitlike features of schizophrenia that are not attributable to potential confounds (Barch, 2005; Gur et al., 2007). Impaired performance on working memory tasks predicts development of psychotic symptoms in high-risk subjects (Smith, Park & Cornblatt, 2006) and marked deficits in the prodromal phase announce the transition to psychosis (Rund et al., 2004). Unaffected biological relatives to schizophrenic patients demonstrate altered physiological activity in the prefrontal cortex while performing working memory tasks (Callicott et al., 2003). Functional abnormalities of prefrontal cortex, particularly the dorsolateral prefrontal cortex, and the dopaminergic system, in conjunction with posterior brain regions such as the posterior parietal cortex have been well established in schizophrenia and figure prominently in etiological theories of this illness (Wager & Smith, 2003; Barch, 2005; Tan, Callicott & Weinberger, 2009). Working memory deficits also relate strongly to a variety of other cognitive domains impaired in schizophrenia that are mediated by prefrontal cortical regions (Callicott et al., 1999). Thus, the neurobiological systems that are essential for working memory are strongly implicated in the pathophysiology of schizophrenia.

Verbal learning and memory

The abilities involved in memory functioning include, but are not limited to, those associated with learning new information, retaining newly learned information over time, and recognizing previously presented material (Cirillo & Seidman, 2003). The ability to encode and retain verbally presented information tends to be the most severely impaired in patients with schizophrenia, also more than in other cognitive ability domains (Saykin et al., 1991, 1994). This is usually evidenced in reduced rates of immediate and delayed recall on verbal list-learning tasks (such as the Buschke Selective Reminding Test that uses a multiple-trial list-learning paradigm to parcel verbal memory into distinct component processes; Buschke, 1973; Buschke & Fuld, 1974). Better memory performance is evidenced on recognition tasks, although some patients with a chronic course of illness and substantial functional impairments show large deficits, along with a global pattern of profound cognitive impairments and deteriorating functional skills (Bowie et al., 2004). Verbal memory performance predicts success in various forms of verbal therapy (Smith et al., 1999) and is associated with social, adaptive, and occupational success (Green, 1996; Green et al., 2000). Deficits appear to be related to earlier onset of psychosis (Tuulio-Henriksson et al., 2004) and (though mildly so) to negative symptoms (Cirillo & Seidman, 2003). The degree of impairment in verbal learning and memory is (unlike in other cognitive domains) different between male and female schizophrenia patients, with women outperforming men, which is typical of the healthy population as well (Bozikas et al., 2010).

Deficits in verbal learning and memory most likely reflect an endophenotype that is related to the underlying neurobiological substrates in the medial temporal and the frontal lobes (Gur et al., 2007). Both of these brain regions mediate component processes contributing to this cognitive dimension, and both are structurally and functionally impaired in schizophrenia, as well as in adult nonpsychotic, first-degree biological relatives (Seidman et al., 2002; Tuulio-Henrikssen et al., 2002). Impaired encoding and retrieval implicates abnormal involvement of prefrontal cortex whereas accelerated forgetting implies impaired consolidation attributable to medial temporal lobe dysfunction (Leeson et al., 2009).

Visual learning and memory

This area of cognitive function is partially separate from verbal learning and memory (Nayak et al., 2004) and has also been found not to be as impaired in patients (Heinrichs & Zaksanis, 1998). The tests developed to be sensitive to this deficit of schizophrenia usually require recognition of faces either immediately or after a delay, memory for nonfamiliar figures, and reproduction of line drawings (Nuechterlein et al., 2004). An example of the latter is the widely used Rey-Osterrieth Complex Figure Test (RCFT) in which one is asked to reproduce a complicated line drawing, first by copying and then from memory (Meyers & Meyers, 1995). A study (Kim, Namgoong & Youn, 2008) on the differences in RCFT performance between schizophrenia patients and matched healthy controls suggests schizophrenia patients are deficient in visual retention and/or retrieval, and that a poor organizational strategy seems related to this visual memory deficit.

Visual learning and memory has been found by some studies to correlate modestly with functional outcome measures such as employment status, job tenure, psychosocial rehabilitation success, social functioning, and quality of life ratings (Mueser et al., 1991; Dickerson et al. 1999; Gold et al., 2002, 2003; Buchanan et al., 2003).

Reasoning and problem solving

The concept of reasoning and problem solving is used to describe a loosely defined collection of processes involved in planning, cognitive flexibility, abstract thinking, rule acquisition, initiating appropriate actions and inhibiting inappropriate actions, and selecting relevant sensory information (Eisenberg & Berman, 2010). Sometimes this conceptual dimension is labelled executive functioning rather than reasoning and problem solving, but the latter term has the advantage of distinguishing the domain from the executive processes of working memory (Baddeley, 1986; Nuechterlein et al., 2004).

There are many neuropsychological tests which are used to test reasoning and problem solving. The most well known and most widely used is the Wisconsin Card Sorting Test (WCST) that measures

the ability to shift attention between different stimulus dimensions on the basis of reinforcing feedback (Heinrichs & Zakzanis, 1998). Chronic patients with schizophrenia, and some first-episode patients, achieve fewer sorting categories than control subjects and display significantly more perseverative errors (Hutton et al., 1998; Addington et al., 2003). It is important to note, however, that the difficulty of the WCST requires the contribution and coordination of numerous complex cognitive processes for successful completion (Pantelis et al., 2009). These include, although are not limited to, working memory, problem solving, reasoning and inhibition (Ragland et al., 2007). As a result, it is often difficult to determine which of these cognitive functions contribute to the deficit observed in patients.

The neural mechanisms by which schizophrenic psychopathology and dysfunctions in reasoning and problem solving arise have traditionally been associated with the frontal lobes (Weinberger et al., 1994; Elvevåg & Goldberg, 2000). This view has been prominent ever since functional imaging studies correlated poor performance of patients with schizophrenia on the WCST to reduced activity of the dorsolateral prefrontal cortex, and gave rise to the hypothesis of frontal hypoactivation in schizophrenia (Weinberger, Berman & Zec, 1986; Berman, Zec & Weinberger, 1986). However, more recent studies (see reviews by Ragland et al., 2007; Eisenberg & Berman, 2010) indicate that functions are far more distributed across the cortex. Activated areas during WCST performance thus include dorsolateral prefrontal, parietal, orbitofrontal and temporal cortex.

The deficits in reasoning and problem solving are unique in schizophrenia. They are present in most patients, regardless of the global level of cognitive function and independently of intelligence (Weickert et al., 2000; Bryson et al., 2001), and are not confounded by education, medication, and duration of illness (Johnson-Selfridge & Zalewski, 2001). The severity of deficits is progressive and correlates partially with both positive and negative symptoms (Johnson-Selfridge & Zalewski, 2001). Why the deficits co-occur with the exacerbation of clinical symptoms and the clinical onset of illness may be explained by the fact that the prefrontal cortex, the center of reasoning and problem solving, does not develop fully until young adulthood, where the first signs of illness usually occur (Tan, Callicott & Weinberger, 2009). This synchronicity in clinical symptoms, specific cognitive dysfunction and neurodevelopment may be a critical determinant of schizophrenia morbidity. Reduced capacity in reasoning and problem solving might thus be a cognitive endophenotype in individuals at genetic high risk for schizophrenia (Wobrock et al.,

2009). Such genetic underpinning of schizophrenia is supported by studies (see meta-analysis by Sitskoorn et al., 2004) that show that the most consistent deficit shown by relatives to patients is impaired performance on frontal-lobe tasks, although in an attenuated and moderate form.

Patients with schizophrenia often have impaired ability to solve problems, to formulate strategies, and to evaluate their usefulness (Hutton et al., 1998). This has numerous practical implications for everyday life and social activities and for performing tasks. Patients with impaired ability thus have difficulty in self-care, social, interpersonal, community, and occupational functions. Impairments are also associated with less engagement in therapy, medication compliance, and longer hospital stays (Bowie & Harvey, 2006).

Social cognition

There is good evidence that social cognition may be functionally and anatomically distinct from the cognitive domains already summarized (Pinkham et al., 2003). The domain includes cognitive components that may be critical for adequate social functioning and interpersonal success, such as the ability to recognize important social cues, infer the mental states of others, appraise the social context and process, interpret, and manage emotions in social situations. In schizophrenia, all of these components are impaired. The particular components that have mainly been the focus of study are theory of mind and social perception.

The term "Theory of Mind" refers to the cognitive capacity to represent the mental state of oneself and others (Pinkham et al., 2003). Patients with schizophrenia perform poorly on ToM tests in comparison to control subjects (Harrington, Siegert & McClure, 2005). Specifically, impairments are most profound in patients with negative features, passivity, and paranoid symptoms and behavioural disturbance (Pickup & Frith, 2001). Evidence suggests that poor ToM ability is a stable trait marker for schizophrenia (Harrington et al., 2005) and that faulty inferences on the mental states of oneself and others might contribute to the formation of psychotic symptoms (Frith, 1992). Impaired self-monitoring might thus lead to externalized attribution of self-generated stimuli, while false inferences about the intentions of others might lead to persecutory delusions. Evidence also

suggests that impairments are most pronounced during acute psychotic episodes and that performance on tests may improve during remission, although not to a degree where impaired ToM can no longer be considered a possible trait marker of schizophrenia (Harrington, Siegert & McClure, 2005; Sprong et al., 2007).

Facial affect recognition and social cue perception are abilities of social perception. Patients with schizophrenia have deficits on tests of facial affect recognition compared with healthy control subjects and psychiatric control subjects. These impairments are more evident for the perception of negative emotional displays compared to positive displays, with perhaps the greatest impairment for the perception of fear (Mandal, Pandey & Prasad, 1998). The deficits in facial affect recognition seem to be stable, although remission of an acute episode has been found to improve performance. Impairments of social cue perception characteristic of schizophrenia appear to be more pronounced for abstract relative to concrete social cues (Leonhard & Corrigan, 2001). Specifically, when presented with videotapes of persons interacting, individuals with schizophrenia have more difficulty discerning the goals and intentions of target people than what they are wearing or saying.

There is strong evidence that social cognition is related to social impairments and functional outcome in schizophrenia, even after controlling for other cognitive deficits (Pinkham et al., 2003). Thus, social cognition can be considered an independent predictor of functional outcome. A review (Couture, Penn & Roberts, 2006) found that social perception is significantly associated with most measures of functional outcome; emotional perception correlates strongly with community functioning, social behaviour in the milieu, and social skills, and there is growing evidence that theory of mind relates to social skills, community functioning, and social behaviour in the milieu.

The course of cognitive deficits

The cognitive deficits in schizophrenia begin very early, long before the clinical onset of the illness. Individuals who are assessed in childhood or adolescence prior to the onset of detectable symptoms of illness perform about 0.5 standard deviations worse than the normative population on mean of measures of cognitive and intellectual functioning (Woodberry et al., 2008). From this early,

premorbid stage and through the prodrome stage, the period of time when subtle (or greater) changes in functioning and symptomatology begin to occur, there is an additional worsening (Harvey, 2009a). So by the time of the first episode (typically in adolescence or early adulthood) the cognitive deficits are large, with generalized deficit approximating 1.0 standard deviation compared to population standards (Mesholam-Gately et al., 2009). These cognitive deficits remain for the duration of life, but do not get worse over time, except perhaps in the case of elderly patients who have experienced long-term institutionalization (Kurtz, 2005).

Finding that cognitive deficits predate the onset of schizophrenia and remain relatively stable after onset may be of fundamental importance for understanding the etiology and pathophysiology of schizophrenia (Rund, 1998, 2009). This is because the findings suggest that schizophrenia may not be a neurodegenerative, progressive disorder, but rather a neurodevelopmental disorder (Haan & Bakker, 2004; O'Donnell, 2007). The course of cognitive deficits in schizophrenia might then reflect an impairment of the growth and development of the brain that contributes to an increased risk of illness (Lawrie et al., 2008; Jindal & Keshavan, 2008a; Pantelis et al., 2009b). Such vulnerability-related and progressive neuroanatomic abnormalities would occur in pre-, peri-, and postnatal developmental periods. During early development genetically (and obstetrically) mediated brain vulnerabilities (abnormal neurogenesis and neuronal migration) may affect later developmental and maturational processes in the brain (aberrant synaptic pruning). These brain processes, interacting with various environmental triggers (social stress and/or drug abuse), may then contribute to the onset of schizophrenia (Niendam et al., 2009).

The neurodevelopmental derailment underlying the risk of schizophrenia is indicated by general cognitive impairment (Whalley et al., 2005; Brewer et al., 2006; O'Donnell, 2007; Jindal & Keshavan, 2008a). The severity of this cognitive impairment is associated with different ages of onset (Rajji, Ismail & Mulsant, 2009), which also has been conceptualized as a surrogate measure of severity of the disease process (Delisi, 1992). Individuals with youth-onset (in childhood or adolescence) schizophrenia have severe cognitive deficits, whereas those with late-onset (in adulthood) schizophrenia have some relatively preserved cognitive functions (Rajji, Ismail & Mulsant, 2009). This implicates age of onset as an outward marker for the degree of abnormality in brain structure and function (principally in prefrontal and temporal lobes), and thus also genetic loading and familial susceptibility (Whalley, Harris & Lawrie, 2007).

Research in the potential vulnerability markers for psychosis and schizophrenia suggests that some cognitive deficits are trait-related and may be considered "de facto" biological markers for illness onset (Cannon, 2005; Brewer et al., 2006). Better understanding of this association can have important value for the early detection of emerging psychosis in the prodromal phase. The transition to full-blown psychosis can perhaps be predicted and thereby allow directed treatment resources to minimize the severity and disability of illness. There are several approaches to identifying the cognitive deficits in individuals at high risk for psychosis. One approach is the genetic high-risk approach, in which cognitive functioning of family members of individuals with psychosis (Sitskoorn et al., 2004; Snitz et al., 2006), usually offspring (that statistically have around ten percent chance of developing illness), or individuals with psychosis spectrum disorders (e.g. schizotaxia or schizotypy) are assessed (Cadenhead & Braff, 2002; Tsuang et al., 2002). Another approach to identifying high-risk cohorts is the retrospective study of patients with established psychosis (Bilder et al., 2006), which also provides clues regarding the nature of more general cognitive deficits many years prior to the onset of illness. A further strategy is to follow large birth cohorts over time (Poulton et al., 2000; Cannon et al., 2002), which invariably incorporates early, broad assessment of individuals who eventually develop schizophreniform disorders.

Although the investigation of general and specific cognitive dysfunction (in clinical high-risk cohorts) as vulnerability markers or endophenotypes of schizophrenia is promising, results have severe limitations (Kéri & Janka, 2004). At present, the available cognitive endophenotypes are not able to sufficiently and selectively identify individuals who are at risk for schizophrenia. Cognitive endophenotypes show high within- and between-subject variability and have low sensitivity and specificity for schizophrenia. A likely reason for this lack of predictive validity may be that the form of cognitive dysfunction is not fixed until established illness. The integrity of brain regions (particularly frontal and temporal lobes) is thus dynamically changing during normal maturation, meaning that any putative neurobiological markers identified at the earliest stages of illness may be relatively unstable (Pantelis et al., 2009b).

Longitudinal studies (see Rund, 1998; Szöke et al., 2008) after the onset of psychosis have typically found that cognitive deficits do not worsen over time. Some of these studies have also found that patients may partially improve during the initial stabilization phase immediately after first onset,

although effects of practice may account for most of these improvements. The cognitive deficits at psychosis onset are broad and appear to be approximately one standard deviation below the mean of healthy comparison subjects. In regard to specific cognitive domains, the strongest effect sizes seem to be associated with tests of episodic memory (particularly free recall), and processing speed, with the least (but still medium to large effect size differences) associated with measures of crystallized verbal knowledge and visual-spatial skill. In addition to episodic memory, working memory and executive functions are typically affected by schizophrenia. From the pattern of effect sizes in the different domains, episodic memory deficits might be considered an especially important or "core" cognitive deficit in schizophrenia. This misconception is brought on by a lack of established psychometric equivalence in sensitivity and specificity of measures of different cognitive constructs (Chapman & Chapman, 1973; Squire, 2004). The same misconception is conferred to non-specific terms of "attention" and "executive functions", and has lead to considerable heterogeneity in effect-sizes between studies of differential "core" deficits (Fioravanti et al., 2005; Mesholam-Gately et al., 2009).

Although the majority of patients with schizophrenia have cognitive impairment, approximately 20 to 25 percent of patients have neuropsychological profiles in the normal range (Heinrichs & Zakzanis, 1998). These patients have less negative and extrapyramidal symptoms, are on less anticholinergic medication, socialize more frequently, and are less likely to have had a recent psychiatric hospitalization (Palmer et al., 1997). However, this minority of patients may still perform below their premorbid cognitive potential (Heinrichs & Zakzanis, 1998), which is indicated by a study (Goldberg et al., 1990) of monozygotic twins discordant for schizophrenia, where the twins with schizophrenia generally performed worse on neuropsychologic measures than their healthy twins, even if their scores fell within the normative range. Clinical disease process (or long duration of treatment) thus seems to have a detrimental effect on cognitive performance, regardless of clinical and cognitive profile.

An approach to the issue of cognitive heterogeneity in schizophrenia has been to use cluster analyses to identify general cognitive subgroups of patients (Weickert et al., 2000; Joyce et al., 2005; Joyce & Roiser, 2007; Palmer, Dawes & Heaton, 2009). These subgroups have been found to be characterized as neuropsychologically normal (with intellectual decline from higher premorbid values); severely and broadly impaired (with low premorbid intelligence); and impaired in differing

degrees of severity, with perhaps one or two areas of neuropsychological impairment standing out (e.g. memory, vigilance or executive functioning). These subtypes that have been classified according to the severity and pattern of cognitive dysfunctions may share similar genetic features in the same way as a subpopulation of schizophrenia patients and their relatives show similar patterns of cognitive dysfunctions (Egan et al., 2001). They may also share similar pathophysiology, symptoms and functional deficits, although the current understanding of these associations is limited and fragmentary (Thaker, 2007). One exception, however, may be the group of patients with deficit syndrome (i.e., with enduring, primaryly negative symptoms) that is relatively homogeneous on dimensions of signs and symptoms, course of illness, pathophysiological correlates, risk and etiological factors, and treatment response (Kirkpatrick & Galderisi, 2008).

The construct of schizophrenia in modern diagnostic classifications is designed to give primacy to subjective symptoms, and does not incorporate cognitive deficits, although such deficits may have diagnostic and predictive utility (Lewis, 2004; Keefe & Fenton, 2007). Compared with patients with affective disorders (specifically major depression and bipolar disorder), cognitive impairment in schizophrenia appears earlier, is more severe (about 0.5 standard deviations larger than those in patients with bipolar disorder), and tends not to fluctuate in parallel with clinical symptom changes over the course of illness (Reichenberg et al., 2009; Zanelli et al., 2010). However, despite cognitive impairment being a core, stable and relatively specific characteristic of schizophrenia, the "differences" between schizophrenia and psychotic affective disorders (share genes and also share partially overlapping neural substrate dysfunction and clinical features) are not considered robust enough to distinguish established diagnosis (Braff et al., 2007). Transition from early psychosis to a diagnosis of either schizophrenia or affective disorder, however, may be better distinguished between, because patients with affective disorders usually do not show cognitive impairment until (adult) onset of their disorders, whereas patients with schizophrenia do (Fuller et al., 2002; Cannon et al., 2002).

Relation of cognitive impairment to psychopathology

Several lines of evidence suggest that cognitive performance is largely independent of symptom severity and type in schizophrenia. Intuitively, it would have made more sense if psychotic symptoms interfered with the test performance of patients. For example, it is possible to think that hallucinations might interrupt the ability to sustain task performance and delusions might lead patients to misconstrue the task demands in a highly idiosyncratic fashion. So it could be argued that if the psychotic symptoms remitted, cognitive test performance would improve and the deficits disappear. However, studies (Harvey et al., 1995; Heaton et al., 2001) on patients with schizophrenia show that they do not change in performance when psychosis remits. Patients thus show similar levels of impairment during periods of clinical remission and absence of symptoms, as when they are acutely symptomatic. This is clearly demonstrated in patients treated with antipsychotic medications that have marked effects on the psychotic symptoms of the illness, but only rather subtle effects on cognitive performance. Cognitive impairments can also not be attributed to institutionalization or long illness duration, as they are clearly demonstrated before the first onset of psychotic symptoms (Bowie & Harvey, 2005). There is also evidence (as mentioned above) that cognitive impairments are potential vulnerability indicators, as these are found to lesser degrees in healthy first-degree relatives of schizophrenic patients (Nuechterlein et al., 1994; Snitz et al., 2006), and are predictive of later schizophrenia in high-risk individuals (Brewer et al., 2006). These lines of evidence clearly indicate that the cognitive impairments are stable trait markers associated with schizophrenia, but are largely independent of clinical state.

The most direct line of evidence concerning the relationship of symptoms and cognition comes from studies that have examined the correlation between symptom severity and type and measures of cognitive performance. These studies suggest in general that performance on cognitive tests does not appear to be entirely orthogonal to psychopathology (see review by Dominguez Mde et al., 2009). Attentional deficits and poor performance in verbal fluency, as well as impairments in executive function and processing speed, have thus been linked to negative symptoms (Nuechterlein et al., 1986; Berman et al., 1997; Howanitz et al., 2000). Symptoms of thought disorder have been linked to deficits in working memory and semantic activation (Salisbury, 2008). However, despite the correlations to types of symptom patterns, cognitive deficits are still largely independent of clinical symptoms. Thus there is a lack of correlation with positive symptoms and only a partial

correlation with negative symptoms and disorganisation symptoms. Furthermore, the partial correlations may to some extent refer to the same dysfunctions expressed at different explanatory levels (Harvey et al., 2006). For example, deficits in verbal fluency and poverty of speech can both be considered measures of generating speech at a slow rate. However, clinical ratings can not be used as proxy measures of cognitive deficits as they lack the sensitivity and specificity required to be fully relied upon (Good et al., 2004).

The modest association of symptoms and cognition suggests that the two dimensions could be mediated by different neural systems. This is fairly obvious when comparing the effects of antipsychotic medications where one system is powerfully modulated by them, while the other system is far less responsive. Still, there is no question that the heterogeneous symptoms of schizophrenia involve cognitive processes, including the cluster of positive symptoms. Auditory hallucinations may thus be mediated through language and perceptual processes, and delusions are mediated through reasoning, inference, and judgment. However, standard neuropsychological tests were never designed to assess cognitive processes thought to be involved in specific symptoms. Even measuring a specific cognitive process that is free from the influence of other cognitive processes, and other factors that can affect cognitive functioning, is difficult (Silverstein, 2008). To better assess the cognitive processes in schizophrenia requires the tools and insights from cognitive neuroscience. Such efforts would greatly inform research and improve treatment of both cognitive impairment and clinical symptoms (Carter & Barch, 2007).

Cognitive deficits and functional outcome

Although cognitive impairment is not strongly correlated with symptoms, it has proven to be a reliable correlate and predictor of functional outcome in schizophrenia (Green, 2006). There is thus good evidence that cognitive impairment correlates strongly with community (social and work) outcome, independent living, and acquiring skills in psychosocial rehabilitation programs (Green, Kern & Heaton, 2004). The magnitude of associations between key cognitive constructs and functional outcomes are all statistically significant with effect sizes in the medium range, meaning that they should all be clinically noticeable. When summary scores of cognition are used instead of

individual cognitive constructs, the magnitude of the associations with functional outcome is even larger.

A specific set of cognitive deficits is shown to be consistently predictive of functional impairment in schizophrenia (Green, 1996; Green et al., 2000). Social and occupational functioning, as well as independent living, has been found to correlate with declarative memory, while executive functioning and working memory are crucial for occupational outcome and independent living. Vigilance (sustained attention) is particularly important for social and occupational functioning. Patients with deficits in working memory, executive functioning, verbal memory, and vigilance are also those who benefit least from a rehabilitation program. Furthermore, there is also evidence that social cognition is an independent predictor to most measures of functional outcome (Pinkham et al., 2003).

The above mentioned findings might be interpreted as indicative of differential importance of specific cognitive domains for functional outcome, but actually the largest amount of variance seems to be predicted by global or composite measures of cognition (Green et al., 2000). This is most likely because schizophrenia is typically associated with multiple deficits in varying patterns, rather than with any single isolated cognitive impairment. Another reason for non-specific associations between cognitive deficits and impairments in functional capacity or status could be the multifactorial nature of standard neuropsychological and functional outcome tests (Dickinson & Gold, 2008; Gladsjo et al., 2004).

The fact that cognitive impairment is a much better predictor of functional outcome than are clinical state and severity of psychotic symptoms does not imply that psychopathology is irrelevant for the prognosis of patients (Grawe & Levander, 2001). Negative symptoms in particular can be strong predictors (Keefe et al., 2006), and may also mediate some of the associations observed between cognitive performance and functional outcome in schizophrenia (Ventura et al., 2009). Even certain positive symptoms appear to make contributions to community functioning (Heinrichs et al., 2009). However, because symptoms can fluctuate considerably, the relatively stable cognitive impairment is a much better indicator of subsequent clinical outcome, particularly in first-episode patients (Moritz et al., 2000) and also in individuals at high-risk for psychosis (Niendam et al., 2009).

The cognitive deficits associated with schizophrenia strongly predict the ease by which patients acquire skills as they progress through skills training and rehabilitation programs (Hoffman et al., 2003; Green, Kern & Heaton, 2004). The effectiveness of psychosocial rehabilitation thus depends on cognitive functioning, and deficits should therefore also make important treatment targets (Green, 2006). Various psychological interventions and approaches (Kern et al., 2009) have been used to reduce or remedy cognitive deficits. Some train specific aspects of cognitive functioning as well as more complex or global functions. The goal of other approaches is to minimize the impact of the deficits by trying to circumvent the impaired functions through compensatory interventions. Promising results have been reported with respect to the efficacy of cognitive remediation in patients with schizophrenia, which could therefore become an integral part of treatment (Demily & Franck, 2008), not least considering that with even the clear amelioration of psychotic symptoms from antipsychotic medication, the patients continue to have poor prognosis and cognitive functioning.

The effects of antipsychotics on cognition

Since cognitive deficits are enduring, core features of schizophrenia, largely independent of clinical symptoms and strongly linked to functional outcome, they have become logical targets of pharmacological intervention. The mainstay treatment of schizophrenia is antipsychotic medication that can reduce the symptoms of psychosis. Persistent efforts have been made to assess the influence of antipsychotic medication on cognitive performance.

Numerous early head-to-head studies (see reviews by Keefe et al., 1999; Blyler & Gold, 2000) suggested that the two groups of antipsychotic medication, the first-generation (or typical) antipsychotics and second-generation (or atypical) antipsychotics, have different effects on cognitive deficits. First generation antipsychotic medications were thus found to only demonstrate minimal positive effects, and second generation antipsychotic medications were found to demonstrate significant improvement. These effects were thought to have resulted from the different receptor binding profile of the medications and the pattern of side effects produced (Weickert & Goldberg, 2005). First generation antipsychotic medication provides (relatively)

selective and potent dopamine blockade, showing strong dopamine D2 receptor binding profiles. However, the strong dopamine blockade often results in extrapyramidal side effects and requires the addition of adjunctive anticholinergic medication that can adversely affect cognitive function. Most second generation antipsychotic medication show binding affinity to multiple receptor types, and generally less affinity for dopamine D2 receptors. It has been suggested that the serotonin 5HT-2A receptor is the principle determinant of the apparent cognitive effects of the second generation antipsychotics (Tyson, Roberts & Mortimer, 2004a), as action on 5HT-2A receptors leads to changes in the level of dopamine in the prefrontal cortex (Glenthøj & Hemmingsen, 1997). Other serotonin, adrenergic, and muscarinic receptors could have beneficial effects in maintaining one or more domains of cognition (Weickert, & Goldberg, 2005).

Recent head-to-head studies (Fagerlund et al., 2004; Keefe et al., 2007a; Davidson et al., 2009) comparing the effects of first and second generation antipsychotics on cognition in schizophrenia have found that perhaps there are no differences in effect after all (see also Mishara & Goldberg, 2004). In the very large Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study that compared the cognitive effects of second generation antipsychotics - olanzapine, quetiapine fumarate, risperidone, and ziprasidone hydrochloride – to the first generation antipsychotic perphenazine in patients with chronic schizophrenia, no differences were thus found (Keefe et al., 2007a). The same results were found in the European First Episode Schizophrenia Trial (EUFEST) that compared the cognitive effects of second generation antipsychotics - amisulpride, olanzapine, quetiapine, and ziprasidone – to the most commonly prescribed first generation antipsychotic haloperidol in patients with first-episode schizophrenia (Davidson et al., 2009). The results from these two studies (Keefe et al., 2007a; Davidson et al., 2009) seriously question the putative cognitive advantage that second generation antipsychotics might provide over the first generation antipsychotics. One likely reason for the discrepancy between early and recent findings is that early studies (Keefe et al., 1999; Carpenter & Gold, 2002) applied inappropriately high doses of first generation antipsychotics and concomitant adjunctive agents such as anticholinergic substances, while recent studies (Keefe et al., 2007a; Wittorf et al., 2008; Davidson et al., 2009) applied first generation antipsychotics in low and individually optimized doses. So it would appear that the release from the detrimental effects of excessive dosing would release the potential of first generation antipsychotics to improve cognition in schizophrenia to the same magnitude as second generation antipsychotics do.

It seems in principle improbable that all types of antipsychotics would engender similar degrees of cognitive improvement in schizophrenia, because they all have different receptor binding profiles. Although there are of course findings (although often contradictory) of differential impact in general and specific cognitive function from treatment with antipsychotics (Woodward et al., 2005; Jindal & Keshavan, 2008; Fumagalli et al., 2009), they more than likely may be caused by factors such as the size and composition of samples, duration of treatment, excessively dosed comparator antipsychotics (often requiring concomitant anticholinergic treatment), industry sponsorship of studies, and the selection and evaluation of neuropsychological tests (Salimi, Jarskog & Lieberman, 2009; Hill et al., 2010). When the scientific rigor of clinical trials is improved, there is a reduction in differential cognitive effects of antipsychotics (Keefe et al., 2007a; Davidson et al., 2009). There is also a reduction in apparent beneficial cognitive effects in general, and the magnitude of these effects has in recent clinical trials been conspicuously small (Keefe et al., 2007a, 2007b; Davidson et al., 2009). So small in fact that they may not reflect true cognitive enhancement from treatment, but rather reflect effects of practice (Goldberg et al., 2007; Boulay et al., 2007). The confounds of practice effects have rarely been addressed in (industry sponsored) clinical trials, but without a healthy control group matched on demographic characteristics (age, gender, etc.) that is tested over a similar time period, it is difficult to determine whether test score improvements at retest result from true enhancement of cognitive abilities or from learning to perform tests more efficiently due to familiarity with the testing procedures (Hill et al., 2010). The concern for this issue was brought to the forefront by recent studies (Fagerlund et al., 2004; Goldberg et al., 2007) that reported improvements associated with both first and second generation antipsychotics in first-episode schizophrenia patients were no greater on most measures than practice effects in healthy controls. Usually the range of practice effects in schizophrenia patients treated with antipsychotics fall within or below that of healthy control groups (Hill et al., 2008b; 2010). Poor changes in cognitive performance by patients relative to healthy controls might be due to illness-related learning deficits (Gold et al., 2000; Weickert et al., 2002) or excessive dosing. A study (Harvey et al., 2000) of the cognitive changes associated with haloperidol treatment thus indicated that, except for very high doses, improvements were similar to practice effects in normative samples. This would explain why early studies of comparative effects in cognition between first and second generation antipsychotics that did not employ healthy control groups reported less positive effects of first generation antipsychotics. The detrimental effects of excessive doses of first generation antipsychotics simply

did not allow patients to benefit from practice-related improvements, which unfairly inflated the benefits attributable to second generation antipsychotics. This reasoning also implies that the lack of practice-related improvements from the first generation antipsychotics might have reflected an actual deterioration in cognition, and that the second generation antipsychotics were not being truly beneficial, but just less cognitively detrimental.

Practice effects have been well demonstrated, and vary by age, inter-test interval, and type of neuropsychological test (Beglinger et al., 2005). Whether practice effects might alone account for the modest and generalized improvement in performance of schizophrenia patients treated with antipsychotics might not be fully settled (Woodward et al., 2007), but the paramount importance of using a (healthy) control group to indicate improvement or deterioration has become clear (Fagerlund et al., 2004; Goldberg et al., 2007; Szöke et al., 2008; Hill 2010). Should practice effects turn out to account for the changes in cognitive performance, this ought not to be so surprising. Antipsychotics were thus never developed with the goal of enhancing cognitive functioning, but to dampen the salience of abnormal experiences and thereby permitting the psychological resolution of psychotic symptoms (Kapur, 2003). Should practice effects (in collusion with placebo effects as well; Keefe et al., 2008) turn out not to account for all the changes in cognitive performance (Woodward et al., 2007), the beneficial effects seem to be so small that they would not be sufficient to reduce disability in any clinically meaningful way (Keefe et al., 2007b; Hill et al., 2010) or in any way help restore or normalize cognitive functioning, since the structural and functional brain abnormalities underlying cognitive impairment in schizophrenia patients became irreversibly fixed around the time of first episode or in the prodrome (Lawrie et al., 2008).

There appears little reason to be enthusiastic about the cognitive benefits of antipsychotics. Efforts to develop more targeted pharmacologic treatments for cognition in schizophrenia have therefore been initiated. One initiative to assess novel pharmacological treatments for cognitive impairment in schizophrenia is the already mentioned MATRICS project that has chosen a standard battery of neuropsychological tests with a view to practicality of administration, high test–retest reliability, small practice effects, lack of ceiling and floor effects, and demonstrated relationship to functional outcome (Nuechterlein et al., 2004; Kern et al., 2007). Another initiative is the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) project that take procedures from cognitive neuroscience that are specific and sensitive to brain function and

dysfunction and turn them into neuropsychological tasks (Carter & Barch, 2007; Barch & Carter, 2008). This includes computer-administered tasks that measure specific cognitive systems as well as the component cognitive processes that comprise these more overarching systems.

The role of computerized neuropsychological assessment in drug treatment of schizophrenia patients has become more prominent in recent years (Kertzman et al., 2008). The reason is that computerized test batteries do not suffer from the many shortcomings of manual administration of test batteries. Some of the general shortcomings of manually performed cognitive assessment include inconsistent presentation of instructions and test items, procedural unreliability, inaccuracy in the timing of tests for which precise measurement is imperative, clerical errors in scoring and transcribing results, manual item-by-item tabulation, and requirement of specialized devices or materials for single tests. The relative efficiency and utility of computerized assessment is also particularly evident in the direct transfer and integration of variables into databases and reports. An example of a computer-based cognitive assessment system is the Cambridge Neuropsychological Test Automated Battery (CANTAB) that consists of a battery of neuropsychological tests, administered to subjects using a touch screen computer interface (Levaux et al., 2007). The "user-friendly" battery examines various areas of cognitive function and has enabled researchers to highlight significant deficits affecting broad cognitive domains in schizophrenia (compared to healthy controls and other patient populations), such as working memory, decision-making, attention, executive functions and visual memory, as well as particular components of these domains. Preliminary evidence points towards the potential use of CANTAB to identify cognitive predictors of psychosocial functioning, to describe the relationships between symptoms and cognition, to divide schizophrenia into subgroups with enhanced phenotypic homogeneity, and of course to measure the impact of pharmacological agents on cognitive functioning.

The increased reliability afforded by computerization decreases sample size requirements for clinical evaluations of putative "cognitive-enhancing" treatments (O'Halloran et al., 2008). Computerization also provides facets of performance typically inaccessible to traditional paper-and-pencil measures that may be more sensitive to specific cognitive endophenotypes with characteristic neurobiology and treatment response (Gur et al., 2007; Thaker, 2007). A reliable and sensitive way to establish optimal treatment responses by cognitive endophenotypes with computerized measures is to include only first-episode schizophrenia patients (Levaux et al., 2007; Salimi, Jarskog &

Lieberman, 2009). This is because first-episode patients, who perhaps represent the pathophysiology of schizophrenia best (Saykin et al., 1994; Davidson et al., 2009), respond in high rates (in terms of effects on psychopathology) to both first and second generation antipsychotics at doses roughly half of those required in chronic patient populations (McEvoy et al., 1991; Bilder et al., 2000). First-episode patients may therefore also be more responsive to cognitive amelioration from drug treatment, i.e. if the targeted neural circuitry of symptoms is not (too) dissociable from the neural circuitry of cognitive deficits (Voruganti et al., 2002; Davidson et al., 2009).

Conceptual and methodological issues

Schizophrenia has become recognized as a neurobiological disorder with a strong cognitive component (MacDonald & Schulz, 2009). With a fair degree of confidence the nature of cognitive impairment in schizophrenia can be described as highly prevalent (if not universal), albeit to varying degrees; generalized with additional impairments in specific domains; present in the premorbid phase of illness; progressive prior to or around the onset of psychotic symptoms, and stable through the subsequent course of illness; marginally reactive to antipsychotic medication, at best; similar to cognitive impairment in non-psychotic relatives as well as in patients with psychotic and non-psychotic affective disorders, albeit of worse severity; and highly predictive of poor social and vocational outcome (Palmer, Dawes & Heaton, 2009).

The high prevalence and pervasive nature of cognitive deficits in schizophrenia has led to the proposal (Lewis, 2004; Keefe & Fenton, 2007) that they should be included as diagnostic (or at least as nonessential) criteria for the illness, but issues of diagnostic nonspecificity - commonness of cognitive impairment in neuropsychiatric disorders, reliability of assessment tools, and predictive value for prognosis and treatment outcome - limit the utility of doing so (Tandon and Maj, 2008). Other conceptual and methodological issues also limit the utility of having cognitive deficits as diagnostic criteria for schizophrenia. It is, for example, still not finally settled to what degree cognitive deficits are affected throughout the life course of schizophrenia, and what the efficacy of antipsychotic treatments for cognitive deficits in schizophrenia is (Palmer, Dawes & Heaton, 2009).

The remainder of this thesis will concern the cognitive profile of first-episode antipsychotic-naïve schizophrenic patients and effects of antipsychotic treatment. Results from a large cohort of first-episode antipsychotic-naïve schizophrenic patients, of which some underwent six months of treatment with the second generation antipsychotic quetiapine, will be presented. The goals are to identify the level and pattern of cognitive impairment in first-episode schizophrenia patients, determine the influence of moderator variables (age, gender, duration of untreated illness/psychosis, socio-economic status, years of education, severity of symptoms, selective cognitive impairment, etc.) on effect size differences between (and within) levels of cognition in patients and matched healthy controls, and finally to determine the influence of antipsychotic treatment on the level of cognitive changes.

To optimize the results coming out of this thesis, the following methodological issues will be addressed and implemented. To reliably identify the level and pattern of cognitive impairment in schizophrenia patients, it is necessary to have a comprehensive battery of neuropsychological tests that is sensitive to specific and general impairment (Nuechterlein et al., 2004), and it is preferable that patients are first-episode (although they are harder to obtain), since they are usually not confounded by effects of age, clinical symptoms, illness duration and severity, and/or treatment (Davidson et al., 2009). To reliably determine the influence of antipsychotic treatment on the level of cognitive changes, it is necessary to compare these changes with untreated healthy controls in order to avoid practice effects (Fagerlund et al., 2004; Goldberg et al., 2007). It is also necessary to have a relatively long duration of treatment (although this will inevitably lead to attrition) in order to attenuate practice effects and allow the antipsychotic treatment to take full effect, which does not occur until after the first few months of treatment (Keefe et al., 2007b; Szöke et al., 2008). Finally, it is pertinent that the effects of selected antipsychotic(s) on cognition can be considered of equal magnitude to other antipsychotics, as indicated by comparative studies (Keefe et al., 2007a, 2007b; Davidson et al., 2009), and it is preferable that included patients are first-episode, since they may be more responsive to cognitive amelioration from treatment (Voruganti et al., 2002; Salimi, Jarskog & Lieberman, 2009; Davidson et al., 2009).

CHAPTER 3 - THE INFLUENCE OF PROCESSING SPEED IN SCHIZOPHRENIA

A central feature of the cognitive impairment in schizophrenia (the individual domains of which have been described in detail in the previous chapter) is a slower speed of information processing (Keefe, Bilder & Harvey, 2006; Dickinson, Ramsey & Gold, 2007; Rodríguez-Sánchez et al., 2007). Impairments on coding tasks have yielded the largest effect size found for cognitive impairment in schizophrenia (Keefe, Bilder & Harvey, 2006; Dickinson, Ramsey & Gold, 2007). The experimental investigation of the *processing speed hypothesis* (Rodríguez-Sánchez et al., 2007) has thus shown that particularly the Digit Symbol Coding Task from the Wechsler intelligence scales (Wechsler, 1997) taps an information processing inefficiency that might determine a broad diversity of cognitive impairments (Dickinson, Ramsey & Gold, 2007). This suggests that the generalized effect of slow processing speed, as measured primarily by digit symbol coding, could possibly be at the core of global impairment in schizophrenia (Dickinson, Ramsey & Gold, 2007; Rodríguez-Sánchez et al., 2007; Dickinson & Harvey, 2009). To what degree the different neuropsychological performance domains in schizophrenia (and their corresponding cognitive measures) was correlated with these substantial deficts of speed of processing, was the topic of interest in this study (Nuechterlein et al., 2004; Dickinson & Gold, 2008; Silverstein, 2008; Dickinson & Harvey, 2009).

Objectives

The present study aimed to characterize the basic cognitive structure and profile of a large sample of antipsychotic-naïve first-episode patients with schizophrenia by comparing their performance to that of a matched group of healthy controls on an extensive battery of neuropsychological tests. It was hypothesized that patients will generally perform an average of 0.5 to 2.0 standard deviations below healthy control means on all the cognitive domains examined, a performance consistent with moderate to severe cognitive impairment. The domains included verbal intelligence, speed of processing, sustained attention, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, reaction time, speed of executive processing, and global cognition.

The study also aimed to examine to which extent deficits in speed of processing can account for the cognitive deficits found in all other cognitive domains. It was hypothesized that speed of processing might be a core deficit that mediates general cognitive functions in schizophrenia.

Methods

A total of 48 antipsychotic-naïve, first-episode patients with schizophrenia were included in this study (35 Male / 13 Female). An additional 48 healthy controls matched one-to-one with patients on age, gender, and parental socioeconomic status (see Table 1 in Appendix I), were included. The computerized version of the structured clinical interview SCAN 2.1 (Schedules for Clinical Assessment in Neuropsychiatry, 1994) was used to classify psychiatric diagnoses according to both ICD-10 and DSM-IV criteria. The severity of symptoms in patients was assessed using consensus rating with the Positive and Negative Syndrome Scale (PANSS) (Kay, 1991). A comprehensive battery of tests was administered to assess different dimensions of cognitive deficits in schizophrenia (see Appendix I for included test measures and Appendix III for detailed description of these). The tests assessed domains of verbal intelligence, processing speed, sustained attention, working memory, reasoning and problem solving, verbal learning and memory, visual learning and memory, reaction time, and speed of executive processing. Cognitive domains were constructed by grouping selected test measures together on conceptual grounds. An additional domain of global cognition was derived from the summary of all cognitive domains.

Results

Demographics

There was no significant age difference (p=0.278) between patients (mean=25.44; SD=5.3) and healthy controls (mean=26.44; SD=5.4). There was also no significant difference between socioeconomic status (χ^2 =2.4; p=0.302) that was calculated from a combined rating of the highest

parental education or occupation and household income between patients and healthy controls (see Table 1 in Appendix I). There were significant correlations between socioeconomic status and cognitive domains, specifically verbal intelligence (Pearson's r = -0.289; p=0.005), processing speed (Pearson's r = -0.271; p=0.013), reasoning and problem solving (Pearson's r = -0.249; p=0.016), and global cognition (Pearson's r = -0.246; p=0.016).

Psychopathology

There were no significant differences in PANSS scores between male and female patients (see Table 2 in Appendix I), although a trend was found for higher general (*p*=0.082) PANSS scores for male patients (mean=41.82; SD=7.8) than the female patients (mean=37.00; SD=9.3) as well as for higher total (*p*=0.070) PANSS scores for male patients (mean=84.24; SD=13.9) than the female patients (mean=75.38; SD=16.1). There were no significant correlations between duration of untreated illness and any PANSS scores. Age was significantly correlated to positive PANSS score (Pearson's r = 0.366; p=0.012). Correlations between duration of untreated illness and cognitive domains showed only a tendential correlation of duration of illness to reaction time (Pearson's r = 0.301; p=0.075).

Cognition

The results of the independent sample t-tests showed significant differences between patients and healthy controls on all cognitive domains (see Table 3 in Appendix I). Results of univariate ANCOVAs investigating the effects of cognitive domains as covariates on global cognition showed that processing speed removed the significant differences between patients and controls. Processing speed as a covariate also removed the significant differences between patients and controls on all cognitive domains.

The profile and severity of cognitive deficits

One of the main findings in this study investigating cognitive function in a large group of antipsychotic-naïve patients with first-episode schizophrenia, compared to a matched group of

healthy control subjects, was that impairments were found in all cognitive domains. The variance of the effect sizes for the individual cognitive domains was medium to large, ranging from -.60 to -1.68, indicating that impairments are reliably and broadly present by the first episode, and that there is considerable heterogeneity in effect sizes across differential "core" impairments. This is similar to what has been found in previous cohorts of first episode patients (Joyce et al., 2005; Fagerlund et al., 2004; González-Blanch et al., 2007; Mesholam-Gately et al., 2009). The largest impairments were in processing speed (-1.68), reasoning and problem solving (-1.51) and sustained attention (-1.40), while speed of executive processing (-.60) and visual learning and memory (-.63) were the least impaired. The level and severity of these impairments approximate or match that of a meta-analytic study (Mesholam-Gately et al., 2009) of cognitive impairment in first-episode schizophrenia, as well as of meta-analytic studies (Heinrichs & Zakzanis, 1998; Fioravanti et al., 2005) of mixed and chronic patient samples, which suggests that illness chronicity and/or treatment exposure probably does not account for the most meaningful share of cognitive impairment in schizophrenia (Goldberg et al., 2007; Szöke et al., 2008). There are of course, however, some inconsistencies of effect sizes between this study and the meta-analytic studies (Heinrichs & Zakzanis, 1998; Fioravanti et al., 2005; Mesholam-Gately et al., 2009). These inconsistencies are likely brought on by differences in sensitivity and specificity of measures of cognitive constructs (Chapman & Chapman, 1973; Miller et al., 1995), and differences in sample characteristics (Loughland et al., 2004).

Speed of processing as a core deficit

The influence of impaired processing speed on cognition in schizophrenia is indicated by the current study to be of central importance. When this influence is controlled for, the cognitive impairments in schizophrenia patients disappear. This is consistent with other studies (see meta-analysis by Dickinson, Ramsey & Gold, 2007) investigating the effects of impaired processing speed on cognition. However, these studies have usually only investigated the influence of processing speed on a limited number of cognitive domains, and have mainly focused on only one test measure of processing speed, the Digit Symbol Coding Task from the Wechsler intelligence scales (Wechsler, 1997). This study extends the *processing speed hypothesis* (Rodríguez-Sánchez et al., 2007) by covering most cognitive domains, and including several reliable measures of

processing speed and combining their effects on a broad range of cognitive functions. So while the coding task of the current study, the SDMT (Smith, 1982), did account for 68.6 percent of the between-group variance on the processing speed composite, and had an effect size of -1.44, the other processing speed measures accounted for similar results (variance ranging from 53.3 percent to 69.3 percent, and effects sizes ranging from -0.94 to -1.35), particularly the SCOLP test (Baddeley et al., 1992) that had near identical results to the SDMT test. This indicates that (some) tests that are putative measures of processing speed, can represent the influence of processing speed on cognition in schizophrenia nearly as well as coding tasks, and can be simple and useful tools in quantifying a form of cognitive impairment that is a central, reliable feature of schizophrenia. One caveat, however, is that tests such as the SDMT and the SCOLP are in fact very cognitively demanding and involve multiple component operations, and may therefore not be very specific measures of processing speed (Chapman & Chapman, 1973; Miller et al., 1995; van Hoof et al., 1998; Jogems-Kosterman et al., 2001; Dickinson, Ramsey & Gold, 2007; Carter & Barch, 2007). It may therefore be the case that the robust effect sizes demonstrated by such tests (in particular coding tasks), which tends to be the highest in almost any comparison of (psychiatric, neurological or pseudo-neurological) patient groups and healthy controls (although the effect size in schizophrenia is significantly stronger), may be caused by the tests being simultaneously sensitive to a greater number of somewhat differentially impaired abilities.

From the results of this study, processing speed might be considered a “core” cognitive deficit in schizophrenia that determines function in cognitive domains. However, other studies (Laws, 1999; Aleman et al., 1999; Lee & Park, 2005; Achim & LePage, 2005; Reichenberg & Harvey, 2007; Ranganath et al., 2008; Barch & Smith, 2008) have found different “core” deficits that also might determine and predict function in cognitive domains. These “core” deficits are the same as the cognitive domains that have the highest effect sizes and account for the most between-group variance in this study, and include, in order of magnitude, reasoning and problem solving, sustained attention, verbal intelligence, reaction time, and working memory. The reason for this contradictory existence of several “core” deficits (of differential magnitude) might possibly be that nearly every neuropsychological test measure involve multiple component operations, and therefore do not separate cognitive deficits so ideally (MacDonald & Carter, 2002; Jonides & Nee, 2005; Silverstein, 2008). Another reason, however, might be that instead of a diverse array of multiple independent deficits, there may be a largely generalized cognitive deficit (Blanchard & Neale, 1994; Dickinson

& Harvey, 2009) that can mimic selective deficits, depending on the complexity and focus of the neuropsychological tests (Chapman & Chapman, 1973; Miller et al., 1995). The cause could be abnormalities in connections among widespread brain regions that lead to an impairment in synchrony or the smooth coordination of mental processes (Andreasen, Paradiso & O'Leary, 1998). Impairment in this basic cognitive process could define the phenotype of schizophrenia and produce its diversity of symptoms. The best measure of this dysfunction may be impaired processing speed, based on the conception that especially coding and fluency tasks (that were all included as component measures of this study's processing speed domain) require the coordination of a series of elementary cognitive operations in distributed networks (Bokat & Goldberg, 2003; Dickinson, Ramsey & Gold, 2007). In accordance with this conception, a deficit in speed of processing in schizophrenia might then reflect reduced grey or white matter volumes in prefrontal and temporal brain regions (Mitelman & Buchsbaum, 2007; Dwork et al., 2007; Witthaus et al., 2008). This is supported by a study (Sanfilipo et al., 2002) that found that performance by schizophrenia patients on digit symbol coding was generally associated with gray matter volumes in bilateral prefrontal cortex, bilateral hippocampus, and left superior temporal gyrus. Another study (Antonova et al, 2005) has also found abnormalities in white matter to be related to deficits in processing speed in schizophrenia (Antonova et al., 2005).

The clear result of this study sharpens the hypothesis of slowed information processing as a central feature of cognitive impairment in schizophrenia. Other studies (see meta-analysis by Dickinson, Ramsey & Gold, 2007) suggest that impaired processing speed might be a possible promising cognitive endophenotype for schizophrenia (Kéri & Janka, 2004). This contention is supported by studies that have found impaired processing speed (as measured primarily by the digit symbol coding task) to be stable (Hill et al., 2004; Verdoux et al., 1995), related to prognosis and functional outcome (Brekke et al., 1997; Schuepbach et al., 2002; Niendam et al., 2003), highly heritable (Swan & Carmelli, 2002), and present in relatives and in high-risk individuals (Byrne et al., 2003; Hawkins et al., 2004). The clinical implications may be that the focus on cognitive impairment in schizophrenia might need to be shifted from separable cognitive domains (Dickinson & Gold, 2008), and towards the construct of processing speed as a generalized measure of level of illness severity (Dickinson & Harvey, 2009), even despite issues of construct validity (Chapman & Chapman, 1973; Miller et al., 1995; van Hoof et al., 1998; Jogems-Kosterman et al., 2001). Further implications include the potential value of therapeutic intervention targeted towards improving

impaired processing speed, since amelioration may transfer to other domains of cognitive functioning as well (Edwards et al., 2002; Carter & Barch, 2007).

Conclusions

The data of the current study show that first-episode, antipsychotic-naïve patients with schizophrenia show deficits in all the major cognitive domains that were assessed, when compared to healthy controls. However, when speed of processing is taken into account, the entire variance of these deficits are explained, suggesting that impaired processing speed may be a key factor behind all the cognitive deficits that were assessed in the current study.

CHAPTER 4 - COGNITIVE EFFECTS OF QUETIAPINE IN SCHIZOPHRENIA

Since cognitive deficits are core deficits with crucial impact on the prognosis of patients, there is considerable incentive to find treatments that target these deficits. Several methodological considerations and confounds limit the conclusions that can be drawn regarding the effects of antipsychotics on cognition in schizophrenia (Salimi, Jarskog & Lieberman, 2009; Hill et al., 2010), such as carry-over effects (both positive and negative) due to prior medication, practice effects due to repeated testing, placebo effects (Fagerlund et al, 2004; Mishara & Goldberg, 2004; Goldberg et al., 2007; Keefe et al., 2008; Szöke et al., 2008), the impact of adjunctive medication such as anticholinergic medication, benzodiazepines, antidepressant medication, and concomitant drug abuse (Woodward et al., 2005; Keefe et al., 2007a; Davidson et al., 2009).

Most of the abovementioned studies have been conducted with mainly chronic, previously medicated patients. It is possible that several factors associated with chronicity of the illness (e.g. previous exposure to other antipsychotic compounds, the impact of illness duration itself, ageing) may limit the possible beneficial effects of antipsychotics on cognition (Bilder et al., 2000). The potential cognition-enhancing effect of antipsychotics may be more evident when it is used among younger, antipsychotic-naïve patients with first-episode schizophrenia (Salimi, Jarskog & Lieberman, 2009). First-episode patients have been shown to be comparatively more treatment responsive in terms of effects on psychopathology than chronic patients (McEvoy et al., 1991). Therefore, they may also be more responsive to cognitive amelioration from antipsychotics (Davidson et al., 2009; Voruganti et al., 2002).

There are some research findings indicating the potential for cognitive enhancement from treatment with quetiapine. This compound has a receptor occupancy profile with relatively higher affinity for the serotonin $5HT_{2A}$ receptor than for the dopamine D_2 receptor and has been found to have no greater extrapyramidal symptoms than placebo across the full dosage range, suggesting minimal requirement for anticholinergic prescription (Seeman & Tallerico, 1998; Kapur et al., 2000; Riedel et al., 2007c). Studies have reported specific effects of quetiapine on sustained attention, reasoning and problem solvings, verbal memory, verbal reasoning, verbal fluency, immediate recall, motor, and visuo-motor skills (e.g. Purdon et al., 2001; Zhong et al., 2006; Keefe et al., 2007a, 2007b; Voruganti et al., 2007). However, only few studies examining the effects of quetiapine on cognition

in a longitudinal design have included first-episode schizophrenia patients that have not received prior antipsychotic medication (Good et al., 2002; Keefe et al., 2007b; Hill et al., 2008; Perkins et al., 2008; Davidson et al., 2009). Few previous studies on effects of antipsychotics on cognition (e.g. Fagerlund et al., 2004; Goldberg et al., 2007; Crespo-Facorro et al., 2009) have included and retested a healthy control group matched to patients in order to establish the expected level of practice effects. Only one previous study examining the effects of quetiapine (Sax et al., 1998) included and retested a comparison sample of healthy subjects, but did not include first-episode schizophrenia patients.

Objectives

The present study aimed to examine the effects on cognition of 6 months of quetiapine treatment in antipsychotic-naïve patients with schizophrenia. It was hypothesized that there will be modest beneficial effects of 6 months quetiapine monotherapy on cognition.
The study also aimed to examine the impact of practice effects on cognitive change, by comparing cognitive change in patients to cognitive change in healthy controls. It was hypothesized that in large part, the effects of quetiapine can be accounted for with practice effects

Methods

A total of 24 antipsychotic-naïve first-episode patients with schizophrenia were included in this study (16 Male / 8 Female). An additional 24 healthy controls matched one-to-one with patients on age, gender, and parental socioeconomic status (see Table 1 in appendix II), were included. The computerized version of the structured clinical interview SCAN 2.1 (Schedules for Clinical Assessment in Neuropsychiatry, 1994) was used to classify psychiatric diagnoses according to both ICD-10 and DSM-IV criteria. The severity of symptoms in patients was assessed using consensus rating with the Positive and Negative Syndrome Scale (PANSS) (Kay, 1991). A comprehensive battery of tests was administered to assess different dimensions of cognitive deficits in

schizophrenia (see Appendix II for included test measures and Appendix III for detailed description of these). The tests assessed domains of verbal intelligence, processing speed, sustained attention, working memory, reasoning and problem solving, verbal learning and memory, visual learning and memory, reaction time, and speed of executive processing. Cognitive domains were constructed by grouping selected test measures together on conceptual grounds. An additional domain of global cognition was derived from the summary of all cognitive domains. Following baseline assessments, patients were teated for a period of 6 months, with quetiapine antipsychotic monotherapy. After this period they underwent the same battery of tests again. In addition, the healthy controls were re-tested after 6 months; however, they received no treatment at all.

Results

Psychopathology

Patients showed a significant reduction in both the positive symptom subscale score as well as the total score of the PANSS scale from baseline to follow-up. In addition, a trend was found for a reduced general symptom score on the PANSS. The negative subscale score of the PANSS at follow-up did not differ significantly from the score at baseline (see Table 2 in Appendix II). Linear regression analyses found psychopathology to be a poor predictor of cognitive change, with the only tendentially significant model showing PANSS general symptoms to be a weak predictor of cognitive change ($r^2 = 0.149$; $p= 0.078$).

Cognitive deficits at baseline

Compared to the healthy control group, the patients were significantly impaired in 5 out of the 8 cognitive domains, and at trend level in the remaining 3 domains. The severity of deficits ranged from 0.7-2.1 standard deviations below the healthy control mean (see Table 3 in Appendix II).

Between-group differences

The results of the repeated measures ANOVA showed a significant time X group interaction effect for two domains: reasoning and problem solving [F(1,44)=6.795, p=0.012] and speed of executive processing [F(1,44)=4.101, p=0.012]. Post-hoc analyses revealed that patients improved significantly more than healthy controls from baseline to follow-up on the reasoning and problem solving domain, while there were no significant changes in either patients or controls on the speed of executive functions domain (the significant time X group interaction reflecting a non-significant deterioration in controls). It should be noted that the significant time X group interaction effect on reasoning and problem solving may likely be the result of a near-ceiling effect in the healthy control group. However, correcting these results for baseline scores, the abovementioned interaction effects were no longer significant, although three new tendencies for a time X group interaction effect appeared, i.e. in speed of processing [F(1,45)=3.073, p=0.086], sustained attention [F(1,43)=3.203, p=0.081], and working memory [F(1,43)=3.858, p=0.056], indicating that patients improved (at trend level) less than healthy controls from baseline to follow-up in these domains (see Table 4 in Appendix II).

Within-group differences

The patients showed significant within-group changes on speed of processing [t(23)=2.320, p=0.030] and reasoning and problem solving [t(22)=3.028, p=0.006], indicating a significantly higher score at follow-up than at baseline. The changes in speed of processing could be attributed to an improved score on the SCOLP [t(23)=4.481, p=0.0002] and the Symbol Digit Modalities Test [t(23)=2.429, p=0.023] at follow-up, while the changes in reasoning and problem solving can be attributed to fewer errors on the IED task (i.e. total errors [t(22)=2.493, p=0.021] and EDS errors [t(22)=3.497, p=0.002]) at follow-up than at baseline (see also Table 4 in Appendix II).

The healthy control group showed significant improvements at follow-up on 3 of 8 composite scores: Sustained attention [t(22)=2.616, p=0.016], speed of processing [t(23)=2.879, p=0.008], and working memory [t(22)=2.749, p=0.012]. The changes in sustained attention can be attributed to the RVP signal detection score A' [t(22)=2.757, p=0.012], the changes in speed of processing can be attributed to both Trail-Making A [t(23)=2.484, p=0.021] and SCOLP [t(23)=3.355, p=0.003], while the changes in working memory can be attributed to the three SWM test measures of strategy

[t(22)=3.027, p=0.006], total errors [t(22)=1.987, p=0.060] and between errors [t(22)=2.025, p=0.055].

The effects of quetiapine monotherapy on cognition

The main result of the study is that there was very little evidence of efficacy of quetiapine on cognition, where improved scores in patients from baseline to follow-up were found on only 2 of 8 cognitive domains (i.e. reasoning and problem solving, and speed of processing). It is possible that the improvement found in reasoning and problem solving in patients represents beneficial effects of quetiapine, as only patients, and not controls, improved on this domain. The improvement in this domain could be attributed to fewer errors on the IED set shifting task, primarily at the extradimensional (ED) shift stage, where subjects need to shift attention from a previously reinforced dimension to a new dimension. It is, however, likely that the differential change in this domain may have been caused by a near-ceiling effect in the component IED measures of the healthy control group at both baseline and follow-up, thus possibly inflating the relative significance of the improved scores in the patient group (Lowe & Rabbitt, 1998). Nevertheless, the results also indicate that the patients achieved nearly normal scores on the IED set shifting task at follow-up, which suggests that the performance of patients at follow-up either improved because of quetiapine treatment, or improved independently of quetiapine treatment, or that quetiapine did not attenuate a normal practice effect on these component measures of reasoning and problem solving (Weickert et al., 2002).

The patients also showed improved results at follow-up on the speed of processing domain, although not significantly different from the practice effects observed in the healthy control group. The component measures that improved within this domain in patients were the SCOLP and the symbol digit modalities test. This is in line with the changes found in the Comparison of Atypicals in First Episode of Psychosis (CAFÉ) study, where specific beneficial effects of quetiapine were found on processing speed measures of verbal fluency and the WAIS-R digit symbol test (Keefe et al., 2007b). However, the CAFÈ study also found modest effects of quetiapine on other aspects of

cognition similar to the effects of olanzapine and risperidone, which were not found in the current study.

The significant effect of quetiapine on positive symptoms was in line with previous studies, but the lack of an effect on negative symptoms is in contrast to other studies that have found quetiapine to have a substantial direct effect on improving negative symptoms of schizophrenia (Good et al., 2002; Nasrallah & Tandon, 2002; Tandon, 2004; Riedel et al., 2007c). Psychopathology scores at baseline were a poor predictor of cognitive change, with only PANSS general symptoms tendentially predicting cognitive change. In addition, there were no significant correlations between change in psychopathology and change in cognition.

The treatment interval in the current study was 6 months, which is the same as the interval used in the European First Episode Schizophrenia Trial (EUFEST) (Davidson et al., 2009). Although it is possible that more beneficial effects of quetiapine on cognition may have been present if patients had been re-examined after a longer time interval than 6 months, this is unlikely based on previous studies. For example, the CAFÉ study suggested that possible beneficial effects of antipsychotics appear in the first months after treatment initiation, and that further benefits over longer time periods may be very small (Keefe et al., 2007b).

It is possible that the dose administered in the current study was either insufficient, or too high to attain cognition enhancing effects (Woodward et al., 2007; Hill et al., 2010), however, dosages were comparable to those used in previous studies of first-episode patients, e.g. the CAFÈ study (Keefe et al., 2007b), and the EUFEST study (Davidson et al., 2009), and even in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which included only chronic patients (Keefe et al., 2007a). We do not consider the largely negative results of the current study to be specifically attributable to treatment with quetiapine, compared to other antipsychotic compounds (although this question cannot be answered by the current study). However, two large studies that compared the cognition enhancing properties of second generation antipsychotics - including quetiapine - and first generation antipsychotics in either chronically ill patients (Keefe et al., 2007a) or patients with first-episode schizophrenia (Davidson et al., 2009) found no overall difference in degree of improvement between compounds.

The impact of practice on test performance

Because the performance of patients differed from controls at baseline, changes over time were also examined and covaried for the differences at baseline. These analyses revealed that patients showed less practice effects than did controls on the speed of processing, sustained attention, and working memory domains. In certain instances (e.g. regarding working memory) the performance gains of the healthy control group markedly exceeded those of the patient group. This may have several important implications. First, there is clear evidence that practice effects are present on some of these measures, which are important to consider in longitudinal effect studies. Second, long test intervals such as 6 months in the present study may attenuate, but do not eliminate practice effects. Third, the magnitude of practice effects appears to differ between cognitive domains. It is unclear whether the insufficient practice effect in patients is caused by detrimental effects of quetiapine, suppressing a practice effect that would otherwise have been present (Harvey & Keefe, 2001; Woodward et al., 2005, 2007), or is caused by the inherent neuropathology involved in the cognitive deficits of schizophrenia that may also limit practice effects on these measures (Gold et al., 2000; Weickert et al., 2002). The current results are in line with results from a previous study from our group (Fagerlund et al., 2004), where antipsychotic-naïve, first-episode schizophrenia patients were randomised to treatment with risperidone and zuclopenthixol (a first-generation compound), and a healthy control group was retested to examine practice effects. Results showed few changes with medication, little distinction between effects of the compounds and further that effects of medication on cognition in patients did not exceed practice effects in the healthy group. The impact of practice effects was later demonstrated in a large study by Goldberg et al. (2007), who reported that cognitive test improvements in a sample of first-episode schizophrenia patients treated with olanzapine or risperidone were in the same range of magnitude as the practice effects in a matched sample of healthy subjects on most measures. Similarly, in a large study of adjunctive donepezil medication, Keefe et al. (2008) found significant practice effects in the placebo group. Since a placebo-treated patient group was not included (for obvious ethical reasons), it is not possible in the current study to distinguish whether practice effects on speed of processing were primarily caused by practice effects (Goldberg et al., 2007; Szöke et al., 2008; Hill et al., 2010), or patient motivation and expectancy of improvements (Velligan, Kern & Gold, 2006).

Conclusions

This is the first longitudinal study to examine the effects of quetiapine on cognitive functions in antipsychotic-naïve first-episode schizophrenic patients, in which a matched healthy control group was also included and retested to control for practice effects. The results of the study did not find evidence of cognition enhancing effects of quetiapine in antipsychotic-naïve, first-episode schizophrenia patients. While quetiapine treatment may have facilitated improvement on errors on the IED set shifting task, the large majority of cognitive measures did not improve with medication, and some normal practice effects were not found in patients after medication. The results clearly suggest that treatment strategies other than antipsychotic medication are warranted to improve the cognitive deficits in schizophrenia.

CHAPTER 5 - CONCLUSIONS

The results of the baseline study revealed that first-episode, antipsychotic-naïve patients with schizophrenia show moderate to severe deficits in all the major cognitive domains that were assessed, when compared to healthy controls. These domains include verbal intelligence, processing speed, sustained attention, working memory, reasoning and problem solving, verbal learning and memory, visual learning and memory, reaction time, and speed of executive processing. After controlling for speed of processing, all significant differences between patients and healthy controls on cognitive domains disappeared.

The results from the follow-up study, in which the patients after the initial baseline assessments were treated for 6 months with quetiapine, while the controls received no treatments, did not indicate evidence of cognition enhancing effects of quetiapine. While quetiapine treatment may have facilitated improvement on a component measure of reasoning and problem solving, the large majority of cognitive measures did not improve with medication, and some normal practice effects were not found in patients after medication.

In conclusion, the results indicate that impaired processing speed may be a substantial general component behind cognitive deficits in schizophrenia patients, and that different treatment strategies are warranted to improve the cognitive deficits in schizophrenia. Results also indicate that much research on cognition in schizophrenia may be confounded by a lack of attention paid to the psychometric properties of neuropsychological tests, most notably by the effects of practice that may misrepresent measures of cognitive change in clinical trials, and ceiling effects that may serve to hide or dampen the effects of practice.

CHAPTER 6 - FUTURE DIRECTIONS

This thesis underlines some of the conceptual and methodological issues that complicate research on cognitive function in schizophrenia. These include the precise measurement of profile and severity of cognitive deficits, the influence of impaired processing speed on cognition, the effects of antipsychotic treatment on cognitive functioning, and the impact of practice effects on test performance. The importance and relevance of the issues raised by this thesis for future research will be made clear in the following.

The profile and severity of cognitive deficits may be central for understanding the pathophysiology of schizophrenia, perhaps even more so than the symptoms that are now used to diagnose the disorder. To reliably measure the differences between patients and healthy controls, some of the computerized neuropsychological tests in CANTAB were included as assessment measures (Levaux et al., 2007). These tests are outstandingly sensitive and extensively validated, and are particularly adept at highlighting significant deficits affecting broad cognitive domains in schizophrenia, as well as for providing facets of performance typically inaccessible to traditional paper-and-pencil measures. The present findings may therefore be more sensitive to specific cognitive endophenotypes with characteristic neurobiology (and treatment response), and further analyses of subgroups (rather than the "average" patient) may provide valuable insights, as will correlations to results from other research paradigms applied in this collaborative study (genetics, psychophysiology, magnetic resonance imaging and positron emission tomography).

The current finding of speed of processing as a possible core deficit in schizophrenia has been reported before (Dickinson, Ramsey & Gold, 2007), but needs to be replicated in further studies, primarily because of the questionable construct validity of assessment measures for processing speed (Carter & Barch, 2007).

There appears little reason to be enthusiastic about the cognitive benefits of current antipsychotics. However, knowledge of ways to improve the search for potentially procognitive agents has been growing (Nuechterlein et al., 2004; Carter & Barch, 2007). The present study and literature review suggests very little efficacy of antipsychotics on cognition. Therefore, novel treatment strategies are warranted, both in terms of medication targeting other transmitter systems, and other promising

strategies, such as cognitive remediation therapy that consistently show moderate treatment effects, which are greater than observed for any drug treatments so far.

The current studies also indicate the need for controlling for practice effects in clinical trials. The potential confound of practice effects has rarely been addressed in clinical trials investigating the cognitive effects of antipsychotics (Fagerlund et al., 2004; Goldberg et al., 2007). However, the impact of practice effects should always be considered in the design of clinical studies. The use of a control group is of critical importance to ensure that results can correctly be interpreted as indicating improvement or deterioration in the cognitive abilities of individuals with schizophrenia.

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The Influence of Impaired Processing Speed on Cognition in First-Episode Antipsychotic-Naïve Schizophrenic Patients

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Abstract

One of the core features of schizophrenia is impaired cognition. However, the severity and pattern of cognitive deficits in antipsychotic-naïve patients with first-episode schizophrenia still remain somewhat unclear, because previous studies have often employed relatively small and heterogeneous samples.

The goals of the current study were to identify the profile and severity of cognitive deficits in antipsychotic-naïve, first-episode patients with schizophrenia across a range of cognitive domains, and to investigate the contribution of impaired processing speed.

Forty-eight antipsychotic-naïve patients with first-episode schizophrenia and 48 matched healthy controls were administered a comprehensive battery of neuropsychological tests to assess domains of cognitive deficits in schizophrenia. Cognitive domains were assessed using composite scores, grouping selected tests together on conceptual grounds.

There were significant differences between patients and healthy controls on global cognition and in all cognitive domains, including verbal intelligence, processing speed, sustained attention, working memory, reasoning and problem solving, verbal learning and memory, visual learning and memory, reaction time, and speed of executive processing. All these significant differences disappeared when processing speed was included as a covariate.

At the first stage of illness, antipsychotic-naïve patients with schizophrenia display moderate/severe impairments in all the cognitive domains assessed. The results support the contention of a global cognitive dysfunction in schizophrenia that to some extent may be determined by impaired processing speed.

Introduction

Cognitive deficits are pervasive in schizophrenia over a wide range of domains (Heinrichs, 2005), and have profound impact on functional outcome (Green, 1996; van Winkel et al., 2007; Bowie et al., 2008). There is substantial cognitive heterogeneity between patients and remarkable stability of cognitive function within patients after onset of illness, despite the fluctuation of clinical symptoms. The cognitive deficits detected at the time of the first episode show a degree of severity ranging from 0.5 to 1.5 standard deviations below normative values (Fioravanti et al., 2005; Mesholam-Gately et al., 2009; Kravariti et al., 2009). The cognitive deficits in schizophrenia are considered to be of a generalized nature (Lencz et al., 2006; Dickinson et al., 2008) although there is also some evidence of disproportionate impairment in sustained attention (Fioravanti et al., 2005), processing speed (Dickinson, Ramsey & Gold, 2007; Rodríguez-Sánchez et al., 2007), episodic memory (Aleman et al., 1999; Achim & LePage, 2005; Ranganath et al., 2008), reasoning and problem solving (Laws, 1999; Reichenberg & Harvey, 2007), and working memory (Lee & Park, 2005; Barch & Smith, 2008). To what degree these different neuropsychological performance domains in schizophrenia (and their corresponding cognitive measures) are independent of one another, weakly correlated, or substantially overlapping, is a topical issue of interest (Nuechterlein et al., 2004; Silverstein, 2008; Dickinson & Gold, 2008; Dickinson & Harvey, 2009).

A central feature of the cognitive impairment in schizophrenia is a slower speed of information processing (Keefe, Bilder & Harvey, 2006; Dickinson, Ramsey & Gold, 2007; Rodríguez-Sánchez et al., 2007). Impairments on coding tasks that reflect speeded performance of a number of straightforward scanning, switching, matching, and writing operations, are significantly more pronounced than impairments on measures from memory, attention, reasoning and problem solving, and working memory domains. However, coding task impairment, the largest effect size found for cognitive impairment in schizophrenia (Keefe, Bilder & Harvey, 2006; Dickinson, Ramsey & Gold, 2007), has not until recently been the focus of sustained experimental investigation, despite of the very general constraint that this performance dimension represents for cognitive processing (Salthouse, 1996). That is, many higher cognitive operations - including perceptual processes, encoding and retrieval operations, transformation of information held in active memory, and decision processes - involve internal dynamics that are speed-dependent to an important extent. The experimental investigation of the *processing speed hypothesis* (Rodríguez-Sánchez et al., 2007) has

thus shown that particularly the Digit Symbol Coding Task from the Wechsler intelligence scales (Wechsler, 1997) taps an information processing inefficiency that might determine a broad diversity of cognitive impairments (Dickinson, Ramsey & Gold, 2007). This suggests that the generalized effect of slow processing speed, as measured by digit symbol coding, could possibly be at the core of global impairment in schizophrenia (Dickinson, Ramsey & Gold, 2007; Rodríguez-Sánchez et al., 2007; Dickinson & Harvey, 2009).

The current study aims to characterize the basic cognitive structure and profile of a large sample of antipsychotic-naïve first-episode patients with schizophrenia by comparing their performance on an extensive battery of neuropsychological tests to that of a matched group of healthy controls. It is hypothesized that the between-groups performance deficits in cognitive domains are mediated mainly through a common cognitive ability factor, specifically processing speed.

Methods

Subjects

Patients were recruited after first-time referral participating psychiatric centres in the capital region of Copenhagen from December 2003 to December 2007. The inclusion criteria were: Antipsychotic-naïve patients between the ages 18 to 45, fulfilling both the International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for schizophrenia or schizoaffective disorder. The exclusion criteria were: Patients who were not voluntarily hospitalised, patients who were deemed in acute need of medication, patients with somatic or neurological illnesses, and patients with known mental retardation.

A total of 55 patients were recruited and tested. Results from 48 of these patients were included (35 Male / 13 Female). The reasons for exclusion were: Structural brain abnormality (N = 2), a final diagnosis of schizotypal personality disorder (N = 3), uncertainty of diagnosis (N = 1), and prior use of antipsychotics (N = 1). The mean duration of untreated illness, which was defined as the time from the first unspecific symptoms related to psychosis until the time of neuropsychological testing (Keshavan et al., 1998), was 182 weeks (range 2 - 780 weeks, median = 78 weeks, SD = 221).

The ICD-10 diagnostic distribution of the 48 participating schizophrenic patients was: Paranoid (*N* = 36), Hebephrenic (*N* = 3), Undifferentiated (*N* = 5), Unspecified (*N* = 2), and Schizoaffective disorder (*N* = 2). Ten patients had prior (*N* = 4) or present (*N* = 6) use of antidepressant medication (in all cases selective serotonin reuptake inhibitors except for one patient, who was treated with a noradrenergic and specific serotonergic antidepressant). Twenty-one patients were prescribed benzodiazepines on an as needed basis. However, benzodiazepines were not allowed on the day of testing. Three patients fulfilled ICD-10 criteria for multiple drug use and the use of other psychoactive substances, 3 patients for the use of alcohol, 2 patients for the use of cannabinoids, and 2 patients for the use of both alcohol and cannabinoids.

Forty-eight healthy controls matched one-to-one with patients on age, gender, and parental socioeconomic status (see Table 1), were recruited from the community by advertisements. Exclusion criteria for controls were the presence of a psychiatric diagnosis, somatic or neurological illness, psychiatric diagnoses in first-degree relatives, a history of drug- or alcohol abuse, and the presence of mental retardation or any known learning disabilities.

The study was approved by the Ethics Committees of Copenhagen and Frederiksberg ([KF]11-061/03). The subjects participated after receiving a full explanation of the study and providing written informed consent according to the Declaration of Helsinki II.

Psychopathology

The computerized version of the structured clinical interview SCAN 2.1 (Schedules for Clinical Assessment in Neuropsychiatry, 1994) was used to classify psychiatric diagnoses according to both ICD-10 and DSM-IV criteria. The severity of symptoms in patients was assessed using consensus rating with the Positive and Negative Syndrome Scale (PANSS) (Kay, 1991). The interrater reliability, estimated by intraclass correlation coefficient for the PANSS total score, was 0.92.

Cognition

A comprehensive battery of tests was administered to assess different dimensions of cognitive deficits in schizophrenia (see Table 3). The test battery, which was administered in a fixed order by the same psychologist (RA) and took approximately 2.5 hours to complete, comprised paper-and-

pencil tests as well as tests from the computerized Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian & Owen, 1992; Levaux et al., 2007). The tests assessed domains of verbal intelligence, processing speed, sustained attention, working memory, reasoning and problem solving, verbal learning and memory, visual learning and memory, reaction time, and speed of executive processing. Cognitive domains were constructed by grouping selected test measures together on conceptual grounds. An additional domain of global cognition was derived from the summary of all cognitive domains.

The test battery of this study (see Table 3) included nineteen tests that assessed nine specific cognitive domains. Some of the cognitive domains consisted of only one selected test measure, while others consisted of up to four tests and six test measures. To assess *verbal intelligence* the Danish Adult Reading Test, and the Vocabulary and Similarities subtests from the Wechsler Adult Intelligence Scale were included. To assess *processing speed* the semantic and phonological fluency test, Trail Making test A, Speed and Capacity of Language-Processing Test (SCOLP), and Symbol Digit Modalities Test (SDMT) were included. To assess *sustained attention* the simple signal detection and complex signal detection measures of the CANTAB Rapid Visual Information Processing Test were included. Measures assigned to the *working memory* domain included spatial span length from the CANTAB Spatial Span test; strategy, total errors and between errors from the CANTAB Spatial Working Memory test; and the WAIS digit span forwards and backwards. To assess *verbal learning and memory* the total recall of words on the Buschke selective reminding test was included. Test results from 16 patients were incomplete and therefore excluded. To assess *visual learning and memory* the immediate recall performance on the Rey-Osterrieth complex figure was included. Measures assigned to the *reasoning and problem solving* domain included the number of cards used and total number of errors from the Wisconsin Card Sorting Test (WCST); mean number of moves and number of problems solved in minimum moves from the CANTAB Stockings of Cambridge (SOC); and total errors (adjusted for stages not completed) and errors at the extra dimensional set shifting stage from the CANTAB Intra-Extra Dimensional set shifting task (IED). The domain of *reaction time*, consists of simple and choice reaction and movement times from the CANTAB Reaction and Movement Time Test. The domain of *speed of executive processing* contains components of both processing speed and reasoning and problem solving, and includes initial thinking time and subsequent thinking time from the CANTAB SOC test; Trail Making B minus the time to complete Trail Making A; and Regard's Figural Fluency Task.

Statistical Analysis

Data were analysed using Statistical Package for the Social Sciences (SPSS), version 11.0. All analyses used two-tailed levels of significance. If data of a subject was missing, then the corresponding data of their match was also excluded from analyses. Results from tasks that did not fit a normal distribution were logarithmically transformed to reduce skew. Parametric statistics were used for all analyses. To compare demographic and clinical characteristics of the patient and control groups, independent samples t-tests and Pearson's χ^2-test were applied as appropriate. Data were standardized to z-scores (with an average of 0 and a standard deviation of 1) using the healthy control group data as reference. When appropriate, z-scores were reversed so that higher scores represent better performance. The mean of subtest z-scores was used to compute composites scores (see also Table 3). Independent sample t-test was carried out to compare means for each of these composite scores. Bivariate analysis was used to describe the relationships between demographics, psychopathology and cognition. Univariate analysis of covariance (ANCOVA) was used to derive the influence of cognitive measures, in particular processing speed, on specific and global cognitive functions.

Results

Demographics

There was no significant age difference (p=0.278) between patients (mean=25.44; SD=5.3) and healthy controls (mean=26.44; SD=5.4). There was also no significant difference between socioeconomic status (χ^2 =2.4; p=0.302) that was calculated from a combined rating of the highest parental education or occupation and household income between patients and healthy controls (see Table 1). There were significant correlations between socioeconomic status and cognitive domains, specifically verbal intelligence (Pearson's r = -0.289; p=0.005), processing speed (Pearson's r = -0.271; p=0.013), reasoning and problem solving (Pearson's r = -0.249; p=0.016), and global cognition (Pearson's r = -0.246; p=0.016).

Psychopathology

PANSS scores are presented in Table 2. There were no significant differences between male and female patients, although a trend was found for higher general (p=0.082) PANSS scores for male patients (mean=41.82; SD=7.8) than the female patients (mean=37.00; SD=9.3) as well as for higher total (p=0.070) PANSS scores for male patients (mean=84.24; SD=13.9) than the female patients (mean=75.38; SD=16.1). There were no significant correlations between duration of untreated illness and any PANSS scores. Age was significantly correlated to positive PANSS score (Pearson's r = 0.366; p=0.012). Correlations between duration of untreated illness and cognitive domains showed only a tendential correlation of duration of illness to reaction time (Pearson's r = 0.301; p=0.075)

Cognition

The results of the independent sample t-tests showed significant differences between patients and healthy controls on all cognitive domains (see Table 3).

Results of univariate ANCOVAs investigating the effects of cognitive domains as covariates on global cognition showed that processing speed removed the significant differences between patients and controls. Processing speed as a covariate also removed the significant differences between patients and controls on all cognitive domains.

Discussion

The main findings in this study investigating cognitive function in a large group of antipsychotic-naïve patients with first-episode schizophrenia, compared to a matched group of healthy control subjects, were that impairments were found in all cognitive domains, as well as the apparent influence of impaired processing speed on cognition. The variance of the effect sizes for the individual cognitive domains was medium to large, ranging from -.60 to -1.68, indicating that impairments are reliably and broadly present by the first episode, and that there is considerable heterogeneity in effect sizes across differential "core" impairments. This is similar to what has been found in previous cohorts of first episode patients (Joyce et al., 2005; Fagerlund et al., 2004; González-Blanch et al., 2007; Mesholam-Gately et al., 2009). The largest impairments were in processing speed (-1.68), reasoning and problem solving (-1.51) and sustained attention (-1.40),

while speed of executive processing (-.60) and visual learning and memory (-.63) were the least impaired. The level and severity of these impairments approximate or match that of a meta-analytic study (Mesholam-Gately et al., 2009) of cognitive impairment in first-episode schizophrenia, as well as of meta-analytic studies (Heinrichs & Zakzanis, 1998; Fioravanti et al., 2005) of mixed and chronic patient samples, which suggests that illness chronicity and/or treatment exposure probably does not account for the most meaningful share of cognitive impairment in schizophrenia (Goldberg et al., 2007; Szöke et al., 2008). There are of course, however, some inconsistencies of effect sizes between this study and the meta-analytic studies (Heinrichs & Zakzanis, 1998; Fioravanti et al., 2005; Mesholam-Gately et al., 2009). These inconsistencies are likely brought on by differences in sensitivity and specificity of measures of cognitive constructs (Chapman & Chapman, 1973; Miller et al., 1995), and differences in sample characteristics (Loughland et al., 2004).

The influence of impaired processing speed on cognition in schizophrenia is indicated by the current study to be of central importance. When this influence is controlled for, the cognitive impairments in schizophrenia patients disappear. This is consistent with other studies (see meta-analysis by Dickinson, Ramsey & Gold, 2007) investigating the effects of impaired processing speed on cognition. However, these studies have usually only investigated the influence of processing speed on a limited number of cognitive domains, and have mainly focused on only one test measure of processing speed, the Digit Symbol Coding Task from the Wechsler intelligence scales (Wechsler, 1997). This study extends the *processing speed hypothesis* (Rodríguez-Sánchez et al., 2007) by covering most cognitive domains, and including several reliable measures of processing speed and combining their effects on a broad range of cognitive functions. So while the coding task of the current study, the SDMT (Smith, 1982), did account for 68.6 percent of the between-group variance on the processing speed composite, and had an effect size of -1.44, the other processing speed measures accounted for similar results (variance ranging from 53.3 percent to 69.3 percent, and effects sizes ranging from -0.94 to -1.35), particularly the SCOLP test (Baddeley et al., 1992) that had near identical results to the SDMT test. This indicates that (some) tests that are putative measures of processing speed, can represent the influence of processing speed on cognition in schizophrenia nearly as well as coding tasks, and can be simple and useful tools in quantifying a form of cognitive impairment that is a central, reliable feature of schizophrenia. One caveat, however, is that tests such as the SDMT and the SCOLP are in fact very cognitively demanding and involve multiple component operations, and may therefore not be very specific

measures of processing speed (Chapman & Chapman, 1973; Miller et al., 1995; van Hoof et al., 1998; Jogems-Kosterman et al., 2001; Dickinson, Ramsey & Gold, 2007; Carter & Barch, 2007). It may therefore be the case that the robust effect sizes demonstrated by such tests (in particular coding tasks), which tends to be the highest in almost any comparison of (psychiatric, neurological or pseudo-neurological) patient groups and healthy controls (although the effect size in schizophrenia is significantly stronger), may be caused by the tests being simultaneously sensitive to a greater number of somewhat differentially impaired abilities.

From the results of this study, processing speed might be considered a "core" cognitive deficit in schizophrenia that determines function in cognitive domains. However, other studies (Laws, 1999; Aleman et al., 1999; Lee & Park, 2005; Achim & LePage, 2005; Reichenberg & Harvey, 2007; Ranganath et al., 2008; Barch & Smith, 2008) have found different "core" deficits that also might determine and predict function in cognitive domains. These "core" deficits are the same as the cognitive domains that have the highest effect sizes and account for the most between-group variance in this study, and include, in order of magnitude, reasoning and problem solving, sustained attention, verbal intelligence, reaction time, and working memory. The reason for this contradictory existence of several "core" deficits (of differential magnitude) might possibly be that nearly every neuropsychological test measure involve multiple component operations, and therefore do not separate cognitive deficits so ideally (MacDonald & Carter, 2002; Jonides & Nee, 2005; Silverstein, 2008). Another reason, however, might be that instead of a diverse array of multiple independent deficits, there may be a largely generalized cognitive deficit (Blanchard & Neale, 1994; Dickinson & Harvey, 2009) that can mimic selective deficits, depending on the complexity and focus of the neuropsychological tests (Chapman & Chapman, 1973; Miller et al., 1995). The cause could be abnormalities in connections among widespread brain regions that lead to an impairment in synchrony or the smooth coordination of mental processes (Andreasen, Paradiso & O'Leary, 1998). Impairment in this basic cognitive process could define the phenotype of schizophrenia and produce its diversity of symptoms. The best measure of this dysfunction may be impaired processing speed, based on the conception that especially coding and fluency tasks (that were all included as component measures of this study's processing speed domain) require the coordination of a series of elementary cognitive operations in distributed networks (Bokat & Goldberg, 2003; Dickinson, Ramsey & Gold, 2007). In accordance with this conception, a deficit in speed of processing in schizophrenia might then reflect reduced grey or white matter volumes in prefrontal and temporal

brain regions (Mitelman & Buchsbaum, 2007; Dwork et al., 2007; Witthaus et al., 2008). This is supported by a study (Sanfilipo et al., 2002) that found that performance by schizophrenia patients on digit symbol coding was generally associated with gray matter volumes in bilateral prefrontal cortex, bilateral hippocampus, and left superior temporal gyrus. Another study (Antonova et al, 2005) has also found abnormalities in white matter to be related to deficits in processing speed in schizophrenia (Antonova et al., 2005).

The clear result of this study sharpens the hypothesis of slowed information processing as a central feature of cognitive impairment in schizophrenia. Other studies (see meta-analysis by Dickinson, Ramsey & Gold, 2007) suggest that impaired processing speed might be a possible promising cognitive endophenotype for schizophrenia (Kéri & Janka, 2004). This contention is supported by studies that have found impaired processing speed (as measured primarily by the digit symbol coding task) to be stable (Hill et al., 2004; Verdoux et al., 1995), related to prognosis and functional outcome (Brekke et al., 1997; Schuepbach et al., 2002; Niendam et al., 2003), highly heritable (Swan & Carmelli, 2002), and present in relatives and in high-risk individuals (Byrne et al., 2003; Hawkins et al., 2004). The clinical implications may be that the focus on cognitive impairment in schizophrenia might need to be shifted from separable cognitive domains (Dickinson & Gold, 2008), and towards the construct of processing speed as a generalized measure of level of illness severity (Dickinson & Harvey, 2009), even despite issues of construct validity (Chapman & Chapman, 1973; Miller et al., 1995; van Hoof et al., 1998; Jogems-Kosterman et al., 2001). Further implications include the potential value of therapeutic intervention targeted towards improving impaired processing speed, since amelioration may transfer to other domains of cognitive functioning as well (Edwards et al., 2002; Carter & Barch, 2007).

A strength of the current study has been the inclusion of a patient sample matched one-to-one to matched controls on age, gender and parental socioeconomic status. The fact that the patient sample was a relatively large and relatively homogeneous group of first-episode, antipsychotic-naïve schizophrenia patients entailed that potentially confounding issues such as effects of chronicity or antipsychotic medication were not present (Davidson et al., 2009).

Limitations of the current study include the grouping of test measures into composite scores. Although great care was taken in the selection of these, it may be the case that some of the measures

may not have been sensitive or specific enough to assess a given cognitive function (Silverstein, 2008; Dickinson & Harvey, 2009). This is a very important consideration in relation to the selected measures for the composite score of processing speed that is the main focus of this study. However, a comparison shows that the selected measures of processing speed have near equal results (in terms of effect size and accounting for variance), and may therefore be considered reliable. Another issue of limitation is the construct validity of the individual processing speed measures, since these, particularly the digit symbol coding task, might be measuring a large number of different cognitive processes (van Hoof et al., 1998; Jogems-Kosterman et al., 2001), which may obscure their true cognitive, neural and genetic basis, as well as inflating effect size.

In conclusion, the data of the current study show that first-episode, antipsychotic-naïve patients with schizophrenia show deficits in all the major cognitive domains that were assessed, when compared to healthy controls. However, when speed of processing is taken into account, the entire variance of these deficits are explained, suggesting that impaired processing speed may be a key factor behind all the cognitive deficits that were assessed in the current study.

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Table 1: Demographics

Demographic data	Patients (N = 48)	Healthy controls (N = 48)	Significance levels
Age	Mean = 25.44 ± 5.3	Mean = 26.64 ± 5.4	df = 94 p = 0.278
Socioeconomic status [a,b]			
High Middle Low	N = 24 N = 20 N = 3	N = 32 N = 14 N = 2	χ^2 = 2.391 df = 2 p = 0.302

df = degrees of freedom; χ^2 = Pearson's Chi-Square

[a] Socioeconomic status was calculated from a combined rating of the highest parental education or occupation and household income.

[b] There was missing data of parental socioeconomic status from one patient.

Table 2: Psychopathology

PANSS ratings	Mean	SD
PANSS positive	19.54	4.40
PANSS negative	21.74	6.47
PANSS general	40.46	8.45
PANSS total	81.74	14.94

Table 3: Cognition

Domains	Tests	Z-scores	*df*	*p*	Covaried speed
Verbal intelligence	– Danish Adult Reading Test (DART) (Nelson & O'Connell, 1978) – WAIS Vocabulary (Wechsler, 1955) – WAIS Similarities (Wechsler, 1981)	-1.280	94	<0.001	speed: p<0.001 corr.model: p=0.045
Speed of processing	– Verbal fluency letter and category verbal fluency (Milner, 1975) – Symbol Digit Modalities Test (SDMT) (Smith, 1982) – Speed and Capacity of Language-Processing Test (SCOLP) (Baddeley et al., 1992) – Trail Making A (Reitan & Wolfson, 1993)	-1.685	82	<0.001	
Sustained attention	– CANTAB Rapid Visual Information Processing Test (RVP)	-1.403	92[a]	<0.001	speed. p=0.001 corr.model: p=0.201
Working memory	– CANTAB Spatial Span (SSP) – CANTAB Spatial Working Memory (SWM) – WAIS Digit span (Wechsler, 1955)	-1.058	92	<0.001	speed. p<0.001 corr.model: p=0.404
Verbal learning and memory	– Buschke Selective Reminding Test (BSRT) (Buschke, 1973)	-0.794	62[a,b]	0.027	speed. p=0.007 corr.model. p=0.870
Visual learning and memory	– Rey-Osterrieth Complex Figure Test (RCFT) (Meyers & Meyers, 1995)	-0.629	94	0.005	speed. p=0.003 corr.model. p=0.879
Reasoning and problem solving	– Wisconsin Card Sorting Test (WCST) (Milner, 1963) – CANTAB Stockings of Cambridge (SOC) – CANTAB Intra-Extra Dimensional set shifting task (IED)	-1.510	92[a]	<0.001	speed. p=0.002 corr.model. p=0.108
Reaction time	– CANTAB Reaction and Movement Time Test (RTI)	-1.178	92	<0.001	speed. p=0.001 corr.model. p=0.185
Speed of executive processing	– CANTAB Stockings of Cambridge (SOC) – Figural fluency (Regard et al., 1982) – Trail Making B-A (Reitan & Wolfson, 1993)	-0.600	92[a]	0.021	speed. p<0.001 corr.model. p=0.399
Global cognition	– Summary score derived from all composite measures	-2.050	94	<0.001	speed. p<0.001 corr.model. p=0.100

[a] Levene's Test for Equality of Variances was used to determine degrees of freedom and p-values.
[b] Reduced N. BSRT: $N = 32$.

Cognitive Effects of Six Months Treatment with Quetiapine in Antipsychotic-Naïve First-Episode Schizophrenia

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Abstract

Most studies on the effects of antipsychotics on cognition in schizophrenia have included previously medicated chronic patients, and have not examined the possible impact of retest effects on improved cognitive scores. Effects of quetiapine on cognition was assessed in a group of first-episode antipsychotic-naïve patients with schizophrenia (N = 24). A comprehensive battery of neuropsychological tests was administered at baseline and after 6 months of treatment with quetiapine. In order to examine retest effects, a matched healthy control group (N = 24) was also tested at baseline and after 6 months. Only few differential changes were observed between patients and healthy controls. Of 8 cognitive domains examined, only significant changes in reasoning and problem solving suggested possible ameliorating effects of quetiapine. Patients also improved on speed of processing; however, this was parallel to the retest effects found in healthy controls. When covaried for differences at baseline, patients showed smaller improvements in speed of processing than the retest effects found in controls, as well as a lack of retest effects on sustained attention and working memory that was found in healthy controls.

This is the first longitudinal study to examine the effects of quetiapine on cognitive functions in antipsychotic-naïve first-episode schizophrenic patients, where retest effects were examined in healthy controls. The main result of the study is that there was very little evidence of efficacy of quetiapine on cognition. The study also indicated a lack of normal retest effects in patients compared to controls.

Introduction

Cognitive impairment is a core feature in the pathology of schizophrenia. Numerous studies report impairments in multiple domains of cognitive functioning, including reasoning and problem solving, memory, sustained attention, and processing speed (e.g. Green & Nuechterlein, 1999; Bilder et al., 2000; Green & Braff, 2001). These impairments have been shown to have an important impact on social functioning, occupational functioning and the capacity for independent living in the community (Green, 1996; Meltzer et al., 1996; Velligan & Miller, 1999). Cognitive enhancement is therefore important for improving functional outcome.

Over the past few decades, a great number of studies have assessed the influence of antipsychotic medication on cognitive performance. Reviews of early studies suggested that second generation antipsychotics may have more beneficial effects on cognition than do first generation compounds, while first generation antipsychotics were found to be more beneficial than placebo alone (Keefe et al., 1999; Blyler & Gold, 2000; Harvey & Keefe, 2001; Mishara and Goldberg, 2004). However, certain confounding factors such as incomparable antipsychotic dosages and adjunctive anticholinergic medication were present in several of the studies in these reviews (Carpenter & Gold, 2002). Recent large studies have found significant cognitive improvement with antipsychotics, but without evidence of differential beneficial effects of second generation over first generation compounds (Keefe et al., 2007a; Wittorf et al., 2008; Davidson et al., 2009). There is currently no evidence of a significant advantage for any second generation antipsychotic compound over another in terms of effects on cognitive function. The specific mechanisms of action by which second generation antipsychotic compounds may provide cognitive benefits, still remain largely unclear (Weickert & Goldberg, 2005). Overall, it has become apparent that the cognition enhancing effects of antipsychotic medications at best are modest (Keefe et al., 2007b).

Several methodological considerations limit the conclusions that can be drawn regarding the effects of antipsychotics on cognition in schizophrenia (Salimi, Jarskog & Lieberman, 2009; Hill et al., 2010). It is unclear whether the modest effects that have generally been found are in fact due to cognitive improvement, or whether they reflect e.g. carry-over effects (both positive and negative) due to prior medication, practice effects due to repeated testing, or placebo effects (Fagerlund et al, 2004; Mishara & Goldberg, 2004; Goldberg et al., 2007;

Keefe et al., 2008; Szöke et al., 2008). Possible confounds such as the impact of adjunctive medication such as anticholinergic medication, benzodiazepines, antidepressant medication, and concomitant drug abuse have also often not been controlled for, which may have impacted the results (Woodward et al., 2005; Keefe et al., 2007a; Davidson et al., 2009).

Most of the abovementioned studies have been conducted with mainly chronic, previously medicated patients. It is possible that several factors associated with chronicity of the illness (e.g. previous exposure to other antipsychotic compounds, the impact of illness duration itself, ageing) may limit the possible beneficial effects of antipsychotics on cognition (Bilder et al., 2000). The potential cognition-enhancing effect of antipsychotics may be more evident when it is used among younger, antipsychotic-naïve patients with first-episode schizophrenia (Salimi, Jarskog & Lieberman, 2009). First-episode patients have been shown to be comparatively more treatment responsive in terms of effects on psychopathology than chronic patients (McEvoy et al., 1991). Therefore, they may also be more responsive to cognitive amelioration from antipsychotics (Davidson et al., 2009; Voruganti et al., 2002).

There are some research findings indicating the potential for cognitive enhancement from treatment with quetiapine. This compound has a receptor occupancy profile with relatively higher affinity for the serotonin $5HT_{2A}$ receptor than for the dopamine D_2 receptor and has been found to have no greater extrapyramidal symptoms than placebo across the full dosage range, suggesting minimal requirement for anticholinergic prescription (Seeman & Tallerico, 1998; Kapur et al., 2000; Riedel et al., 2007c). Studies have reported specific effects of quetiapine on sustained attention, reasoning and problem solving, verbal memory, verbal reasoning, verbal fluency, immediate recall, motor, and visuo-motor skills (e.g. Purdon et al., 2001; Zhong et al., 2006; Keefe et al., 2007a, 2007b; Voruganti et al., 2007). However, only few studies examining the effects of quetiapine on cognition in a longitudinal design have included first-episode schizophrenia patients that have not received prior antipsychotic medication (Good et al., 2002; Keefe et al., 2007b; Hill et al., 2008; Perkins et al., 2008; Davidson et al., 2009). Few previous studies on effects of antipsychotics on cognition (e.g. Fagerlund et al., 2004; Goldberg et al., 2007; Crespo-Facorro et al., 2009) have included and retested a healthy control group matched to patients in order to establish the expected level of practice effects. Only one previous study examining the effects of quetiapine (Sax et al., 1998) included and retested a comparison sample of healthy subjects, but did not include first-episode schizophrenia patients.

The purpose of the present study was to examine the effects on cognition of six months of quetiapine treatment in antipsychotic-naïve patients with schizophrenia. To reliably examine the effects of quetiapine on cognition without confounding effects of long illness duration and previous antipsychotic medication, a relatively homogenous group of only antipsychotic-naïve first-episode schizophrenic patients was included. A healthy control group was included and re-examined after 6 months in order to control for retest effects.

Methods

Subjects

Patients were recruited after first-time referral to participating psychiatric centres in the capital region of Copenhagen from December 2003 to December 2007. The inclusion criteria were: Antipsychotic-naïve patients between the ages 18 to 45, fulfilling both the International Classification of Diseases (ICD-10) and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for schizophrenia or schizoaffective disorder. The exclusion criteria were: Patients who were not voluntarily hospitalised, patients who were deemed in acute need of medication, patients with somatic or neurological illnesses, and patients with known mental retardation.

A total of 46 patients were recruited and tested at baseline. Of these, 24 completed the study (16 male / 8 female). The reasons for drop-out were: Clinically inadequate effect (N = 3); intolerable side-effects (N = 4); pregnancy (N = 1); unwillingness to undergo treatment (N = 8) or repeated testing (N = 6). Comparisons between the groups of completers vs. dropouts on demographic data and psychopathology measures showed that patients who dropped out demonstrated significantly [$t(42)=2.111$, $p=0.041$] fewer positive symptom scores (mean = 18.20) at baseline than did completers (mean = 20.92). The mean duration of untreated illness, which was defined as the time from the first unspecific symptoms related to psychosis until the time of neuropsychological testing (Keshavan et al., 1998), was 207 weeks for the patients who completed the study (range 4 - 780 weeks, median = 106 weeks, SD = 252), and 165 weeks for the patients who dropped out (range 2 - 676 weeks, median = 78 weeks, SD = 201), a difference that was not significant [$t(38)=0.573$, $p=0.570$].

The ICD-10 diagnostic distribution of the 24 participating schizophrenic patients was: Paranoid type (N = 19), Undifferentiated (N = 4), Schizoaffective disorder (N = 1). The patients were administered quetiapine at a mean dose of 519.6 mg/day (S.D. = 297.4). Four patients had prior (N = 2) or present (N = 2) use of antidepressant medication (in all cases selective serotonin reuptake inhibitors). Concomitant treatment with benzodiazepines was allowed and was prescribed on an as needed basis for 12 patients at baseline, and 2 patients at follow-up. However, benzodiazepines were not allowed on the day of testing. One patient fulfilled ICD-10 criteria for multiple drug abuse and the abuse of other psychoactive substances, 3 patients for the abuse of alcohol, 2 patients for the abuse of cannabinoids, and 1 patient for the abuse of both alcohol and cannabinoids. None of the patients were treated with anticholinergic medication at any time during the study.

Twenty-four healthy controls matched 1:1 with patients on age, gender, and parental socioeconomic status were recruited from the community by advertisements (see Table 1). Exclusion criteria for controls were the presence of a psychiatric diagnosis, somatic or neurological illness, psychiatric diagnoses in first-degree relatives, a history of drug- or alcohol abuse, and the presence of mental retardation or any known learning disabilities. In order to assess retest effects, the matched healthy controls were administered the same cognitive tests as patients at inclusion and after 6 months.

The study was approved by the Ethics Committees of Copenhagen and Frederiksberg ([KF]11-061/03). The subjects participated after receiving a full explanation of the study and providing written informed consent according to the Declaration of Helsinki II.

Psychopathology

The computerized version of the structured clinical interview SCAN 2.1 (Schedules for Clinical Assessment in Neuropsychiatry, 1994) was used to classify psychiatric diagnoses according to both ICD-10 and DSM-IV criteria. The severity of symptoms in patients was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay, 1991). The interrater reliability, estimated by intraclass correlation coefficient for the PANSS total score, was 0.92.

Cognition

A comprehensive battery of tests was administered to assess different domains of cognitive deficits in schizophrenia. The included battery of tests assessed estimated premorbid

intelligence (only performed at baseline) and the cognitive domains of speed of processing, sustained attention, working memory, executive reasoning and problem solving, verbal learning and memory, visual learning and memory, reaction time, and speed of executive processing (see Table 3). The test battery was administered in a fixed order by the same psychologist (RA) at inclusion and retest, and took approximately 2.5 hours to complete. The mean test-retest interval was 6.6 months (SD = 0.7) for patients and 6.9 months (SD = 1.4) for controls, a difference that was not significant [t(46)=0.944, p=0.350]. The test battery comprised paper-and-pencil tests as well as tests from the computerised Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian & Owen, 1992; Levaux et al., 2007). Some of the neuropsychological tests have been described in detail by Fagerlund el al. (2004), whose battery of tests was precursory for the selected tests of the present study.

Statistical Analysis

Data were analysed using Statistical Package for the Social Sciences (SPSS), version 11.0. All analyses used two-tailed levels of significance. If data of a subject was missing, then the corresponding data of their match was also excluded from analyses. Results from tasks that did not fit a normal distribution were logarithmically transformed to reduce skew. Parametric statistics were used for all analyses.

Cognitive domains were examined using composite scores, calculated by grouping selected tests, based on which cognitive domain they theoretically assessed, although some domains were examined using a single test. Composites at both baseline and follow-up were created by first calculating z-scores for each individual test score based on the distribution of healthy controls at baseline. Then z-scores for each domain were averaged and restandardised, again based on the composite average and standard deviation of the controls at baseline. If subjects had only one or two incomplete results within a domain, they were still included in the domain, based on their remaining results within that domain. If a subject missed the majority of tests within a domain, they were excluded from that domain. This was the case for 9 patients in the verbal learning and memory domain and 1 patient in all the domains that included a majority of CANTAB tests (see Table 3).

Changes over time were examined using repeated measures ANOVA, with between factor "group" (patients or controls) and within factor "time" (baseline or follow-up). Paired t-tests were used to measure within-group changes over time for both patient and control groups in

post-hoc analyses, only on domains where time or group X time interactions were significant in the repeated measures ANOVA. Linear regression analyses were used to model predictors of cognitive change using the baseline level of cognitive function and psychopathology changes on PANSS (positive, negative, general, and total scores) as separate predictors. Due to the significant impact of the baseline level of deficits in cognitive change, between-group analyses (patients vs. controls) was also examined in post-hoc analyses, covaried for the baseline level of cognitive performance. Secondary analyses examined which of the sub-measures within cognitive domains contributed to cognitive change on that domain, only in domains where time or group X time interactions were significant in repeated measures ANOVA. These analyses were purely exploratory in nature.

Results

Psychopathology

Patients showed a significant reduction in both the positive symptom subscale score as well as the total score of the PANSS scale from baseline to follow-up. In addition, a trend was found for a reduced general symptom score on the PANSS. The negative subscale score of the PANSS at follow-up did not differ significantly from the score at baseline (see Table 2). Linear regression analyses found psychopathology to be a poor predictor of cognitive change, with the only tendentially significant model showing PANSS general symptoms to be a weak predictor of cognitive change ($r^2 = 0.149$; $p= 0.078$).

Cognitive deficits at baseline

Compared to the healthy control group, the patients were significantly impaired in 5 out of the 8 cognitive domains, and at trend level in the remaining 3 domains. The severity of deficits ranged from 0.7-2.1 standard deviations below the healthy control mean (see Table 3).

Between-group differences

The results of the repeated measures ANOVA showed a significant time X group interaction effect for two domains: reasoning and problem solving [$F(1,44)=6.795$, $p=0.012$] and speed of executive processing [$F(1,44)=4.101$, $p=0.012$]. Post-hoc analyses revealed that patients improved significantly more than healthy controls from baseline to follow-up on the reasoning and problem solving domain, while there were no significant changes in either

patients or controls on the speed of executive functions domain (the significant time X group interaction reflecting a non-significant deterioration in controls). It should be noted that the significant time X group interaction effect on reasoning and problem solving may likely be the result of a near-ceiling effect in the healthy control group. However, correcting these results for baseline scores, the abovementioned interaction effects were no longer significant, although three new tendencies for a time X group interaction effect appeared, i.e. in speed of processing [F(1,45)=3.073, p=0.086], sustained attention [F(1,43)=3.203, p=0.081], and working memory [F(1,43)=3.858, p=0.056], indicating that patients improved (at trend level) less than healthy controls from baseline to follow-up in these domains (see Table 4).

Within-group differences

The patients showed significant within-group changes on speed of processing [t(23)=2.320, p=0.030] and reasoning and problem solving [t(22)=3.028, p=0.006], indicating a significantly higher score at follow-up than at baseline. The changes in speed of processing could be attributed to an improved score on the SCOLP [t(23)=4.481, p=0.0002] and the Symbol Digit Modalities Test [t(23)=2.429, p=0.023] at follow-up, while the changes in reasoning and problem solving can be attributed to fewer errors on the IED task (i.e. total errors [t(22)=2.493, p=0.021] and EDS errors [t(22)=3.497, p=0.002]) at follow-up than at baseline.

The healthy control group showed significant improvements at follow-up on 3 of 8 composite scores: Sustained attention [t(22)=2.616, p=0.016], speed of processing [t(23)=2.879, p=0.008], and working memory [t(22)=2.749, p=0.012]. The changes in sustained attention can be attributed to the RVP signal detection score A' [t(22)=2.757, p=0.012], the changes in speed of processing can be attributed to both Trail-Making A [t(23)=2.484, p=0.021] and SCOLP [t(23)=3.355, p=0.003], while the changes in working memory can be attributed to the three SWM test measures of strategy [t(22)=3.027, p=0.006], total errors [t(22)=1.987, p=0.060] and between errors [t(22)=2.025, p=0.055].

Discussion

This is the first longitudinal study to examine the effects of quetiapine on cognitive functions in antipsychotic-naïve first-episode schizophrenic patients, in which a matched healthy control group was also included and retested to control for retest effects.

The main result of the study is that there was very little evidence of efficacy of quetiapine on cognition, where improved scores in patients from baseline to follow-up were found on only 2 of 8 cognitive domains (i.e. reasoning and problem solving, and speed of processing). It is possible that the improvement found in reasoning and problem solving in patients represents beneficial effects of quetiapine, as only patients, and not controls, improved on this domain. The improvement in this domain could be attributed to fewer errors on the IED set shifting task, primarily at the extradimensional (ED) shift stage, where subjects need to shift attention from a previously reinforced dimension to a new dimension. It is, however, likely that the differential change in this domain may have been caused by a near-ceiling effect in the component IED measures of the healthy control group at both baseline and follow-up, thus possibly inflating the relative significance of the improved scores in the patient group (Lowe & Rabbitt, 1998). Nevertheless, the results also indicate that the patients achieved nearly normal scores on the IED set shifting task at follow-up, which suggests that the performance of patients at follow-up either improved because of quetiapine treatment, or improved independently of quetiapine treatment, or that quetiapine did not attenuate a normal retest effect on these reasoning and problem solving component measures (Weickert et al., 2002).

The patients also showed improved results at follow-up on the speed of processing domain, although not significantly different from the retest effects observed in the healthy control group. The component measures that improved within this domain in patients were the SCOLP and the symbol digit modalities test. This is in line with the changes found in the Comparison of Atypicals in First Episode of Psychosis (CAFÉ) study, where specific beneficial effects of quetiapine were found on processing speed measures of verbal fluency and the WAIS-R digit symbol test (Keefe et al., 2007b). However, the CAFÈ study also found modest effects of quetiapine on other aspects of cognition similar to the effects of olanzapine and risperidone, which were not found in the current study.

Because the performance of patients differed from controls at baseline, changes over time were also examined covaried for these differences at baseline. These analyses revealed that patients showed less retest effects than did controls on the speed of processing, sustained attention, and working memory domains. In certain instances (e.g. regarding working memory) the performance gains of the healthy control group markedly exceeded those of the patient group. This has several important implications. First, there is clear evidence that retest

effects (likely practice effects) are present on some of these measures, which are important to consider in longitudinal effect studies. Second, long test intervals such as 6 months in the present study may attenuate, but do not eliminate practice effects. Third, the magnitude of retest effects appears to differ between cognitive domains. It is unclear whether the insufficient retest effect in patients is caused by detrimental effects of quetiapine, suppressing a practice effect that would otherwise have been present (Harvey & Keefe, 2001; Woodward et al., 2005, 2007), or is caused by the inherent neuropathology involved in the cognitive deficits of schizophrenia that may also limit practice effects on these measures (Gold et al., 2000; Weickert et al., 2002). The current results are in line with results from a previous study from our group (Fagerlund et al., 2004), where antipsychotic-naïve, first-episode schizophrenia patients were randomised to treatment with risperidone and zuclopenthixol (a first-generation compound), and a healthy control group was retested to examine practice effects. Results showed few changes with medication, little distinction between effects of the compounds and further that effects of medication on cognition in patients did not exceed practice effects in the healthy group. The impact of practice effects was later demonstrated in a large study by Goldberg et al. (2007), who reported that cognitive test improvements in a sample of first-episode schizophrenia patients treated with olanzapine or risperidone were consistent in magnitude with the retest effects in a matched sample of healthy subjects on most measures. Similarly, in a large study of adjunctive donepezil medication, Keefe et al. (2008) found significant practice effects in the placebo group. Since a placebo-treated patient group was not included, it is not possible in the current study to distinguish whether retest effects on speed of processing were primarily caused by practice effects (Goldberg et al., 2007; ; Szöke et al., 2008; Hill et al., 2010), or patient motivation and expectancy of improvements (Velligan, Kern & Gold, 2006).

The significant effect of quetiapine on positive symptoms was in line with previous studies, but the lack of an effect on negative symptoms is in contrast to other studies that have found quetiapine to have a substantial direct effect on improving negative symptoms of schizophrenia (Good et al., 2002; Nasrallah & Tandon, 2002; Tandon, 2004; Riedel et al., 2007c). Psychopathology scores at baseline were a poor predictor of cognitive change, with only PANSS general symptoms tendentially indicating cognitive change. There were no significant correlations between change in psychopathology and change in cognition.

The treatment interval in the current study was 6 months, which is the same as the interval used in the European First Episode Schizophrenia Trial (EUFEST) (Davidson et al., 2009). Although it is possible that more beneficial effects of quetiapine on cognition may have been present if patients had been re-examined after a longer time interval than 6 months, this is unlikely based on previous studies. For example, the CAFÉ study suggested that possible beneficial effects of antipsychotics appear in the first months after treatment initiation, and that further benefits over longer time periods may be very small (Keefe et al., 2007b).

It is possible that the dose administered in this study was either insufficient, or too high to attain cognition enhancing effects (Woodward et al., 2007; Hill et al., 2010), however, dosages were comparable to those used in previous studies of first-episode patients, e.g. the CAFÈ study (Keefe et al., 2007b), and the EUFEST study (Davidson et al., 2009), and even in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which included only chronic patients (Keefe et al., 2007a). We do not consider the largely negative results of the current study to be specifically attributable to treatment with quetiapine, compared to other antipsychotic compounds (although this question cannot be answered by the current study; Hill et al., 2010). However, two large studies that compared the cognition enhancing properties of second generation antipsychotics - including quetiapine - and first generation antipsychotics in either chronically ill patients (Keefe et al., 2007a) or patients with first-episode schizophrenia (Davidson et al., 2009) found no overall difference in degree of improvement between compounds.

One of the strengths of the current study is the inclusion of only antipsychotic-naïve, first-episode schizophrenia patients (Salimi, Jarskog & Lieberman, 2009). In this sense, the patient group was homogenous, and avoided several possible confounding factors associated with illness chronicity, age, and prior exposure to antipsychotic medication. This sample appears to be representative of first-episode schizophrenia patients, in being similar to other first-episode studies in terms of severity of psychopathology scores, and profile of cognitive deficits (Fioravanti et al., 2005; Kravariti et al., 2009; Mesholam-Gately et al., 2009). The inclusion and retest of a healthy control group enabled the determination of retest effects on the cognitive tasks, and testing of whether cognitive changes in the patients were present beyond the expected retest effects found in healthy controls. A further strength of the study (most likely attributable to quetiapine's receptor profile) was that anticholinergic medication,

(which has known deleterious effects on cognition) was not used. While benzodiazepines were allowed on a per-need basis, they were not allowed on days of assessment.

A limitation to the current study is the inclusion of patients with adjunctive antidepressants, anxiolytic medication and substance abuse, which may have detrimental effects on already compromised cognitive functioning and on the potential cognitive benefits of quetiapine treatment. The sample was heterogeneous in terms of duration of untreated illness, something which is difficult to avoid in first-episode samples. However, illness duration did not impact the current results. A further limitation is that the patient and control groups differed significantly on pre-morbid verbal intelligence. It was not possible in the current study to distinguish practice effects from placebo effects, since inclusion of a placebo-treated group was not viable for obvious ethical reasons. The inclusion of a comparator compound in a double-blind design would have strengthened the conclusions that can be drawn from the current study, for example due to known limitations to open-label designs (Heres et al., 2006). However, we do not expect issues such as investigator biases to have impacted the results in either direction. The inclusion of only antipsychotic-naïve, first episode schizophrenia patients makes it difficult to attain sufficiently large samples to achieve adequate power, especially when detecting change in a longitudinal design, where drop-out is an issue. The attrition rate of almost 48 percent from baseline to the 6 month follow-up in the current study was rather large. Antipsychotic-naïve first-episode patients that are able to stay on stable medication for an extended period of time and undergo many different examinations may represent a biased selection of high functioning patients (Lieberman et al., 2005). The patients that remained in the study did not differ from the patients that dropped out on demographic measures of age and parental socioeconomic status, however, they did have significantly more positive symptoms than the patients that dropped out of the study. Therefore, the patients that remained in the study were not less severely ill than the ones that dropped out of the study, and we consider the patients that completed the study to be representative of the entire sample of patients. Whether the current results can be generalized to patients at other stages of the illness cannot be answered by the current study.

In conclusion, the present results did not find evidence of cognition enhancing effects of quetiapine in antipsychotic-naïve, first-episode schizophrenia patients. While quetiapine treatment may have facilitated improvement on errors on the IED set shifting task, the large majority of cognitive measures did not improve with medication, and some normal retest

effects were not found in patients after medication. The results clearly suggest that treatment strategies other than antipsychotic medication are warranted to improve the cognitive deficits in schizophrenia.

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Table 1
Demographics

Demographic data	Patients (N = 24)	Healthy controls (N = 24)	Significance levels
Age	Mean = 25.7 ± 5.5	Mean = 27.1 ± 6.0	df = 46 p = 0.40
Socioeconomic status[a]			
High Middle Low	N = 11 N = 11 N = 2	N = 16 N = 7 N = 1	χ^2 = 2.15 df = 46 p = 0.16

df = degrees of freedom; χ^2 = Pearson's Chi-Square

[a] Socioeconomic status was calculated from a combined rating of the highest parental education or occupation and household income.

Table 2
Changes in psychopathology from baseline (antipsychotic-naïve state) to 6 months of treatment with quetiapine

PANSS ratings	Baseline		After 6 months treatment		Significance levels	Percentage changes
	Mean	SD	Mean	SD		
PANSS positive	20.68	4.38	16.18	5.77	0.00007	27.8 %
PANSS negative	22.64	6.62	20.18	5.54	0.142	12.2 %
PANSS general	41.05	8.73	37.32	10.11	0.090	10.0 %
PANSS total	84.36	15.54	73.68	19.86	0.013	14.5 %

Table 3
Z-scores for patients at baseline, compared to controls

Cognitive domains	Tests	Z-scores	*df*	*p*
Premorbid verbal IQ	– Danish Adult Reading Test (DART) (Nelson, 1982)	-0.96	46	0.004
Speed of processing	– Verbal fluency letter and category verbal fluency (Milner, 1975) – Symbol Digit Modalities Test (SDMT) (Smith, 1982) – Speed and Capacity of Language-Processing Test (SCOLP) (Baddeley et al., 1992) – Trail Making A (Reitan & Wolfson, 1993)	-1.57	46	0.00001
Sustained attention	– CANTAB Rapid Visual Information Processing Test (RVP)	-0.82	35[a]	0.06
Working memory	– CANTAB Spatial Span (SSP) – CANTAB Spatial Working Memory (SWM) – WAIS Digit span (Wechsler, 1955)	-0.71	44	0.06
Verbal learning and memory	– Buschke Selective Reminding Test (BSRT) (Buschke, 1973)	-1.11	21[a,b]	0.07
Visual learning and memory	– Rey-Osterrieth Complex Figure Test (RCFT) (Meyers & Meyers, 1995)	-0.95	46	0.01
Reasoning and problem solving	– Wisconsin Card Sorting Test (WCST) (Milner, 1963) – CANTAB Stockings of Cambridge (SOC) – CANTAB Intra-Extra Dimensional set shifting task (IED)	-2.06	28[a]	0.001
Reaction time	– CANTAB Reaction and Movement Time Test (RTI)	-1.44	33	0.003
Speed of executive processing	– CANTAB Stockings of Cambridge (SOC) – Figural fluency (Regard et al., 1982) – Trail Making B-A (Reitan & Wolfson, 1993)	-1.08	31[a]	0.03

[a] Levene's Test for Equality of Variances was used to determine degrees of freedom and p-values.
[b] Reduced N. BSRT: $N = 15$.

Table 4
Effects of medication and practice: Difference scores from baseline to 6 months

Composite domains	**Time**	**Time X group**	**Time X group, covaried baseline**	**Within-group changes patients**		**Within-group changes controls**	
	p-value	*p-value*	*p-value*	*p-value*	*z-score change*	*p-value*	*z-score change*
Speed of processing	0.001	0.992	0.086	0.030	0.375	0.008	0.377
Sustained attention	0.013	0.800	0.081	0.179	0.374	0.016	0.456
Working memory	0.016	0.140	0.056	0.472	0.123	0.012	0.493
Verbal learning	0.897	0.990	0.167	0.946	0.030	0.894	0.036
Visual learning	0.514	0.268	0.963	0.299	0.311	0.675	-0.081
Reasoning and problem solving	0.133	0.012	0.577	0.006	1.201	0.469	-0.313
Reaction time	0.181	0.598	0.135	0.250	0.311	0.499	0.136
Speed of executive processing	0.817	0.049	0.567	0.239	0.433	0.107	-0.545

Description of the Cognitive Test Battery

A comprehensive battery of tests was administered to assess the major dimensions of cognitive impairments in schizophrenia. The included battery of tests assessed intelligence and the cognitive domains of speed of processing, sustained attention, working memory, executive functions, verbal learning and memory, visual learning and memory, reaction time, and speed of executive processing. The test battery was administered in a fixed order, and took approximately two and a half hours to complete.

The test battery comprised paper-and-pencil tests as well as computerised tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) that consists of a standardized series of interrelated non-verbal tests of memory, attention, and executive function (Sahakian & Owen, 1992). Over the last decade CANTAB has become widely utilized in cognitive studies of schizophrenia and effects of pharmacological treatment (Fagerlund et al., 2004; Levaux et al., 2007).

Verbal intelligence

To estimate premorbid intelligence the Danish Adult Reading Test (*DART*) was used (Dalsgaard, 1998). This is the Danish version of the New/National Adult Reading Test (NART) that is a widely accepted method for estimating premorbid intelligence (Nelson, 1982). The DART comprises a list of 50 words with irregular pronunciation, and subjects are asked to read aloud words in an order of increasing difficulty.

An abbreviated 20-word version of the *Vocabulary* subtest from the Wechsler Adult Intelligence Scale (WAIS) was used to indicate full-scale IQ as well as premorbid IQ (Wechsler, 1955; Hess, 1974). The test consists of a list of words that subjects are required to try to define. The definitions are scored according to accuracy, and abstract- or concreteness of answers.

Similarities from WAIS is a concept formation test (Wechsler, 1981). Each of the thirteen items consists of two words for which you have to find a common concept. The usual scoring procedure is followed: The score 2 is given for a good abstraction, 1 is given for a more concrete solution, and 0 for an irrelevant solution (Newcombe, 1969; McFie, 1975).

Speed of processing

Verbal phonological fluency was assessed by subjects generating as many words as possible in 60 seconds beginning with the letter "S". *Verbal semantic fluency* was assessed by subjects generating words from the category "animals" in 60 seconds (Milner, 1975).

The *Symbol Digit Modalities Test* (SDMT) involves a simple substitution task. Subjects were presented rows of empty boxes labelled by a symbol. They were required to fill out these boxes one by one, as quickly as they could with a corresponding digit, according to a digit/symbol code that was permanently displayed. The total number of boxes accurately filled in within 90 seconds was used as a measure for attention and mental speed (Smith, 1982).

The *Speed and Capacity of Language-Processing Test* (SCOLP) measures the speed of comprehension and rate of information processing. The subject verifies as many sentences as possible in two minutes. The sentences are all obviously true or are false, being based on a mismatch of subject and predicate from true sentences. Such combinations can be rather bizarre, hence the test is sometimes referred to as 'Silly Sentences'. The outcome measure is the number of correct verifications (Baddeley, Emslie, Nimmo-Smith & Edmunds, 1992).

The *Trail Making test A* assesses visuospatial scanning and psychomotor speed by subjects combining circles with ascending numbers (1,2,3, etc.). The outcome measure is the time to complete the test (Reitan & Wolfson, 1993; Buchanan et al., 1994; Lezak, 1995).

Sustained attention

The *Rapid Visual Information Processing Test* (RVP) from CANTAB is a continuous performance test that assesses selective attention and vigilance with a small working memory component. The test requires subjects to detect consecutive odd or even sequences of digits (3-5-7 and 3-5-7 + 2-4-6) and to register responses using a press-pad. Target sequences occur at the rate of 16 every 2 minutes. For scoring purposes CANTAB records the number of correct hits, misses, false alarms, defined as occasions upon which the subject incorrectly identified a target sequence, and signal detection sensitivity, a measure of the ability to distinguish signals (e.g. 3-5-7 in sequence) from noise (all other numbers). Finally, CANTAB also records and reports the mean hit response latency.

Working memory

The *CANTAB Spatial Working Memory* (SWM) is a test of spatial working memory and strategy performance. The test begins with a number of coloured squares (boxes) being shown on the screen.

The aim of this test is that, by process of elimination, the subject should find one blue 'token' in each of a number of boxes and use them to fill up an empty column on the right hand side of the screen. The number of boxes is gradually increased, until it is necessary to search a total of eight boxes. The colour and position of the boxes used are changed from trial to trial to discourage the use of stereotyped search strategies.

The *CANTAB Spatial Span* (SSP) tests the capacity for spatial memory span. In the test a pattern of white squares is shown on the screen. Some of the squares change in colour, one by one, in a variable sequence. At the end of the presentation of each sequence a tone indicates that the subject should touch each of the boxes in the same order as they were originally coloured by the computer. The number of boxes in the sequence is increased from a level of 2 at the start of the test to a final level of 9. There are three sequences at each level. The sequence and colour used change from sequence to sequence to minimise interference.

The *WAIS Digit span test* examines auditory/vocal short-term memory and attention, and requires the repetition of number strings forwards and backwards (Wechsler, 1955). Testing starts with sequences of three digits and discontinues when the subject twice fails all strings presented of a particular length. This measures forward span; backward span is measured by the same method except that the subject is asked to repeat the string in reverse order and starts with sequences of two digits.

Verbal learning and memory

The differentiation of retention, storage, and retrieval of memory is assessed with the *Buschkes selective reminding test* (Buschke, 1973; Buschke & Fuld, 1974). The procedure for the test involves subjects being read a list of ten unrelated words for immediate recall. On all subsequent trials, subjects are only told those words they omitted on the previous trial. The procedure continues until the subject recalls all words on two successive trials or to the tenth trial. After 10 minutes the subjects are given a delayed recall trial as well as a cueing procedure by means of multiple choice.

Visual learning and memory

The *Rey-Osterrieth complex figure test* is a drawing and visual memory test that examines the ability to construct a complex figure and remember it for later recall. It measures a variety of cognitive processes, including planning, organizational skills, and problem-solving strategies, as well as perceptual, motor, and memory functions. No time limit was given and the drawings were

scored for both accuracy and correct placement of each of these elements irrespective of the order of drawing (Meyers & Meyers, 1995).

Reasoning and problem solving

The standard 128 card version of the *Wisconsin Card Sorting Test* (WCST) was administered (Milner, 1963). The WCST assesses the ability to form and maintain hypotheses by sorting cards according to the categories colour, shape, or number, and assesses attentional set shifting ability by requiring subjects to utilize feedback to shift hypotheses when relevant (i.e. when the correct sorting category occasionally changes). Outcome measures are number of categories achieved, total number of cards used, total number of errors, perseverative errors, perseverative-Nelson, unique errors, and other errors.

The *CANTAB Stockings of Cambridge* (SOC) presents two arrays of coloured balls, where subjects are required to move the balls at the bottom of the screen to match the array presented at the top of the screen. The SOC assesses planning ability, strategy formation and execution similar to the Tower of London test. Outcome measures are number of problems solved with minimum number of moves (i.e. most efficiently) and mean number of moves used to solve problems (averaged from 2, 3, 4, and 5 move-problems).

The *CANTAB Intra-Extra Dimensional set shifting task* (IED) consists of 9 different stages of increasing difficulty that test the ability to utilize feedback to discriminate between figures, as well as to form, maintain, and shift hypotheses within and between categories. The IED assesses attentional set shifting similarly to the WCST. The outcome measures are number of stages completed, total errors (adjusted for stages not completed), errors made at the extra-dimensional set shifting stage, number of trials (adjusted for stages not completed).

Reaction time

The *CANTAB Reaction and Movement Time Test* presents yellow dots on a touch-screen, to which subjects respond by releasing a press pad and touching the dot on the screen as fast as possible. The reaction time is the time taken to release the press pad in response to the stimulus, while the movement time is the time taken to touch the stimulus on the screen after the press pad has been released. Simple Reaction Time and Simple Movement Time is when there is only one location on the screen, in which the stimulus can appear, while Choice Reaction Time and Choice Movement Time is when the stimulus can appear in any of 5 locations.

Speed of executive processing

The already mentioned executive task of *CANTAB Stockings of Cambridge* (SOC) also assesses processing speed. The outcome measures are initial thinking times (i.e. planning time, from the problem is presented on the screen until the subject touches the screen) and subsequent thinking times (i.e. time from first touching the screen until the problem is solved; controlled for motor times).

Figural fluency was assessed using *Regard's Figural Fluency Task* (Reitan & Wolfson, 1993), in which subjects draw as many figures as possible in 3 minutes, by combining two or more of 5 dots in different combinations.

The *Trail-making test* is a neuropsychological test of visual attention and task switching. The task requires a subject to 'connect-the-dots' of 25 consecutive targets on a sheet of paper. Two versions are available: The *Trail Making test A* assesses visuospatial scanning and psychomotor speed by subjects combining circles with ascending numbers (1,2,3, etc.). The *Trail Making test B* assesses attentional set shifting ability by subjects combining circles, continuously alternating between ascending numbers and letters in alphabetical order (1, A, 2, B, etc.). The goal of the subject is to finish the test as quickly as possible, and the time taken to complete the test is used as the primary performance metric. The outcome measure is the time to complete Trail Making B minus the time to complete Trail Making A (Reitan & Wolfson, 1993; Buchanan et al., 1994; Lezak, 1995).