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Cognitive functioning after
first psychotic episode

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LIST OF ORIGINAL PUBLICATIONS

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II. **Haring L**, Mõttus R, Kajalaid K, Koch K, Uppin K, Maron E, & Vasar E (2017). The course of cognitive functioning after first-episode of psychosis: A six month follow-up study. *Schizophrenia Research* 182, 31–41.

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Author of the present dissertation contributed to the publications as follows: Paper I, II, and III: the author designed the studies, planned and coordinated clinical data collection and conducted an assessment of neuropsychological performance of patients and control subjects, participated in data analysis, wrote the manuscripts as the main author and handled the publication process.

ABBREVIATIONS

AP DC	antipsychotics equivalent dose change
BPRS	Brief Psychiatric Rating Scale
BPRS CS	BPRS, psychopathology change score
CA	cortical area
CANTAB	Cambridge Neuropsychological Test Automated Battery
CFA	confirmatory factor analysis
CFI	comparative fit index
CPZ	chlorpromazine
CSs	control subjects
CTh	cortical thickness
DA	dopamine
FEP	first-episode psychosis
FDR	false discovery rate
FGA	first generation antipsychotic
GABA	gamma-aminobutyric acid
GLMs	general linear models
Glu	glutamate
GM	grey matter
ICSs	individual-level changes in cognitive ability test scores
IED	CANTAB test, intra/extradimensional shift
MGCFA	multi group confirmatory factor analysis
MI	measurement invariance
MRI	magnetic resonance imaging
NMDA	N-methyl-D-aspartate
PAL	CANTAB test, paired associates learning
PCA	principal component analysis
PRM	CANTAB test, pattern recognition memory
RCMs	random coefficients models
RMSEA	root mean square error of approximation
RVP	CANTAB test, rapid visual information processing
SGA	second generation antipsychotic
SOC	CANTAB test, Stockings of Cambridge
SRM	CANTAB test, spatial recognition memory
SSP	CANTAB test, spatial span
SWM errors	CANTAB test, spatial working memory, error score
SWM strategy	CANTAB test, spatial working memory, strategy score
SWN-K	Subjective Well-Being under Neuroleptics – Short Form
SWN-K-E	SWN-K, Estonian version
WM	white matter

1. INTRODUCTION

Schizophrenia is a severe psychiatric disorder that has a strong biological basis and is characterized by significant impairments in reality testing, behaviour and functioning.

Enormous efforts have been made to understand the brain functioning that is related to schizophrenia at the molecular, cellular, and system level. Arguably, however, these advances in neuroscience have been slow in translating into clinical practice (Insel 2010). One considerable problem here may be the nature of psychiatric disease entities themselves. Since its designation as *dementia preacox* by Emil Kraepelin (Kraepelin 1896) and schizophrenia by Eugen Bleuler (Bleuler 1911), schizophrenia has been defined by an account of symptoms that are obtained from the patient during clinical interview or by observation, combined with certain inclusion and exclusion criteria regarding the course of the illness and impairment of functioning. Although the diagnoses are reliable, the disease has no unified biological parameters that define its diagnosis (Kapur *et al.* 2012). This means that biological validity of the clinically observed phenotype is low.

To broaden the understanding of psychiatric disorders, Kendler et al. (2011) have put forward the mechanistic property cluster model. In this view mental disorders can be represented as multi-dimensional matrices that reflect various attributes of human mind/brain such as genes, neural systems, physiological states, particular symptoms and environmental contributions. This model suggests that there are robust explanatory structures to be discovered underlying most psychiatric disorders, but these structures are multifaceted and complicated: no psychiatric disease has a singular cause (Kendler *et al.* 2011). Finding a solution to these yet incompletely characterized processes that underlie the psychiatric disorders, and particularly the cluster of clinical symptoms collectively referred to as schizophrenia is a great challenge for neuroscientists.

Among other things, neurobiological differences in widely-acting neurotransmitter systems, subtle changes in brain microstructure, and neuronal network connectivity give rise to a variety of affective, psychotic, and cognitive symptoms seen in schizophrenia (Schaefer *et al.* 2013).

Mounting evidence suggests that compromised cognitive function is a central feature of schizophrenia (Gold & Harvey 1993; Heinrichs & Zakzanis 1998)**.** There is a frequently occurring and characteristic pattern of cognitive deficits, which is relatively stable over time and somewhat independent of the other manifestations of the psychotic symptoms. Among the most striking aspects of the cognitive profile of individuals with schizophrenia is that, at the group level, no cognitive function operates comparably to age- and gender-matched healthy control subjects. It has therefore been suggested that cognitive performance is a powerful predictor, correlate or perhaps even a causal determinant of the impaired functionality in schizophrenia patients (Harvey 2013).

Schizophrenia is certainly a longitudinal concept, and in order to reach a better understanding of its neurobiological basis, attempts need to focus on the different phases of the illness, distinguishing its prodromal, first- and multiple-episode phases. In the field of psychiatric research, there is growing interest in the early stage of the psychosis.

Investigating clinical manifestations, particularly cognitive performance in patients at the early stages of the illness, has the advantage of identifying cognitive deficits more likely to reflect the neurodysfunction that underlies schizophrenia rather than possible disease or treatment related processes following the chronic course of the illness.

The overall aim of the research presented within this thesis was to investigate cognitive functioning of the first-episode psychosis/schizophrenia patients using Cambridge Neuropsychological Test Automated Battery (CANTAB), and to study its relationships with clinical, demographic and brain morphological parameters.

The work reported herein will enhance our understanding about the cognitive deficits as a characteristic feature of the first episode psychosis patients and expand the existing knowledge in this field.

2. REVIEW OF LITERATURE

2.1. Definitions and diagnosis

Psychosis is a syndrome – a mixed set of symptoms that characterize how a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others is impaired (Stahl 2013). Psychotic disorders are neuropsychiatric illnesses and the most common of them is *schizophrenia.* The ICD-10 (10th revision of the International Statistical Classification of Diseases) diagnostic criteria for schizophrenia are summarized in Table 1. In addition, to meeting these criteria, an individual must have experienced pervasive disturbance of social or vocational functioning resulting from the symptoms.

Table 1. Summary of the ICD-10 general diagnostic criteria for schizophrenia.

A diagnosis of schizophrenia is satisfied whereas either at least one of the syndromes, symptoms and signs listed below under (1), or at least two of the symptoms and signs listed under (2), should be present for most of the time during an episode of psychotic illness lasting for at least one month (or at some time during most of the days).

(1)　At least one of the following:
　　a)　Thought echo, thought insertion or withdrawal, or thought broadcasting.
　　b)　Delusions of control, influence or passivity, clearly referred to body or limb movements or specific thoughts, actions, or sensations; delusional perception.
　　c)　Hallucinatory voices giving a running commentary on the patient's behaviour, or discussing him between themselves, or other types of hallucinatory voices.
　　d)　Persistent delusions of other kinds that are culturally inappropriate and completely impossible.
(2)　Or at least two of the following:
　　e)　Persistent hallucinations in any modality, when accompanied by delusions, without clear affective content, or when accompanied by persistent over-valued ideas.
　　f)　Incoherent or irrelevant speech.
　　g)　Catatonic behaviour.
　　h)　"Negative" symptoms.

Above-mentioned diagnostic criteria may leave a mistaken impression that people with chronic psychotic disorder have a uniform illness. In fact, they vary greatly with respect to their symptoms, course of illness, treatment response, and other characteristics – no two cases are ever exactly the same.

The current thesis focuses on the stage of psychotic disorder that is commonly referred to as *first-episode psychosis* (FEP). Although there is no consensus regarding the operational definition of FEP, it is typically used to

characterize individuals early in the course of a chronic psychotic disorder or its treatment. Recommended operational definition for FEP should contain at least three categories: (*i*) verifying first (antipsychotic) treatment contact; (*ii*) identifying duration of antipsychotic medication use; and (*iii*) offering information about duration of above-mentioned psychotic symptoms (Breitborde *et al.* 2009). Although this strategy will not control for the true underlying heterogeneity of the disorder, and firstly ascribed diagnoses, it provides a valuable method for homogenizing variability of patients used in such research projects.

2.2. Clinical characteristics

Schizophrenia is heterogeneous in its clinical presentation. However, there are believed to be at least five distinct symptom domains (Stahl 2013).

Positive symptoms are psychotic behaviours not generally seen in healthy people. People with positive symptoms may "lose touch" with some aspects of reality. Positive symptoms include the following: hallucinations (sensory experiences that occur in the absence of a stimulus), delusions (strongly held false beliefs that are not consistent with the person's culture), thought disorders (unusual or dysfunctional ways of thinking), movement disorders (may appear as catatonia as well as agitated body movements).

Negative symptoms are associated with disruptions in emotions and behaviours. These symptoms include the following: "flat affect" (reduced expression of emotions via facial expression or voice tone), reduced feelings of pleasure in everyday life, difficulty beginning and sustaining activities, reduced speaking, lack of interest in other people, and lack of spontaneity.

Affective symptoms such as depressed mood, suicidal thoughts or behaviour, anxious, guilt, tension, irritability, and worry frequently accompany schizophrenia.

Aggressive and hostile symptoms include overt hostility, such as verbal or physical abusiveness; self-injurious behaviours; and different forms of property damage.

Cognitive symptoms are widely recognized as a central core feature of the chronic psychotic disorder (Saykin *et al.* 1991; Gold & Harvey 1993; van Os & Kapur 2009). More than hundred years ago when the original name for schizophrenia was first used in its current form (model of Emil Kraepelin), it was called *dementia praecox* (premature dementia)*,* a term that reflected the fundamental role of cognitive impairments associated with the disorder.

Cognition can be defined as mental action or process (closely linked to the function of particular areas, neural pathways or cortical networks in the brain) that lead to acquiring information and knowledge, and drive how an individual understands, and acts in the world. Cognitive or neuropsychological functions

encompass such processes as perception, reasoning, memory and working memory, attention, problem solving, decision making, information processing speed, production of language and possess general knowledge, among others. The terms cognitive and neuropsychological will be implemented interchangeably in this thesis.

Cognitive deficits are decline or impairment of cognitive function in one of the above-mentioned areas, which neuropsychological tests can be used to confirm. The concepts of deficit and impairment will also be used interchangeably in this thesis. Clinically significant cognitive impairment refers to the following condition: person's performance is one or more standard deviations below the control group mean in at least one or more cognitive domains, and the magnitude of the impairment is expected to have an impact on their everyday life.

In schizophrenia, cognitive impairments are found across most domains: working memory (the ability to maintain and manage information for brief periods); verbal learning and memory (recalling verbal information for longer periods of time); attention/vigilance (the ability to stay focused on the task at hand without being distracted by other stimuli); processing speed (quickly responding to simple tasks); social cognition (recognizing facial expressions and understanding their meaning); reasoning and problem solving (effective strategy application); visual learning and memory (the ability to remember visual information for longer periods of time); episodic memory (mnemonic processes that record, retain, and retrieve autobiographical knowledge about experiences that occurred at a specific time and place); and executive functions (ability to plan, organize and complete tasks) (Gold & Harvey 1993; Heinrichs & Zakzanis 1998; Cirillo & Seidman 2003; Green *et al.* 2004; Reichenberg & Harvey 2007).

Meta-analytic studies have shown that across cognitive domains the average impairment among patients with schizophrenia tends to be approximately one or more standard deviation below the healthy population mean (Dickinson *et al.* 2007; Reichenberg & Harvey 2007; Mesholam-Gately *et al.* 2009).

Although the cognitive deficit is considered to be universal in schizophrenia, there is considerable heterogeneity among patients (Joyce *et al.* 2005), and whether this heterogeneity reflects specific brain dysfunctions within distinct endophenotypes or individual variation in the effects of a general underlying pathophysiology is not entirely understood (Gur *et al.* 2006; Dickinson & Harvey 2009). Moreover, there are also schizophrenia patients with normal cognitive functioning (Palmer *et al.* 1997; Reichenberg *et al.* 2009). Estimates of the proportion of schizophrenia patients without neuropsychological impairment varying from 16% (Reichenberg *et al.* 2009) to 27.5% (Palmer *et al.* 1997). Being cognitively intact does not mean that patients necessarily have normal cognitive functioning as their impairment may be subclinical in absolute terms (Kremen *et al.* 2000). However, their profile of performance across multiple cognitive domains (i.e. relative strengths and weaknesses) is very similar to that of patients with obvious cognitive impairments (Holthausen *et al.*

2002), and their performance tends to be lower compared to their expected premorbid functioning (Reichenberg *et al.* 2002). Therefore, it is likely that almost all patients with schizophrenia are functioning below the level that would be expected in the absence of the illness (Keefe & Harvey 2012).

Cognitive underperformance is consistently been shown to be present at onset of the illness (Bilder *et al.* 2000; Addington *et al.* 2003). Several studies have demonstrated that objectively measured impairments in cognitive functioning precede the onset of psychosis by almost decade (Seidman *et al.* 2010), and cognitive deficits are found in the biological relatives of subjects with schizophrenia (Snitz *et al.* 2006), suggesting that aspects of cognition impaired in schizophrenia may be under genetic control. While positive and negative symptoms of schizophrenia can fluctuate, cognitive deficits remain relatively stable from first-episode through to late middle age (Rund 1998; Heaton *et al.* 2001; Albus *et al.* 2006; Reichenberg *et al.* 2010; Aas *et al.* 2014), and it has been suggested that most of the decline occurs just before or within few years after the onset of psychosis (Bora & Murray 2014). Moreover, cognitive dysfunction tends to be fairly independent of psychotic symptoms (O'Leary *et al.* 2000), minimally influenced by antipsychotic treatment (Kahn & Keefe 2013), related to underlying neuronal dysfunction (Kéri & Janka 2004), and predict patients' everyday functioning in the community (Green 1996; Green *et al.* 2004).

Given the multitude of tests that show significant impairment, from basic sensory and perceptual functions through preconscious information processing and early attention to higher order cognition, there is clear evidence for a broad cognitive deficit in patients with schizophrenia (Dickinson *et al.* 2008).

In nonclinical groups, the extensive factor analyses of John Carroll and others have firmly established that different cognitive measures correlate with each another positively. Data pertaining to scores of almost whichever cognitive test conform to a factor structure in which individual measures load on broader cognitive ability factors, which in turn load on a higher order factor (*g*) representing general cognitive ability (Carroll 1993; Deary *et al.* 2010). This is one of the most consistent observations in psychology, dating back to the work of Charles Spearman (1904). In schizophrenia, factor analysis supports sorting of cognitive test variables into cognitive domains that is at first sight largely consistent with the nonclinical literature (Allen *et al.* 1998; Dickinson *et al.* 2002, 2011; Nuechterlein *et al.* 2004; Genderson *et al.* 2007), thereby supporting the hypothesis that these constructs have similar meaning in the contexts of schizophrenia and healthy variability in cognitive abilities.

However, schizophrenia studies have revealed that aforementioned cognitive domains (other than *g*) are highly overlapping and not necessarily valid independent constructs (Gold *et al.* 1997). Moreover, even if the domains are distinguishable in one group of people, this does not guarantee the validity of their derived measures in different types of samples (e.g. inpatients/outpatients, first-episode/chronic or the same sample at different time points). In other words,

covariance matrices of cognitive test scores may differ between different samples or within the same sample over time (Jaeger *et al.* 2003).

The overwhelming evidence suggests that schizophrenia is essentially a disorder of subtle aberrations of brain development, plasticity, alterations of dopamine and glutamate as well as an interactive role between both neurotransmitters among others mechanisms and these disruptions manifest itself in cognitive impairment (Jindal & Keshavan 2008; Falkai *et al.* 2015; Howes *et al.* 2015).

While the investigations into impaired cognition in schizophrenia – its mechanisms, neural underpinnings, and methods for its treatment and rehabilitation – have become one of the most dynamic areas of schizophrenia research, the field has begun to take advantage of the tools and constructs of experimental cognitive psychology (MacDonald & Carter 2002). Though no real consensus has been reached on cognitive test batteries for schizophrenic patients in non-pharmaceutical trials (Nielsen 2011).

The use of computerized testing has increased during the later years providing methodological advantages compared to standard paper pencil tests. The main advantages are standardization of tests, greater accuracy and appropriateness for cross-cultural comparison (Levaux *et al.* 2007).

The CANTAB is a battery of computerized neuropsychological tests which have been developed by Cambridge Cognition company. CANTAB uses touchscreen technology and tests are designed in a game-like manner (Sahakian & Owen 1992). Neuropsychological tests from CANTAB provide opportunity to evaluate the individual's test performance on the level of fundamental cognitive processes (Hutton *et al.* 1998; Leeson *et al.* 2009b) that are conceptually linked to known neuroanatomical substrates (Owen *et al.* 1991; Pantelis *et al.* 1997; Rogers *et al.* 2000; Levaux *et al.* 2007; Leeson *et al.* 2009b). Our investigation was based on eight CANTAB tests scores measuring a wide range of cognitive skills potentially sensitive to psychotic disorders.

In order to establish the distinctive profile of cognitive functioning of patients experiencing FEP (i.e. how patients differ from healthy people), traditionally the average performance of a patient sample in a set of tests is compared to that of control subjects with the same educational level and age. In contrast, patients' change in cognitive performance is evaluated by comparing their cognitive test scores at baseline with follow-up scores. Patients' cognitive changes over time do not have to parallel how they differ from healthy people; in any given measure they can be stable, improve or decline, regardless of how they differed from healthy people at the baseline.

An assumption underlying both between- or within-group comparisons is that the measurements are invariant – the tests have equivalent psychometric properties. In the other words, tests are measuring the same construct in the same way in different groups or over time/condition (Meredith 1993). However, in practice measurement invariance (MI) is rarely tested and therefore the conclusions may be incorrect. For example, an observed difference in test scores may result from a difference in only one specific type of items in the test:

in this case, the group difference does not in fact pertain to the general cognitive skill the test purports to measure but to the narrow one reflected in the specific group-sensitive type of items.

Longitudinal studies may be characterized by several methodological issues, which need to be taken into consideration, such as growing familiarity with the test or testing environment, improvement of underlying functions, practice effects (McCaffrey *et al.* 2000), enhanced test taking strategies (Hausknecht *et al.* 2007) or individual characteristics (i.e. age, educational level) (Lezak 2012), as well as test-retest interval (Dikmen *et al.* 1999).

Traditionally, cognitive dysfunctions as measured by objective tests have been considered as the gold standard of patients' "true" cognitive functioning. However, besides the objectively measured profile of neuropsychological strengths and weaknesses of an individual, their subjectively perceived cognitive dysfunction may reveal patients' level of everyday functioning (Chaytor & Schmitter-Edgecombe 2003). Subjectively perceived cognitive impairment tends to be an important early indicator of schizophrenia as it precedes prodromal symptoms (Nuechterlein & Dawson 1984; Hambrecht *et al.* 2002), and is prevalent among patients with FEP (Moritz *et al.* 2000) and during the chronic psychotic disorder (Stip *et al.* 2003; Homayoun *et al.* 2011). It is currently unclear to which extent subjective and objective cognitive dysfunction track each other (Zanello & Huguelet 2001; Prouteau 2004; Homayoun *et al.* 2011). Findings suggest that subjectively perceived and objectively measured cognitive functioning might make unique contributions to advance our understanding of cognitive functioning in patients with schizophrenia (Stip *et al.* 2003). Therefore, both should be implemented to give a broader perspective about patient's cognitive functioning in deciding upon the appropriate clinical practice regarding the assessment and management of cognitive problems.

2.3. The course of the disease

The clinical and pathophysiological course of schizophrenia follows a fairly characteristic pattern depicted in Figure 1. (Lewis & Lieberman 2000).

The typical course of schizophrenia includes a relatively normal childhood, interruptions in late adolescence or early adulthood accompanied by a dramatic deterioration from which few remit (Lewis & Lieberman 2000). Premorbid phase indicates the patient's level of psychosocial functioning before any evidence of specific psychotic disorder; prodromal phase comprises the onset of mild fluctuating psychotic symptoms below the threshold for a psychosis diagnosis (it can last for weeks, months or even years, and symptoms in this phase include depressed mood, anxiety, irritability, disorganized thought, ideas of reference, magical thinking, illusions, deterioration in personal hygiene, social withdrawal, difficulties communicating with others, restricted drive, initiative or interest, and problems in cognitive functioning); the onset of symptoms is usually gradual and intermittent (Yung & McGorry 1996).

Psychiatric symptoms before the first-episode are not necessarily unique to schizophrenia. Progressive or psychotic phase marks the formal onset of schizophrenia and this is indicated by the FEP. Clinical deterioration is evident during this phase, and the psychotic phase progresses through an acute, a recovery or stabilization and a stable phase. The onset of symptoms in the acute phase is usually abrupt (mainly positive symptoms; i.e. delusions and hallucinations) or insidious (mainly negative symptoms, such as social withdrawal). Residual phase describes the occasion when patients have residual enduring symptoms and functional disability. Outcome varies considerably across patients.
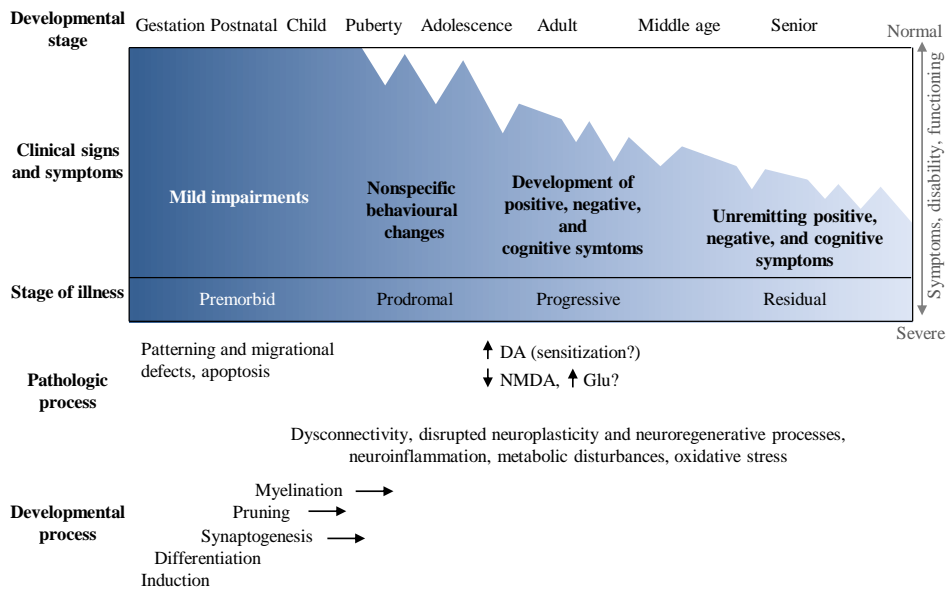
Figure 1. Pathophysiological course of schizophrenia (adapted from Lewis & Lieberman 2000).

There is a consensus that only one episode and remission are seen in 15–20% of patients. At the other side, about 15% will never effectively recover from their first episode, remaining symptomatic. Between these two poles, most patients will recover at least partly from their FEP, but will not return to their premorbid level of functioning or will suffer future relapses and a chronic course of the disorder with increasing residual symptoms (van Os *et al.* 2008).

2.4. Epidemiology

The incidence of schizophrenia is about 0.20/1000/ per year (Messias *et al.* 2007). Due to the often chronic course of the illness, its prevalence is higher, being reported between 0.2 and 0.87% (Perälä *et al.* 2007; Wittchen *et al.* 2011). Men and women are approximately equally affected, but the peak incidence of onset tends to be later in females at around late-20s compared with early- to mid-20s for males (American Psychiatric Association 2013). Compared to other diseases of similar disabling effects but far higher prevalence, schizophrenia is one of costlier, if not the costliest burden to society, requiring a disproportionate share of mental health services and leading to significant work place drop out. In Estonia, schizophrenia ranked 15th and 8th in the list of causes of burden of disease, respectively for men and women (Reinap *et al.* 2005).

2.5. Etiology

2.5.1. Proposed causes of schizophrenia

The pathogenesis of schizophrenia is presently hypothesized to comprise complex interactions between genetic and environmental factors (van Os *et al.* 2008). In particular, the occurrence of such interactions is thought to underlie disease initiation during critical phases of human neurodevelopment (Rapoport *et al.* 2012).

2.5.1.1. Genetic risk factors

The genetic basis of schizophrenia is widely acknowledged. The Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC-SCH) reported a minimum of 108 conservatively defined schizophrenia-associated genetic loci (Ripke *et al.* 2014). Several of these associations corroborate to the hypothesis that links dopamine (DA) with the etiology and treatment of schizophrenia. Also, the genetic associations support the roles of glutamatergic neurotransmission and synaptic plasticity (Ripke *et al.* 2014). Furthermore, inflammatory and immune response genes have significantly altered expression in schizophrenia (Stefansson *et al.* 2009; de Jong *et al.* 2012) offering support for the general hypothesis that immune dysregulation plays a role in the disease manifestation (Tansey *et al.* 2015).

2.5.1.2. Environmental factors

Genotype interacts with negative life events to contribute to individual differences in the vulnerability and resilience to schizophrenia (Daskalakis & Binder 2015). For mental disorders, the most influential environmental factors are adverse life events, such intra-uterine and perinatal complications (i.e. intra-uterine growth retardation, viral infections, hypoxia, malnourishment), physical,

psychological and sexual abuse, negative emotionality in family environment, social adversity, complicated relationships, migration, urban residence, stress and drug abuse (especially cannabinoids, cocaine, amphetamine and phencyclidine/ketamine), among others (Kelly & Murray 2000; van Os & Kapur 2009). The role of these environmental exposures is moderated by their timing during the lifespan (Lupien *et al.* 2009; Daskalakis *et al.* 2013).

2.5.1.3. Epigenetic mechanisms

The common link between genes, environment and development of schizophrenia is attributable to the epigenetic modifications (i.e. active DNA methylation and/or demethylation of genes, especially within promoter regions; histone modifications, and noncoding RNAs) (Petronis 2004; Rutten & Mill 2009).

2.6. Pathophysiology

Despite considerable research into the origin and development of schizophrenia, the exact pathophysiological mechanisms of the disease have not yet been elucidated. The causes and mechanisms of the illness are complex; alterations in several brain regions and changes in the neurocircuits, neurochemical, metabolic, oxidative balance and inflammatory system have been implicated.

2.6.1. Alterations in neurotransmitter systems

The neurobiology of schizophrenia is complex and involves the interplay of a number of neurotransmitter systems, including, among others, DA, serotonin, glutamate (Glu), gamma-aminobutyric acid (GABA), neuropeptides and catecholamines (Carlsson 1988; Davis *et al.* 1991; Carlsson *et al.* 2001; Howes & Kapur 2009; Kantrowitz & Javitt 2010; Seeman & Seeman 2014). As neurotransmitter systems are dynamic, dysfunction in one system will lead to variations or compensatory mechanism in others (Figure 2).

As depicted in Figure 2., main symptoms of schizophrenia can be theoretically explained by a hyperdopaminergic state existing in the mesolimbic pathway and a hypodopaminergic state in the mesocortical pathways. The former results in positive symptoms and the latter leads to negative, and cognitive symptoms. Recent findings, however, indicate that disturbances in dopaminergic transmission are probably secondary to aberrant N-methyl-D-aspartate (NMDA) receptor/glutamate system function (Carlsson *et al.* 2001; Kantrowitz & Javitt 2010; Howes *et al.* 2015).

Furthermore it has been suggested, that dopaminergic model may be most appropriate for patients with primarily positive symptoms and rapid response to antipsychotic treatment, while NMDA glutamate receptor model may be more appropriate for individuals with more balanced positive/negative and cognitive symptoms and poor antipsychotic response (Kantrowitz & Javitt 2010).
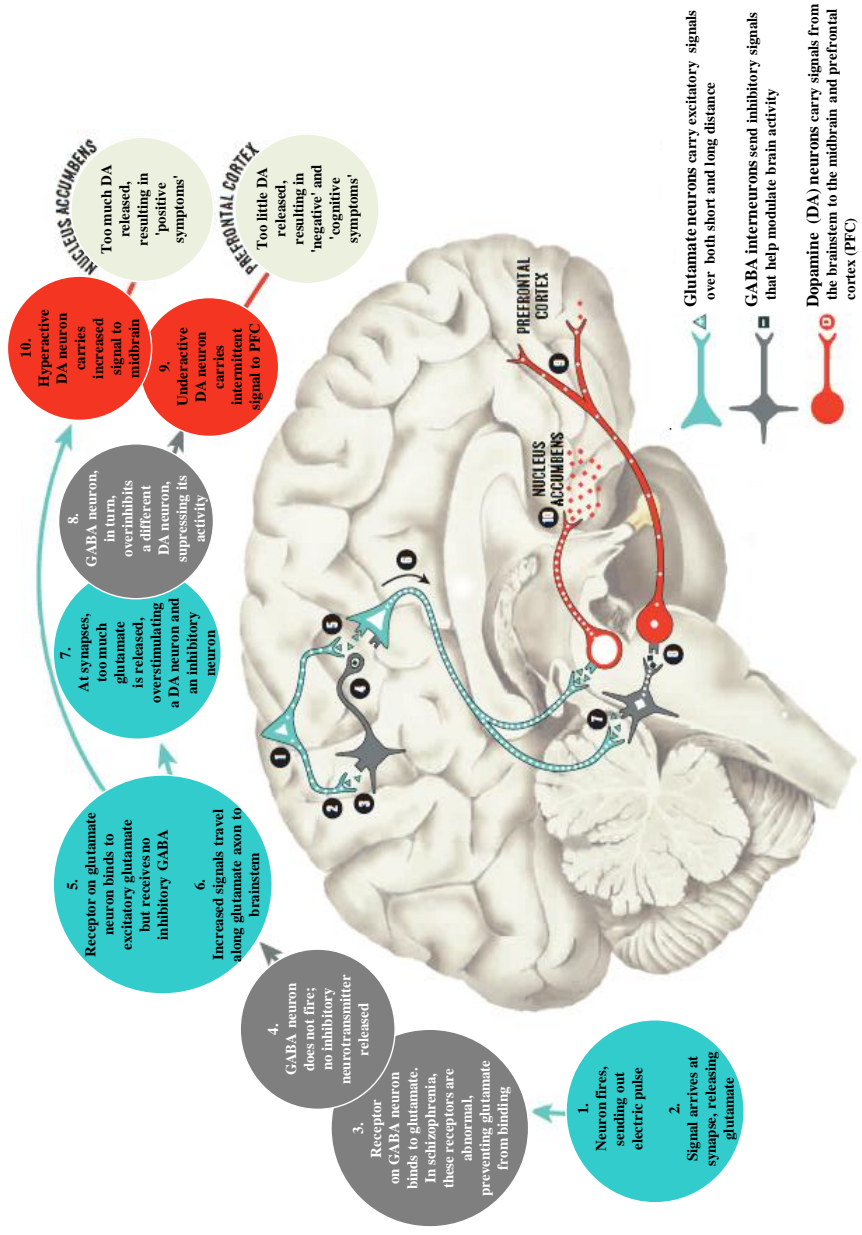
Figure 2. Integrated model of the interactions between the glutamate and dopamine systems in schizophrenia (adapted from Elert 2014).

2.6.2. Inflammatory, metabolic and oxidative stress processes in schizophrenia

Several findings point to a link between neuroinflammation and or altered peripherial inflammatory processes and the pathophysiology of schizophrenia (Potvin *et al.* 2008; Meyer *et al.* 2011; Miller *et al.* 2011; Beumer *et al.* 2012; Müller *et al.* 2015). Moreover, studies have highlighted that perturbations in immune system function seen in chronic psychotic disorders are related to impaired metabolism status of the patients (Mondelli & Howes 2014). In the case of psychiatric disorders, it is still not clear whether such peripherial effects on metabolism or on immune function are a cause or consequence of central nervous system disturbances. In addition, a growing body of evidence indicates that schizophrenia is associated with elevated oxidative stress status and impaired antioxidant defence (Flatow *et al.* 2013) and FEP is accompanied by oxidative stress (Sarandol *et al.* 2015).

2.6.3. Neuropathological abnormalities

Much of our current knowledge on the neuroanatomical basis of chronic psychotic disorder derives from structural imaging studies. It is now well established that schizophrenia is associated with structural brain abnormalities (Wright *et al.* 2000). Cerebral ventricular enlargement is one of the best replicated neuropathological finding (Selemon & Goldman-Rakic 1999), which is likely related to changes in other brain structures, including thinning of the surrounding cortex. Among FEP patients, multiregional and heterogeneous structural brain changes have been suggested, including grey matter (GM) volume reductions in frontal and temporal regions, the anterior cingulate cortex, the insula, the hippocampus, the parahippocampal gyrus and, possibly across the whole brain (Vita *et al.* 2006). However, these results have not always been replicated (DeLisi *et al.* 1991; Molina *et al.* 2004). It has been suggested that cortical thinning (Rimol *et al.* 2012) or the surface area reduction (Sanabria-Diaz *et al.* 2010) is the most important factor in volume reduction, with some suggesting that cortical folding differences could account for the some of the regional differences (Palaniyappan *et al.* 2011). Precise delineation of the neuropathology underlying schizophrenia in general, or its relations to neuro-cognitive deficits, have remained elusive. Brain structural changes in psychotic disorder involve not just GM but also white matter (WM), which shows volume reduction across the whole brain (Wright *et al.* 2000), and alterations in a wide range of WM tracts within prefrontal and temporal lobes, as well as abnormalities within the fibre bundles connecting these regions (i.e. uncinate fasciculus, cingulum bundle and arcuate fasciculus) (Kubicki *et al.* 2007).

2.6.4. Decreased synaptic connectivity and dysconnection hypothesis

There are several lines of evidence that developmentally reduced synaptic connectivity in the neocortex and the hippocampus as well as quantitative and qualitative deficits in neuronal processes can account for important aspects of the schizophrenia (Panksepp 2004). In addition to neurodevelopmental disturbances (Weinberger 1987), a concept of failure in regenerative capacities in disorder has been proposed (Falkai *et al.* 2015), involving disturbed neurogenesis (Toro & Deakin 2007), impaired synaptic plasticity (Schmitt *et al.* 2011), and dysfunction of the dynamic interplay between neurons and oligodendrocytes, which can lead to deficits in axonal function (Morrison *et al.* 2013). A large number of neurophysiological and neuroimaging studies of patients with schizophrenia have provided evidence for dysconnectivity (i.e. abnormal functional integration of brain processes), which could manifest anatomically, through structural changes of association fibres at the cellular level, and/or functionally, through aberrant control of synaptic plasticity at the synaptic level (Stephan *et al.* 2009). The dysconnection hypothesis incorporates neurobiological findings (i.e. psychosis could result from abnormal modulation of NMDA-dependent plasticity by other neurotransmitter systems) with clinical and cognitive functioning findings (i.e. cognitive deficit) in individuals with schizophrenia (Friston 1998; Stephan *et al.* 2009).

2.7. Treatment

Currently there is no cure for schizophrenia. The primary goal of pharmacological treatment is to control psychotic symptoms. However, the ultimate goal is to optimize clinical outcomes by improving the patients' subjective well-being and quality of life (Lambert *et al.* 2006). It is clear that existing antipsychotics (antidopaminergic drugs) are able to reduce positive symptoms of schizophrenia in a significant number of patients, but the failure is most obvious in the case of negative symptoms and cognitive deficits, which remain key predictors of functional disability (Goldberg *et al.* 1993; Goldberg & Weinberger 1996). Major initiatives are under way to find new nonpharmacological approaches for cognitive enhancement in schizophrenia. Cognitive remediation interventions are promising rehabilitation methods with the aim of improving cognitve performance, symptoms, and also patients' psychosocial outcomes (McGurk *et al.* 2007b). At present, the optimal management of a patient with schizophrenia requires the integration of a range of disciplines and approaches including antipsychotic medication, education and counselling of the patient and their family, and community-based rehabilitation as well as psychological and social support programmes, as indicated by case-management models of treatment (van Os & Kapur 2009).

3. STUDY RATIONALE

The research presented in the current dissertation started in 2008. To the best of our knowledge, there have been no previous comprehensive studies of FEP in Estonia. To fill this gap we designed a longitudinal study of FEP patients to assess their cognitive functioning, brain anatomical structure, metabolic, inflammatory and oxidative stress biomarkers, genetic factors, as well as subjective well-being. To demonstrate disease specific factors, control subjects from the same geographical area were also recruited.

4. AIMS OF THE STUDIES

The primary objective of the present thesis was to characterize the patients cognitive functioning at the early stage of the psychotic disorder and, in particular, to describe patients' cognitive dysfunction and investigate its relationships with brain morphology. The thesis also set out to examine the effects of demographic and clinical characteristics on cognitive function at the early stage of the psychotic disorder.

The specific aims were the following:

1) To characterize the structure of the cognitive functioning as well as cognitive performance profile and impairment magnitude of FEP patients compared to control subjects (CSs), measured by computer based cognitive tests from CANTAB (Paper I).

2) To evaluate the rank-order and mean-level stabilities of FEP patients' cognitive abilities over a six month period immediately following diagnosis. To examine longitudinal measurement (CANTAB) equivalence and determine factors potentially linked to cognitive performance change in patients with FEP such as age, gender, educational level, treatment and psychopathology change scores. In addition, to compare patients subjectively perceived cognitive functioning level with objective results of neuropsychological assessment (Paper II).

3) To identify the brain regions where morphological parameters, particularly cortical thickness (CTh) and cortical area (CA) relate to cognitive functioning, by performing magnetic resonance imaging (MRI) and measuring neurocognitive performance using the CANTAB, in order to investigate any significant differences in brain structure/function associations between FEP patients and CSs (Paper III).

5. SUBJECTS AND METHODS

The research project was approved by the Ethic Review Committee on Human Research, University of Tartu, Estonia. All procedures contributing to this work complied with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

In terms of ethical, legal and human rights issues, individuals with psychotic disorder have long been considered a vulnerable group in the scientific research (Welie & Berghmans 2006). This group of persons may be restricted in their freedom to decide whether or not to participate in research. The answer to this question is essentially determined by the persons' mental capacity to make an informed decision (Carpenter *et al.* 2000). However, having mental capacity is not equivalent to not having a specific psychiatric diagnosis, and *vice versa* (Berghmans 2001). Given the inherent potential for investigator bias, patients' phychiatrists independently ascertained subjects' mental capacities and provided information about the study. Afterward, there was possibility to discuss the study with principal investigator and other members of the research team. The research did not intervene in the treatment options and had minimal burdens and risks to the patients. More likely, participating was associated with potential benefits for the subjects, as they got more attention from healthcare workers.

Prior to taking part, all participants were informed of the aims of the study, and of their freedom to participate or not, and their right to leave the study at any time. Patients were informed that their final decision would not influence the medical care they received. All participants provided written informed consent.

5.1. Subjects

The patient sample was recruited within an on-going longitudinal research project of first-episode psychosis of the Psychiatry Clinic of Tartu University Hospital, Estonia (Paper I, II, and III) and partially from the North Estonia Medical Centre, Tallinn Psychiatric Hospital (Paper I). The patients fulfilled the following inclusion criteria: aged between 18 and 45; experience of the first psychotic episode; duration of untreated psychosis less than 3 years; no anti-psychotic treatment received before the first contact with medical services for psychosis. When recruited, patients were in the stabilization phase of the FEP (F23 or F20._9). Diagnoses were based on clinical interview according to ICD-10 (WHO, 1992) criteria, medical chart review, interviews with collateral infor-mants, and were consented within two clinical psychiatrists. Patients were taking their regular medications, including antipsychotics, during the study period. Patients were excluded from the study if they had psychotic disorders due to a general medical condition or substance induced psychosis.

A sample of CSs was recruited by advertisement from hospital staff and the general public of the same geographical area. The CSs were questioned

regarding their current health status and medical history in order to exclude those with conditions that might interfere with cognitive performance. Conditions that resulted in rejection of participants included neurological disorders, mental retardation or significant learning disorder, and major sight and hearing impairment. Exclusion criteria for the control group also included psychotic disorder among close relatives. Both FEP patients and CSs were required to be proficient in Estonian language.
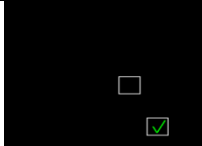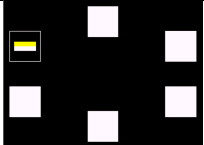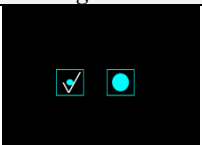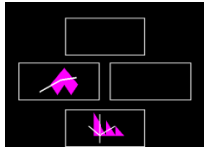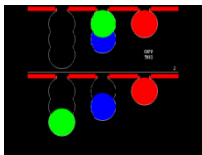
5.2. Methods
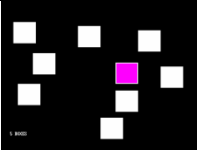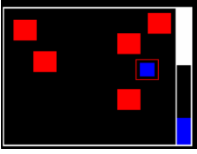
5.2.1. Neuropsychological assessments

Objective neuropsychological status was assessed using the comprehensive Cambridge Neuropsychological Test Automated Battery (CANTAB) (Robbins & Sahakian 1994). The ten tests included in the CANTAB have shown to be sensitive predominantly to the functioning of the frontal, temporal, frontotemporal, frontostriatal, frontoparietal and cingulate brain regions were administered to the participants. These tests were considered likely to reflect a wide spectrum of cognitive dysfunctions among FEP patients. Computerized tasks from the CANTABeclipse version 3.0.0 were run on a personal computer with a high resolution touchscreen. All task stimuli were visual in nature, consisting of geometric designs or simple shapes, and required non-verbal responses. Instructions were given in Estonian from a literal translation of the CANTAB test manual produced by three clinical psychologists fluent in both English and Estonian. The employed neuropsychological tasks are briefly described in the Table 2 (and were characterized in the Supplementary materials of Paper I, not added extra to the dissertation). More detailed descriptions of these tests are available on the CANTAB® website (www.cambridgecognition.com).

Table 2. Used CANTAB test battery description.

MOT *Motor Screening test*	
	The test familiarise participants with the touchscreen tablet computer. The procedure consists of a series of crosses shown in different locations on the screen, and the participant is asked to touch each cross using the forefinger of the dominant hand. *This test was not used in the further analyses*.
Visual memory tests	
PRM *Pattern Recognition Memory*	
	The test relies on cued memory functions. It is presented in two phases. In the presentation phase, 12 abstract visual patterns are presented sequentially, in the centre of the screen. In the recognition phase, the subjects are required to choose between a familiar stimulus and a novel pattern. *The total number of correct responses was used as the outcome.*

SRM *Spatial Recognition Memory*	
	Subjects were required to learn the location of five identical squares, which were appearing one at time in different locations on the screen. In the recognition phase, two squares appeared simultaneously on the screen and the subject had to target the one in a familiar location. *The total number of correct responses was used as the outcome.*
PAL *Paired Associates Learning*	
	The test assesses visual memory and learning. The task requires subjects to learn and then replicate the matching of two complex pattern-location associations. The number of pattern-location pairs then increases to three, six and finally to eight. At each stage, boxes are displayed on the screen and are opened in a randomized order. Two or more of them contain a pattern. The patterns shown in the boxes are then displayed in the centre of the screen, one by one, and the subject should touch the box where the pattern was initially placed. If the subject makes an error, the patterns are presented again to remind the subject of their locations. *The first trial memory score (the number of patterns correctly located after the first trial summed across the stages completed) was used as the outcome.*
Executive function, planning, and working memory tests	
BLC *Big/Little Circle*	
	This test assesses comprehension, learning and reversal learning (the process of learning to inhibit previously rewarded actions), and is also intended to accustom participants on the general idea of following and reversing rule. This is screening test for IED. *The test was not used in the further analyses.*
IED *Intra/Extradimensional Shift*	
	This test taps visual discrimination and selective attentional set formation, and evaluates the maintenance, shifting, and flexibility of attention. Two dimensions are used in the test: colour-filled shapes and white lines. Subjects are required to alter behaviour according to changes in dimensional relevance of stimuli. At first, maintain attention to examples within a rewarded stimulus dimension (intradimensional shift), and then to shift attention to a different category that was previously irrelevant and unrewarded stimulus dimension (extradimensional shift). This test is primarily sensitive to changes to the fronto-striatal areas of the brain. *The total number of reverse errors at the level of extradimensional shift was used as the outcome.*
SOC *Stockings of Cambridge*	
	This is a spatial planning test, which gives a measure of frontal lobe function. The subjects must operate with the coloured balls in the lower display to reproduce the pattern shown in the upper display by moving balls with minimum number of runs. The time taken for completing the task and the number of moves required are taken as measures of the subject's planning ability. *The total score of problems solved in minimum moves was used as the outcome measure in this research.*

SSP *Spatial Span*	
	This test gives a measure of the subject's visuo-spatial short term memory span. A set of squares is shown on the screen. Some of the squares change in colour, one at time. The subject has to touch each of the boxes highlighted by the computer and do it in the same order. The task starts with a small number of blocks presented at a time and gradually increases up to nine blocks. The test measures both the number of correct sequences and the longest sequence remembered. The dorsolateral prefrontal cortex (DLPFC) plays a key role in short memory span. *The longest sequence successfully recalled by the subject was used as the outcome.*
SWM *Spatial Working Memory*	
	This test evaluates the subject's ability to retain spatial information and to manipulate memorized items in the working memory. A trial begins with a number of coloured squares (boxes) being shown on the screen. The overall aim is that the subject should find a blue 'counter' in each of the boxes, by using a process of elimination, and use them to fill up an empty column on the right hand side of the screen. The subject must touch each box in turn until one opens with a blue 'counter' inside. Participants must avoid touching boxes that they have been found to be empty, and revisiting any box in which a blue 'counter' has already been found. Choosing these options are encoded as errors. The subjects choose the order in which the boxes are searched, and an estimate of the use of the heuristic strategy is measured by counting the number of times the subject begins a new search with a different box. A high score represents poor use of the suggested heuristic strategies. *The total number of errors and ineffective strategy score were used as the outcomes.*
RVP *Rapid Visual Information Processing*	
	This test is a sustained vigilance task, and the subject must identify consecutive odd or sequences of digits, which appear in a pseudo-random order, at the rate of 100 digits per minute. Participants are instructed to detect target sequences of digits (3-5-7, 2-4-6, and 4-6-8) and to register responses using the press pad. The test outcome measures are based on the signal detection theory and cover latency, sensitivity and specificity for detecting goal sequences. *The probability of a correct hit (sensitivity for detecting sequences) was used as the outcome.*

The participants completed the tests in a fixed order: MOT, PRM, SRM, PAL, BLC, IED, SOC, SSP, SWM, RVP.

5.2.2. Magnetic resonance imaging acquisition and processing

Multi-modal MRI scans were obtained using a Philips Achieva 3 Tesla MRI scanner at Tartu University Hospital, Estonia.

Cortical surface reconstruction, volumetric segmentation and inter-group comparative correction were performed using the software FreeSurfer v5.1.0 (http://surfer.nmr.mgh.harvard.edu), according to standardized procedures (Sled *et al.* 1998; Dale *et al.* 1999; Fischl & Dale 2000; Fischl *et al.* 2002, 2004; Ségonne *et al.* 2007). The surfaces were averaged across participants using a non-rigid high-dimensional spherical averaging method that aligned cortical folding patterns and matched morphologically homologous cortical locations across subjects on the basis of each individual's anatomy while minimizing metric distortion (Fischl *et al.* 1999).

The CTh was calculated as the average of the distance from the WM surface to the closest point on the pial surface and back (Fischl & Dale 2000).

The CA estimation was generated according to WM surface geometry and characteristics obtained by computing the area of a triangle in a standardized, spherical atlas space surface tessellation when mapped in an individual subject's space. We utilised the mapped differences between FEP and CSs in CTh and CA across the whole brain.

Computations were carried out in the High Performance Computing Centre of the University of Tartu, Estonia.

5.2.3. Clinical assessments

Clinical symptoms were rated using the Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham 1962), which is a widely used instrument for assessing the positive, negative, and affective symptoms of individuals who have psychotic disorders. The BPRS consists of 18 symptom constructs and each item is measured along a seven-point continuum from 'not present' to 'extremely severe'. A total score, as well as positive and negative BPRS symptom scores (derived from the subscales identified by Ventura *et al.* 2000), were used as the outcomes.

5.2.4. Subjective cognitive functioning

Patients' subjectively perceived cognitive functioning was evaluated by 'Mental functioning' subscale, obtained from Subjective Well-Being under Neuroleptics-Short Form (SWN-K, Naber *et al.* 2001) Estonian version (SWN-K-E, Haring *et al.* 2013). The SWN-K consists of 20 items that are rated on the 6 point Likert type self rating scale referring to the subjective experiences in the past 7 days. One of the subdimension, specifically the *Mental functioning* subscale was used, which comprised following four items: "I find it easy to think", "I am imaginative and full of ideas", "My thinking is difficult and slow" and "My thoughts are flighty and undirected. I find it difficult to think clearly".

Values of last two items were reversed during the scoring and higher global score indicated better mental functioning.

5.3. Statistical analysis

5.3.1. Demographic and clinical variables

Associations with demographic variables were analysed using *t*- and chi-square tests.

5.3.2. Cognitive variables

Differences in neuropsychological performance between FEP patients and CSs (Paper I, III) were evaluated using general linear models (GLMs) and were adjusted for age, gender, and educational level. In both groups, cognitive test scores were transformed into standard scores based on the means and standard deviations of the respective tests in CSs.

GLMs were also performed to quantify individual-level changes in cognitive ability test scores over time (Paper II), wherein follow-up scores were predicted from baseline scores, controlling for age, gender and educational level. Deviations from individuals' predicted scores (regression residuals) at the follow up were taken as their individual change scores (ICSs).

Effect sizes were interpreted as small, moderate, and large, with corresponding Cohen's *d* ranging from 0.2–0.49, 0.5–0.79, and ≥ 0.8, respectively (Cohen 1977).

To compare the co-variance structure of the measured neuropsychological tests across the groups (Paper I), and to investigate the structure of the patients ICSs (Paper II), a principal component analyses (PCA) were performed as the first steps.

Second, for each PCA a parallel analysis (Horn 1965) helped determine the most appropriate number of components to be retained.

As the components were expected to be correlated each PCA was followed by an oblique (oblimin) rotation.

In order to determine whether PCA results were plausible reflections of latent cognitive constructs confirmatory factor analyses (CFAs) were conducted.

Third, to assess whether: *a*) the structure of latent cognitive traits was similar in patients and controls; *b*) the mean scores of each group could be meaningfully compared (i.e. measurements were invariant across the groups, MI) (Paper I), and *c*) the cognitive traits structure replicated across the two testing occasions (Paper II) multi group confirmatory factor analyses (MGCFA) (Joreskog 1971; Widaman & Reise 1997; Widaman *et al.* 2010) were used. As is common in MI testing (Wicherts & Dolan 2010) a series of multi-group CFA models were fitted with systematically increasing parameter equality constraints across groups (Paper I) or within the group, across testing occasions (Paper II) (Horn & McArdle 1992; Vandenberg & Lance 2000).

For MI testing, *configural invariance* was met if the same variables were associated with the same latent factors between groups or within the FEP group over time. No parameter equality constraints were imposed at this point other that the same tests defined the same latent constructs. The configural invariance model served as a baseline for further comparisons.

Weak invariance was achieved when the factor loadings of the CANTAB tests on the latent variables could be held constant across the groups or within the FEP patients group over time without a significant deterioration of model fit. Weak invariance provides evidence that latent factors have the same meaning across FEP patients and CSs as well as for FEP patients group over time.

To establish a stronger form of invariance, *strong invariance*, both factor loadings and intercepts of tests were constrained to be the equal across conditions. In the case of no significant deterioration in model fit, scores of latent factors could be considered comparable across the groups and for the FEP patients group over time.

Strict invariance (residual variance invariance) was also explored. No deterioration of model fit with strict invariance indicated that neuropsychological variables were measured with the same precision in both occasion.

Finally, *variances and covariances* of the latent traits were constrained to be equal between groups and within the patients group across testing occasions to test whether the variability and inter-correlations of the latent variables were similar. Models were fitted using the robust maximum-likelihood (MLR) estimator in the 'lavaan' package (Rosseel 2012). Models fit was estimated using the chi-square (χ^2) goodness-of-fit statistic (Hu & Bentler 1999), the Comparative Fit Index (CFI) (Bentler 1990) and the Root Mean Square Error of Approximation (RMSEA) (Browne & Cudeck 1993; Hu & Bentler 1999; Steiger 2000).

Any given type of MI was supported when the fit of the more parsimonious model (e.g. the model with intercept equality constraints) was not significantly poorer than that of the less constrained model (e.g. the one without intercept equality constraints). Differences in models fit were tested using the chi-square difference test (Horn & McArdle 1992), where a statistically significant ($p <$ 0.05) $\Delta\chi^2$ indicated a difference in fit. Differences in latent factors were estimated by fixing the mean scores in one group or mean scores at first testing at zero and freely estimating the means of the other group or follow-up testing.

Next, in order to examine rank-order stability across the two testing occasions, Pearson's correlation analysis was used (Paper II).

In order to evaluate whether significant change in the cognitive characteristics had occurred because of FEP patients age, gender, educational level, clinical symptom severity or treatment-related variability, psychopathology change score (BPRS CS), antipsychotics equivalent dose change (AP DC) were calculated and cognitive ICSs were separately regressed on BPRS CS's, AP DC's and demographic variables, using random coefficients models (RCMs) (Paper II). Furthermore, correlations between performance in cognitive test scores and subjectively perceived mental functioning were analysed at baseline and after the six month follow-up using a Pearson correlation test (Paper II).

Analyses were conducted using the R Statistical software package (R: Core Team 2013, 2015).

5.3.3. Imaging variables

For the analysis of whole brain neuroanatomical alterations (Paper III), the vertex-by-vertex analysis was used and CTh and CA values from the significant clusters of all subjects were modeled as a function of group (FEPs *vs.* CSs). The simulation and clustering approach is implemented in FreeSurfer and significance level ($p < 0.05$) is obtained through a combination of a probability threshold and cluster size threshold. The *p*-values of the resulting clusters of the original data are expressed as cluster-wise probability (P_{cw}), and hereby P_{cw} is equivalent to the overall significance level ($p < 0.05$). The statistical maps of voxels sensitive to cognitive tasks were created using GLMs. The voxel-based GLMs were utilised to determine the unique contribution of MRI measures on cognitive test raw scores that were significantly different between groups. Tool from the FreeSurfer - QDEC (Query, Design, Estimate, Contrast) was used. Age and gender were used as covariates in all models. Left and right hemispheres were analyzed separately. To correct for multiple comparisons, statistical maps were thresholded to yield an expected false discovery rate (FDR) of 5% (Genovese *et al.* 2002) and that threshold was subsequently applied to the all CTh and CA maps.

6. RESULTS

6.1. Paper I

6.1.1. Demographic features of the subjects

One hundred and nine (54.1% males, mean age 26.9 years) clinically stabilized patients with FEP participated in the study. CSs consisted of 96 subjects (40.6% males, mean age 25.7 years). No significant differences in age or gender were found. The patients average formal educational experience was significantly lower ($t = -3.51$, $p < 0.01$) compared to CSs.

6.1.2. Principal component analysis and confirmatory factor analysis

PCAs and CFAs were carried out separately in CSs and FEP patients groups.

Whereas the scree plot and parallel analysis suggested extracting two components for CSs and one component for FEP group, both solutions were tested in both groups.

In the CSs group, the results indicated that five CANTAB subtest scores (PRM, PAL, SRM, RVP and SSP) primarily defined a component representing "attention/memory" (factor loadings 0.46–0.73) and four variables (SWM errors, SWM strategy, SOC and IED) primarily defined a component of "executive function" (factor loadings 0.40–0.84). The two-factor loading pattern with regard to FEP patients group demonstrated that: two variables (PRM and PAL) primarily defined the "memory component", whereas seven variables (SRM, RVP, SSP, SWM errors, SWM strategy, SOC and IED) defined the "attention/ executive function component" (with primary loadings ranging from 0.42 to 0.76). Importantly, we demonstrated that component intercorrelations also differed across groups, with 0.15 for controls and 0.30 for patients. Intercorrelations suggested a higher-order factor, a putative single common cause for all tests performance may underly the memory/attention- and executive function-related sources of variance especially strongly among patients.

Examination of the one-component PCAs solutions indicated that the CANTAB tests could also be grouped into a single high-order factor such that all variables loaded on a broad cognitive variable, with loadings of 0.19–0.66 in the control group and 0.30–0.85 in the patient group.

Above-mentioned one- and two-component models derived from the PCAs results were subsequently converted to latent trait models for single-group CFAs (i.e. separate models were specified for FEP and CSs groups).

In the two-factor model latent factors ("attention/memory" and "executive function") were defined by the same variables for both the patient and control groups (see Figure 3 a) and b) for factor loadings and covariance estimates). All factor loadings (excepted IED) were significant at $p < 0.01$. Although interrelations among cognitive factors are typical, our results revealed a very strong inter-

correlation between "attention/memory" and "executive function" among patients ($r = 0.83$) that supported the low distinctiveness of the two cognitive domains and provided strong evidence for a higher-order trait among them. In the CSs group the intercorrelation of "attention/memory" and "executive function" was much lower ($r = 0.31$). In other words, the two cognitive domains were more coherent among patients – when patients' cognitive functioning was poor, it tended to be poor across most skills measured in the study, more so than among CSs.

In the one-factor model (see Figure 3 c) and d)) all loadings were significantly different from zero in the patient group (z-values ranged from 2.14 to 9.00), whereas SWM errors, SWM strategy and IED had non-significant factor loadings ($p = 0.09$, $p = 0.23$ and $p = 0.66$, respectively) in the control group, indicating that this model may be less appropriate than the two-factor model for the latter group.
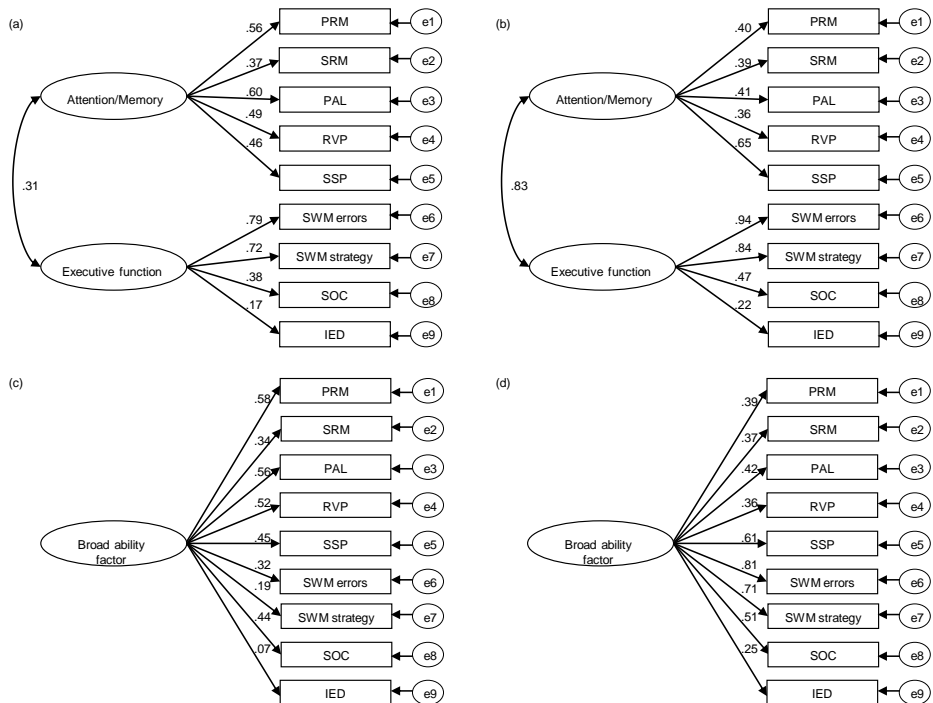
Figure 3. Representation of the two- (a, b) and one- (c, d) latent factor structural models derived from principal component analysis for the control (a, c) and FEP (b, d) samples, respectively. Variables in boxes represent observed measures and variables in ovals represent latent variables. The paths from the latent constructs to the observed variables demonstrate the parameter estimates onto its representative constructs. Two-headed arrows connecting latent variables represent correlations between the constructs. The 'e' represents the unique variance and error associated with observed variable.

PRM, pattern recognition memory; SRM, spatial recognition memory; PAL, paired associates learning; RVP, rapid visual information processing; SSP, spatial span; SWM, spatial working memory; SOC, Stockings of Cambridge; IED, intra/extradimensional shift.

The CFA models provided support for the hypothesized two- and one-factor solution. Model fit was good in both cases ($\chi^2_{(25)}$ = 14.85; CFI = 1.00; RMSEA = 0.00 and $\chi^2_{(25)}$ = 13.54; CFI = 1.00; RMSEA = 0.00, respectively for FEP patients group). Also for CSs group, both two- and one-factor models demonstrated acceptable fit ($\chi^2_{(25)}$ = 29.07; CFI = 0.96; RMSEA = 0.04 and $\chi^2_{(25)}$ = 28.95; CFI = 0.96; RMSEA = 0.04, respectively).

Whereas, both one- and two-factor models fitted well in both samples, the decision was made to take both models forward to MGCFA.

6.1.3. Measurement invariance analysis

Multi-group CFA can be used to simultaneously test whether a hypothesized factor structure fits equally well in different groups.

For the two-factor solution, the fit of the configural MI model (i.e. configural invariance is met when indicator variables load on the same factors across groups) was good ($\chi^2_{(50)}$ = 42.61; CFI = 1.00; RMSEA = 0.00), indicating that the two-factor dimensional structure was shared across groups and justifying the evaluation of more restrictive invariance models.

Weak MI (i.e. weak invariance is met with adequate model fit when factor loadings are held constant across groups) was marginally supported ($\Delta\chi^2_{(9)}$ = 15.68, p = 0.07 (p-value corresponds to $\Delta\chi^2$) ; CFI = 0.998; RMSEA = 0.01), suggesting that the CANTAB subtests measured the cognitive abilities more or less similarly across groups.

Strong MI (i.e. strong invariance is met when both factor loadings and intercepts are held constant across groups) was clearly not supported in these data ($\Delta\chi^2_{(7)}$ = 200.73, $p < 0.00$; CFI = 0.54; RMSEA = 0.14), indicating that the same observed CANTAB test scores corresponded to different latent trait levels in the two groups, making comparisons of their mean latent scores effectively meaningless. As strong MI was not met, testing for stricter forms of MI was not justified.

In MGCFA specifying just one latent factor, the configural MI model fitted data well ($\chi^2_{(50)}$ = 41.97; CFI = 1.00; RMSEA = 0.00).

The weak MI model was accompanied by a clear drop in model fit ($\Delta\chi^2_{(9)}$ = 21.89, $p < 0.01$; CFI = 0.98; RMSEA = 0.03), suggesting that stricter forms of MI would not be met and latent factor means would not be comparable across groups.

6.1.4. Comparison of cognitive performance

According to MI results, comparison of cognitive performance measured by CANTAB between CSs and FEP patients could not be compared based on latent traits and group differences therefore had to be tested using observed test scores. GLM analyses were performed to demonstrate group differences in each cognitive measure, including age, gender and years in education as covariates in

all comparisons. In general, patients exhibited widespread cognitive impairments compared to CSs. The profile of neuropsychological impairment in FEP patients (Figure 4) was most prominently characterized by diminished processing speed (RVP) and impaired executive functioning (SWM errors, SOC and IED).

In more details, there were significant main effects for visual (PRM) and spatial recognition memory (SRM) ($F_{(4,200)}$ = -5.65, $p < 0.001$, Cohen's d = -0.69, and $F_{(4,200)}$ = -7.73, $p < 0.001$, d = -0.78, respectively), indicating that FEP patients gave a lower number of correct responses than CSs. Patients also showed diminished ability to learn and remember pattern-location associations during the first trial (PAL) compared to CSs ($F_{(4,200)}$ = -11.98, $p < 0.001$, d = -0.73), demonstrated difficulties in detecting important sequences during the sustained attention task (RVP) ($F_{(4,199)}$ = -18.02, $p < 0.001$, d = -1.17) and had a shorter spatial span length in the working memory capacity task (SSP) ($F_{(4,200)}$ = -10.4, $p < 0.001$, d = -0.61). In the executive functioning task (SOC), patients ability to solve problems with minimum number of runs was to a great extent diminished ($F_{(4,200)}$ = -18.28, $p < 0.001$, d = -1.36), and in the attentional shifting and flexibility task (IED), they made significantly more total reverse errors ($F_{(4,200)}$ = 11.38, $p < 0.001$, d = 1.25) compared to CSs.
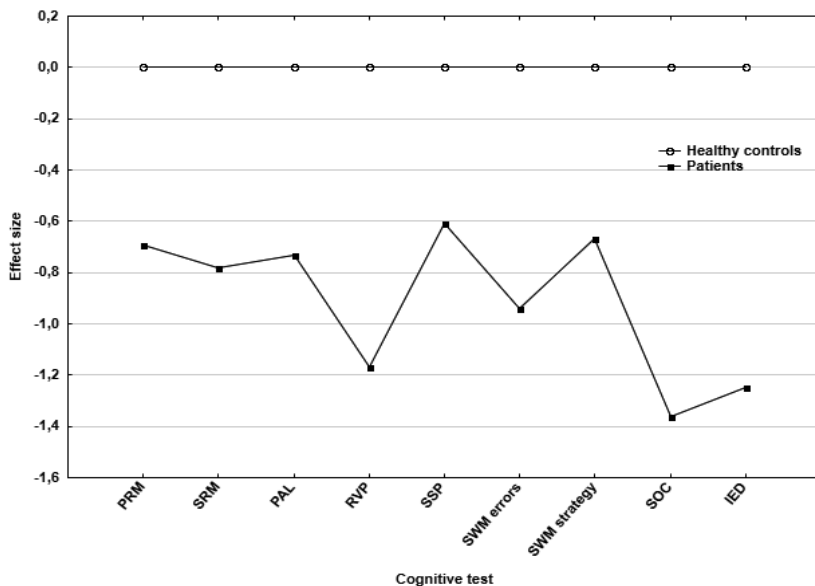
Figure 4. Cognitive impairment profile: performance of FEP patients expressed as effect sizes. The sign of the effect size values was changed for IED and SWM domains in order to have the dysfunctional poles as negative values.

PRM, pattern recognition memory; SRM, spatial recognition memory; PAL, paired associates learning; RVP, rapid visual information processing; SSP, spatial span; SWM, spatial working memory; SOC, Stockings of Cambridge; IED, intra/extradimensional shift.

Furthermore, FEP patients gave less correct responses in the SWM task (SWM errors) that measured a subject's ability to retain spatial information and manipulate remembered items in working memory ($F_{(4,200)} = 9.92$, $p < 0.001$, $d = 0.94$), and also used heuristic strategies (SWM strategy) less efficiently than did CSs ($F_{(4,200)} = 8.92$, $p < 0.001$, $d = 0.67$).

6.2. Paper II

6.2.1. Demographic and clinical features of the subjects

Eighty-five patients (mean age 26.99, s.d = 6.96, 54.12% males) with FEP were included in the study. At the time of recruitment, patients were in the stabilization phase of the disease (mean general psychopathology score, measured by BPRS was 24.18 (s.d. = 12.80)). The mean medication exposure time at baseline neuropsychological testing was 21.42 (s.d. = 8.92) days and the mean daily dose of the antipsychotic treatment in chlorpromazine (CPZ) equivalent (Gardner *et al.* 2010) was 387.38 mg/day (s.d. = 165.44). Follow-up measurements were conducted approximately six months later (mean duration between baseline and follow-up testing was 191 (s.d = 27) days), and data were available for a total of 82 patients (96.47%), two patients drop out from mental health care system, and one refused to participate in the follow-up. During the follow-up mean psychopathology (BPRS) score was 19.31 (s.d. = 11.37), and mean CPZ dose equivalent was 319.97 mg/day (s.d. = 183.31). BPRS scores and CPZ equivalents differed significantly between two sessions ($t_= -4.24$; $p < 0.0001$, and $t = -3.02$; $p = 0.003$, respectively).

6.2.2. Mean-level change

When patients' tests pattern of mean-level changes across occasions were examined, there appeared small improvements in set-shifting (IED, $t = -2.64$, $p < .05$), speed of processing (RVP, $t = 2.96$, $p < .05$) and executive functioning (SOC, $t = 3.80$, $p < .001$) as well as in strategy usage and ability to manipulate spatial information in working memory (SWM strategy score, $t = -5.25$, $p < .001$, SWM errors score $t = -5.40$, $p < .001$). The differences in effect size units were: -0.33, 0.29, 0.42, -0.45, -0.42, respectively.

Additionally, at the group level patients demonstrated worsening performance in episodic memory (PAL, $t = -10.84$, $p < .001$) and spatial recognition memory (SRM, $t = -6.20$, $p < .001$) tasks; the magnitudes of these changes were large (-1.31, and -0.94, respectively). Spatial working memory (SSP, $t = 0.49$, $p > 0.05$) and pattern recognition memory (PRM, $t = 1.35$, $p > 0.05$) tests showed mean-level stability over time.

6.2.3. Six months stability of cognitive functioning

FEP patients rank order of measured tests scores showed very high stability over time. Following rank-order stability coefficients of the cognitive tests were found: PRM, $r = 0.89$; SRM, $r = 0.94$; PAL, $r = 0.84$; IED, $r = 0.80$; SOC, $r = 0.82$; SSP, $r = 0.92$; SWM strategy score, $r = 0.90$, SWM errors score, $r = 0.84$, and RVP, $r = 0.83$. All correlation coefficients were significant at $p < 0.001$.

Patients' relative standings within the group across the six months interval being very stable suggested that mean-level changes tended to characterize most of them in similar ways. These estimates also represent the lower-boundary estimates of the reliability of the tests in psychotic patients (true reliability might be higher because the observed changes could reflect substantive changes in addition measurement error).

6.2.4. Structure of cognitive function and measurement invariance between six month time interval among FEP patients

To investigate the structure of the patients ICSs (i.e. deviations from individuals' predicted scores at the follow up), a PCA was performed as the first step.

One-factor (broad ability factor) solution accounted for 19% of the total variance among the nine CANTAB subtest scores in the baseline assessment of the FEP patient group and primary loading values ranged between 0.13 and 0.82.

CFA confirmed that the empirical model in which measures of CANTAB subtests loaded on one "broad ability" domain demonstrated excellent fit for the data ($\chi^2_{(27)} = 25.45$; CFI = 1.00; RMSEA = 0.00).

In order to evaluate MI across two time-point factor analyses, MGCFA was used. One-factor model demonstrated excellent fit ($\chi^2_{(54)} = 69.28$; CFI = 0.95; RMSEA = 0.058), suggesting it could be considered a feasible representation of the data across both time-points and justifying the evaluation of more restrictive invariance models.

At the level of weak invariance testing, model fit remained acceptable ($\Delta\chi^2_{(8)} = 6.43$, $p = 0.60$; CFI = 0.96; RMSEA = 0.051), indicating that estimated factor loadings were not significantly different between two time-points.

Indices of both relative and absolute model fit did not support the existence of the strong invariance ($\Delta\chi^2_{(8)} = 121.32$, $p < 0.001$; CFI = 0.59; RMSEA = 0.147), showing that intercepts values varied significantly between two assessments. As strong measurement invariance was not met, testing for stricter forms of invariance were not justified.

6.2.5. The relationship of cognitive change with other variables

In order to evaluate individual-level effects of demographic characteristics (age, gender, educational level), BPRS CSs and AP DCs on ICSs of neuropsychological functioning over time, RCMs were used. For SRM, PAL, IED, SOC, SWM errors and strategy usage scores the models reached statistical significance levels ($t = -6.26$, $p < 0.001$; $t = -10.33$, $p < 0.001$; $t = -2.02$, $p < 0.05$; $t = 2.76$, $p < 0.01$; $t = -4.14$, $p < 0.001$; $t = -4.38$, $p < 0.001$; $t = 2.29$, $p < 0.05$, respectively).

Gender was a significant predictor of IED, SOC, SSP, and SWM test performances. Specifically, Figure 5 shows that gender differences (a) at baseline levels of performance and (b) in longitudinal rates of change were significant for the IED, SOC, SSP, and SWM (i.e. SWM errors and strategy score) tests, with males outperforming females ($\beta = 0.44$, $p < 0.01$, $\beta = -0.49$, $p < 0.01$, $\beta = -0.58$, $p < 0.01$, $\beta = 0.50$, $p < 0.01$ and $\beta = 0.58$, $p < 0.01$, respectively).
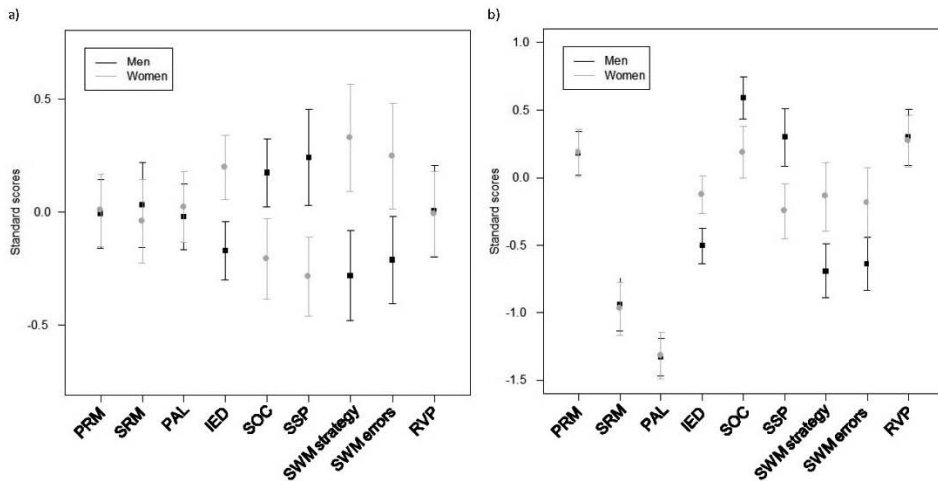
Figure 5. Predicted mean levels of cognitive performance separately for men and women at baseline (a) and follow-up (b). Results are based on random coefficient models.

PRM, pattern recognition memory; SRM, spatial recognition memory; PAL, paired associates learning; IED, intra/extradimensional shift; SOC, Stockings of Cambridge; SSP, spatial span; SWM strategy, spatial working memory, strategy score; SWM errors, spatial working memory, errors score; RVP, rapid visual information processing.

Lower values (less errors and less ineffective strategy usage) for IED and SWM measures and higher values for PRM, SRM, PAL, SSP, and RVP indicate better performance.

Therefore, cognitive decline tended to be somewhat more pronounced among the female patients. In addition, longer time in education was predictor for downward change in IED ($\beta = -0.22$, $p < 0.05$) and upward change in the RVP

($\beta = 0.30$, $p < 0.01$) test performances. Younger age was associated with decreases in SRM ($\beta = -0.26$, $p < 0.05$), PAL ($\beta = -0.26$, $p < 0.01$), and SSP ($\beta = -0.22$, $p < 0.05$) and increases in the strategy score of SWM ($\beta = 0.20$, $p < 0.05$). BPRS CS was not found to be a significant predictor of changes in the scores of any cognitive test. We conducted additional RCM analyses to separately evaluate the BPRS negative and positive symptoms change scores effects (in addition to gender, age, education and AP DCs) on the cognitive tests ICSs. We did not detect any statistically significant effects of negative symptoms change score, measured by BPRS negative symptoms subscale, on the cognitive performance ICSs (t-values ranged between -1.84 to 1.16). BPRS positive symptoms subscale change score was a significant predictor for SWM errors ICSs ($t = 2.17$, $p < 0.05$) and information processing (RVP) ICSs ($t = -2.21$, $p < 0.05$).

In addition, significant associations were found between the mean daily AP DCs and patients' changes in the performance of SOC ($\beta = -0.16$, $p < 0.05$), and SSP ($\beta = -0.16$, $p < 0.05$), indicating that significant improvement in the performance occurred when AP dose diminished.

Individual antipsychotic dose and psychopathology raw scores were significantly correlated at the baseline and during the follow-up assessment ($r = 0.35$, $p = 0.001$; $r = 0.34$, $p = 0.002$, respectively).

6.2.6. Correlation between objective and subjective cognitive functioning

No significant associations were found between the objectively and subjectively measured cognitive functioning neither at baseline nor at follow-up in FEP group (correlation coefficients ranged from $r = -0.22$ to 0.17, $p > 0.05$).

6.3. Paper III

6.3.1. Demographic and clinical features of the subjects

The FEP patient sample consisted of 63 participants (mean age 25.6, s.d = 5.5; 52.38% males). Patients had received an average of 22 (s.d. = 9) days of treatment prior to the neuropsychological testing. Neuropsychological assessments and image acquisition (an average of 2 (s.d. = 6) days apart) were performed when the patients were clinically stable (mean general psychopathology score, measured by BPRS was 23.42 (s.d. = 12.81)) and able to tolerate these procedures.

A CSs sample included 30 participants. The mean age of this sample was 25.1 years (s.d. = 6.1) and a gender composition of 50% males. Differences between the groups with respect to the age, gender and years of formal education were not significant ($t_{(91)} = 0.37$, $p = 0.71$; $\chi^2_{(1)} = 0.05$, $p = 0.83$; $t_{(91)} = -1.59$, $p = 0.12$, respectively).

6.3.2. Group differences in cognitive performance

Main effects of group were significant in all measured domains: set shifting task (IED) ($F_{(4,88)}$ = 3.40, p = 0.001, Cohen's d = 1.22), executive functioning task (SOC) ($F_{(4,88)}$ = 5.35, p < 0.001, d = -1.72), working memory task (SSP) ($F_{(4,88)}$ = 10.39, p < 0.001, d = -0.91), spatial working memory (SWM errors score) ($F_{(4,88)}$ = 5.71, p < 0.001, d = 1.54), spatial working memory (SWM strategy score) ($F_{(4,88)}$ = 4.31, p < 0.001, d = 0.61), and information processing (RVP) ($F_{(4,88)}$ = 9.64, p < 0.001, d = -1.55). Positive parameter estimates (effect sizes) for SWM and IED indices demonstrate higher scores but worse performance in FEP patients group, and negative parameter estimates for SOC, SSP, and RVP refer to lower scores and worse performance in FEP patients group.

Cognitive functioning characteristics presented in effect size units here are somewhat different compared to the values demonstrated before (Paper I, Figure 3): this is because we used only partly overlapping subsamples (i.e. here, the sample comprised FEP patients and CSs who had both cognitive functioning and MRI data). Nevertheless, the same trend emerged: FEP patients performed significantly worse than CSs on all measured neuropsychological tests, indicating broad impaired cognitive functioning.

6.3.3. Disease related cortical thickness and area differences

6.3.3.1. Group comparisons of CTh and CA

Brainmaps of the significance of group differences in CTh and CA were visualized by colour bar (Figure 6). Red/yellow colours encode the significance of thicker cortex (a) and larger surface area (b), blue colours encode the significance of thinner cortex (a), and grey for zero difference in FEP patients as compared to CSs.

In general, FEP patients had significantly thinner cortex compared to CSs in two clusters in the left superior frontal (size = 1283 mm^2 and size = 1193 mm^2, respectively) and in the same region in the right superior frontal gyrus (size = 5158 mm^2). In contrast, FEP patients had significantly increased CTh in the left temporal pole (size = 1051 mm^2) and in two areas of the right hemisphere: precentral (size = 1371 mm^2) and temporal region (size = 1107 mm^2). FEP patients had an increased CA in the left middlefrontal (size = 1055 mm^2) and in the right occipito-parietal (size = 2359 mm^2) anatomical area.
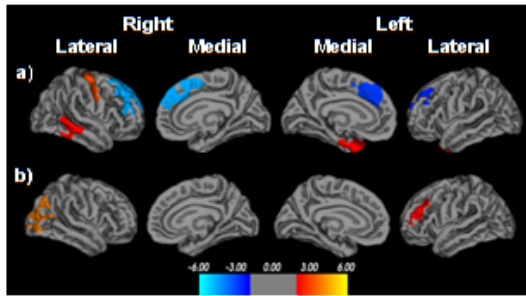
Figure 6. Statistical maps of right and left hemispheres lateral and medial views demonstrating significant cortical thickness (a) and cortical area (b) differences between FEP patients and CSs. The maps were produced from general linear models, comparisons were made controlling for the effects of age and gender. The *p*-values set at the FDR level 0.05 are presented in the colour bar (logaritmic value). Particular clusters, corresponding anatomical region names, cluster sizes, and P_{cw} values are presented in details in an Appendix (Table A1).

6.3.3.2. The associations of neuropsychological tests scores with CTh and CA

Neuropsychological tests scores were linked with brain morphological measures (CTh and CA) separately in the groups of FEP patients and CSs for associations and corresponding *p* values (Appendix, Table A2).

Figure 7 (a, b) shows spatially distributed statistically significant CTh difference maps indicating the contribution levels of brain regions identified by GLM analysis for each cognitive component.

Within the FEP patients group, there were significant negative linear correlations between CTh and IED reversal learning scores, indicating that worse performance was related to cortical thinning in the left fusiform, superior frontal, isthmus cingulate and rostral middle frontal as well as right superior frontal and posterior cingulate regions. The same trend emerged in both groups between CTh and SWM strategy and SWM errors scores, demonstrating associations of poor spatial working memory manipulation and strategy usage with widespread bilateral cortical thinning, predominantly in clusters which contained voxels from frontal, temporal, parietal, and cingulate gyruses. Most of these associations were also observed in the CSs. We also observed a significant positive correlation between better performance of the spatial planning test (SOC) and bilaterally thicker cortex of temporal gyrus clusters, though only in the CSs group. In contrast, sustained vigilance task (RVP) scores correlated positively with left hemisphere cingulate cortex parameters within the FEP patients group. Associations between CTh and spatial working memory task (SSP) scores were also observed, but did not survive corrections of multiple comparisons in either of the groups.

Figure 7. Statistical maps of right and left hemispheres lateral and medial views of partial correlations of cortical thickness with neuropsychological tests scores among FEP patients (a) and CSs (b). The maps were produced from general linear models, comparisons were made controlling for the effects of age and gender. The *p*-values set at the FDR level 0.05 are presented in the colour bar (logaritmic value). Particular clusters, corresponding anatomical region names, cluster sizes, and P_{cw} values are presented in details in the Appendix (Table A2).

IED, intra/extradimensional shift, SWM-errors, spatial working memory, errors score; SWM strategy, spatial working memory, strategy score; SOC, Stockings of Cambridge; RVP, rapid visual information processing.

Figure 8 (c, d) shows spatial *p*-maps of linear correlations between CANTAB scores and CA in a vertex-wise manner.

Among the FEP patients group, a diminished capability to perform set-shifting tasks was significantly correlated with a smaller cortical area of the left frontal hemisphere, and SWM strategy scores were significantly correlated with superior frontal and temporal pole clusters in the left hemisphere and a superior temporal cluster in the right hemisphere, indicating associations between poorer strategy usage (SWM strategy score) and smaller CA in these regions. The ability to retain spatial information and manipulate remembered items in working memory (SWM errors score) was significantly negatively correlated with temporal and frontal surface regions in the FEP patients group. A trend for similar correlations (lower performance, smaller CA) emerged among the CSs in the left superior and middlefrontal and superior parietal areas, as well as in the right hemisphere (clusters: pars triangularis and rostral middlefrontal). Working memory capacity was significantly negatively correlated with right hemisphere occipital areas for both groups. No significant CA parameter effects

were observed for the spatial planning and rapid visual information processing task after controlling for multiple comparisons.
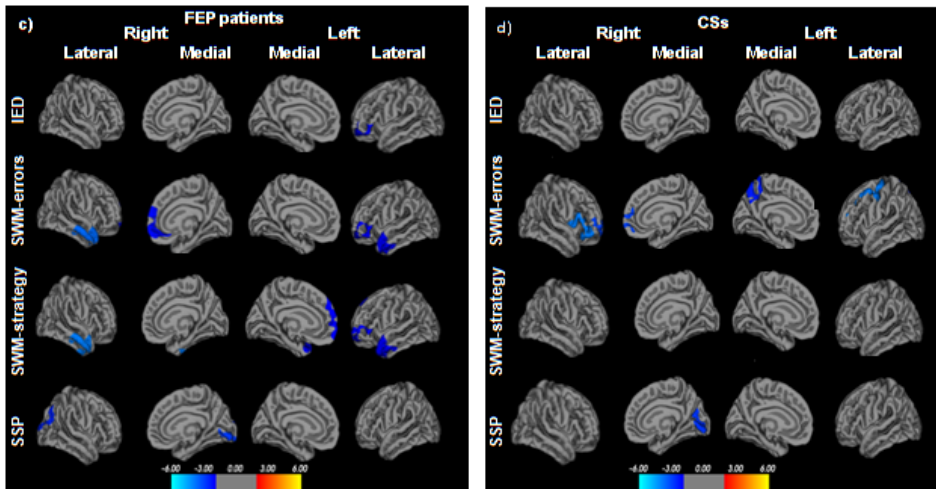
Figure 8. Statistical maps of right and left hemispheres lateral and medial views of partial correlations of cortical area with neuropsychological tests scores among first FEP patients (c) and CSs (d). The paramtres were derived from GLM, controlling for the effects of age and gender. The *p*-values set at the FDR level 0.05 are presented in the colour bar (logaritmic value). Particular clusters, corresponding anatomical region names, cluster sizes, and P_{cw} values are presented in details in the Appendix (Table A2). IED, intra/extradimensional shift, SWM-errors, spatial working memory, errors score; SWM strategy, spatial working memory, strategy score; SSP, spatial span.

6.3.3.3. Between-group differences in the associations of CTh and CA and neuropsychological tests scores

We previously demonstrated that several CTh and CA clusters' morphological parameters were associated with cognitive performance indices in both groups, and partial conformity emerged across the groups. However, to provide more specified information about how brain morphological (CTh and CA) parameters differentially contribute to cognitive performance heterogeneity in FEP patients compared to CSs, we conducted additional analyses. The results of the group-wise regression-analyses, where correlation coefficients derived from both group were contrasted, are in details demonstrated in the Appendix, Table A3.

Topographical maps (Figure 9) show spatially distributed group differences in the correlations between CTh (a) /CA (b) and cognitive measures.

FEP patients had significantly different cortical structure – cognitive function relationships compared to CSs, which primarily pertained to the frontal, temporal, and occipital lobes. The relationship of spatial planning (SOC) with CTh in the left enthorhinal and right middle temporal, temporal pole and

inferior parietal clusters as well as the relationship between the strategy usage (SWM strategy score) and right supramarginal cluster were significantly weaker in FEP patients.
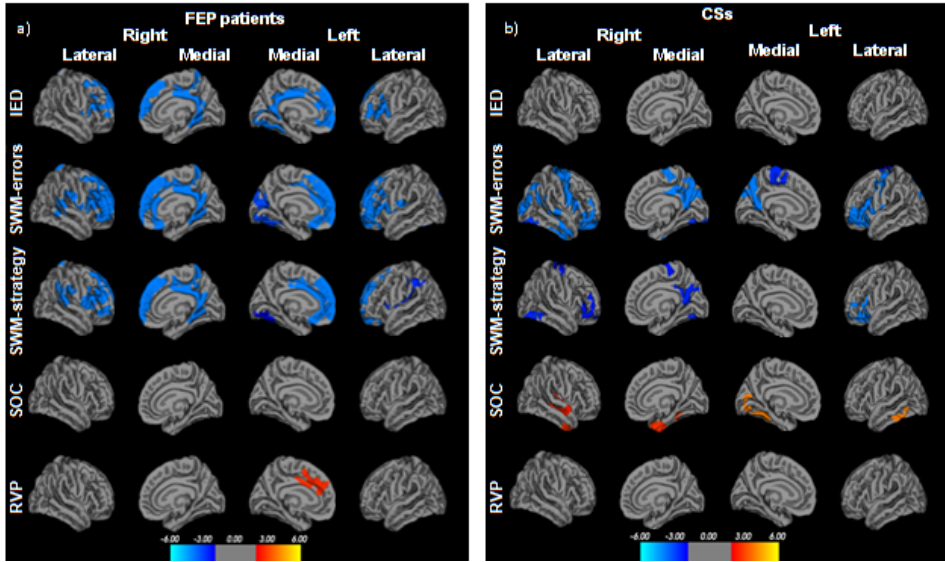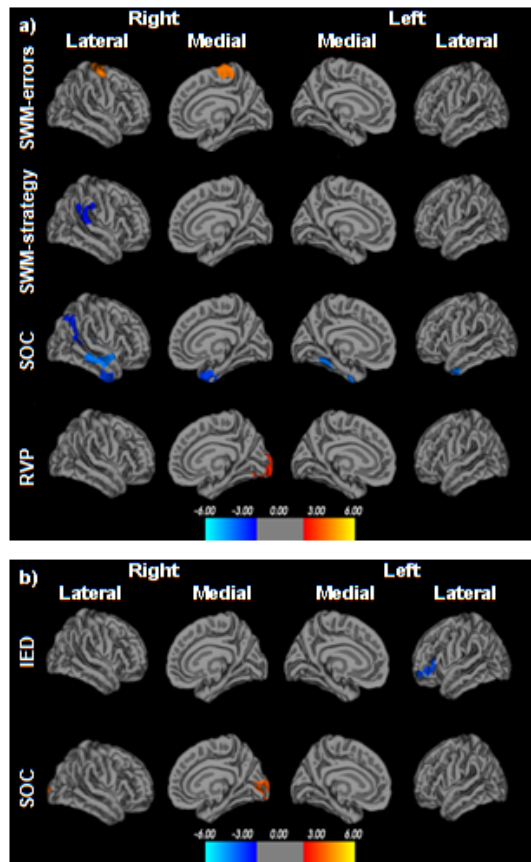

Figure 9. Statistical maps of right and left hemispheres lateral and medial views of partial correlations differences of cortical thickness (a) and cortical area (b) with neuro-psychological tests scores in FEP patients compared to CSs. Comparisons of FEP patients versus CSs brain-cognition relationship differences are taken from the GLM analysis. All comparisons were made controlling for the effects of age and gender. Significance is presented on a logaritmic (*p*-value) scale ($p < 0.05$, false discovery rate corrected), red–yellow indicates clusters where CANTAB test score-thickness (a) / -area (b) relationships are significantly stronger for the FEP patients; blue indicates clusters where the CANTAB test score-thickness (a) / -area (b) relationships are significantly weaker for the FEP patients. Particular clusters, corresponding anatomical brain region names, cluster sizes, and P_{cw} values are presented in details in the Appendix (Table A3). IED, intra/extradimensional shift, SOC, Stockings of Cambridge; SWM-errors, spatial working memory, errors score; SWM strategy, spatial working memory, strategy score; RVP, rapid visual information processing.

The relationship of spatial planning (SOC) with CTh in the left enthorhinal and right middle temporal, temporal pole and inferior parietal clusters as well as the relationship between the strategy usage (SWM strategy score) and right supra-marginal cluster were significantly weaker in FEP patients. In contrast, FEP patients demonstrated statistically significantly stronger relationship between working memory manipulation component (SWM errors) and CTh in the right paracentral cluster as well as between rapid visual information processing (RVP) and CTh in the right lingual cluster. There were also group differences in CA-cognition correlations for the set-shifting task (IED), with FEP patients having a statistically significant weaker association between test scores and CA in the left pars triangularis cluster as well as a significantly stronger relationship pattern between spatial planning (SOC) and CA in the right lateral occipital cluster.

7. DISCUSSION

The studies comprising the present thesis focus on characterizing the basic cognitive structure and profile of patients with FEP, emphasizing the view that cognitive deficit is a feature of the disease that has a neuroanatomical signature. Moreover, the present evidence suggests that there are broad as well as specific psychotic disorder-related deficits in different cognitive domains, which converge with the correlations of these domains with brain's morphological features. Furthermore, our results provide confirmatory evidence that there is relative stability in cognitive functioning over a six-month period among FEP patients and that there are relationships between clinical symptoms as well as demographic characteristics and cognition. In addition, our findings support the hypothesis of independence of self-perceived cognitive functioning from objective neuropsychological deficits in FEP patients.

Below is a detailed account of the implications of our findings.

7.1. Cognitive deficit as a core feature in first-episode psychosis (Paper I)

The objectives of the study presented in Paper I were to characterize the structure of the cognitive functioning as well as the cognitive performance profile and overall magnitude of cognitive impairment of FEP patients compared to healthy peers of similar age measured by a computer-based comprehensive cognitive test battery (i.e. PRM, SRM, PAL, IED, SOC, SSP, SWM, and RVP) derived from CANTAB.

Traditional neuropsychological batteries typically contain a heterogeneous set of tests, and many tests may not fit neatly into a single domain (Keefe & Harvey 2012). Therefore, the first aim of this study was to define the latent structure of the test battery currently being used.

There are two techniques (i.e. principal component analysis and exploratory factor analysis) which can be used to examine which combinations of features are appropriate for data, and for reducing the dimensionality of features. With regard to our sample composition (i.e. FEP patients and healthy subjects) and selected CANTAB tests scores, previous literature did not provide a well-grounded theory to base our analysis on. Under this certain circumstance, it is suggested to use PCA to reduce the number of variables whereas retaining as much of the original variance as possible (Conway & Huffcutt 2003). We relied on PCA as it is based on all of the variance in test scores rather than only tests' common variance, being thereby less hypothesis-free.

According to the results of the exploratory PCA and subsequent single group CFA we found that the selected CANTAB tests may group into two different cognitive factors in both FEP patients and healthy people. Whereas two relatively distinct factors (i.e. "attention/memory" and "executive factor")

appeared to be a tenable solution among controls, a single broad ability factor however was clearly evident among patients. Our results are in agreement with previous studies (Gladsjo *et al.* 2004; Dickinson *et al.* 2006; Burton *et al.* 2013) which demonstrated that inter-correlations of cognitive domains are higher for FEP patients than CSs. In other words, patients appeared to rely more heavily on general cognitive ability than on individual cognitive processes; or put differently, when FEP-related cognitive decline sets in, it tends to be pervasive and pull along all cognitive skills. In particular, the more homogeneous cognitive profile of patients may reflect a similar impairment of cognitive skills resulting from disease-related or disease-preceding processes. Furthermore, we replicated the findings of a confirmatory factor analysis (CFA) of FEP patients cognitive test scores (Leeson *et al.* 2009a), revealing that cognitive functioning in control and patient groups could not be explained by similar measurement models.

Once the latent structures were defined by a sequence of factor analytic models, we extended the analysis by formally testing for the presence or lack of MI of the constructs across subgroups. MI in psychology is obtained when the relations between observed scores and latent constructs are identical across relevant groups (Drasgow 1984). However, because measuring instruments are often group-specific in the way they operate, baseline models could not expected to be identical across groups.

Our results indicate that the cognitive differences between FEP patients and CSs may not be limited to quantitative (i.e. nomothetic) variability, but there may also be qualitative (i.e. structural) differences. Regardless of the MGCFA results which indicated that the cognitive domains could be constructed in the same way in controls and patients (configural invariance held for both one and two- trait models), the nature of the relationships between observed test scores and their purported underlying constructs tended to be dissimilar. This suggested that the latent factor scores were not comparable because observed test scores were probably influenced by characteristics other than the latent ability. In other words, patients' cognitive profiles were less diverse than those of CSs and this may be a result of neurodevelopmental or psychosis-related processes which impacting cognitive domains in particular ways.

Results of this study emphasizes the importance of establishing MI, which can cover nuanced group differences that might otherwise remain undetected.

In addition, our results reinforce the view that there is broad cognitive deficit associated with FEP. At the group level patients exhibited worse performance than CSs on all measured CANTAB subtest scores, indicating substantial cognitive impairment. According to our results, impairments were present in several aspects of attentional functioning (including set shifting and sustained attention), speed of processing information, working memory (including storage and manipulation), visual and episodic memory, and executive functioning. Executive functioning, set shifting, and processing speed emerged as the most affected cognitive domains, followed by working memory, spatial memory, episodic memory, and visual recognition memory, in patients' group. Performance differences between FEP patients and CSs remained significant even

after adjusting for years of education, age and gender, which is consistent with a number of others studies (Heinrichs & Zakzanis 1998; Townsend & Norman 2004; Dickinson *et al.* 2007).

Our findings provide supportive evidence for the qualitative and quantitative cognitive functioning impairment as core feature of many patients with chronic psychotic disorder as it is present already at the early stage of the disease.

7.2. The course of cognitive functioning after first-episode of psychosis (Paper II)

The second study provides comprehensive cognitive functionality characterization of patients at the early stage after the FEP in terms of rank-order and mean-level stabilities as well as MI.

Measurement of cognitive functions at baseline and at six month period allowed an evaluation of their variation over time and their association with clinical and demographic indicators. In addition, correspondence between subjective and objective cognitive functioning was evaluated.

One can suppose that cognitive abilities demonstrate highly stable course during the six month period in each individual and distinguish him or her from other individuals. Otherwise, cognitive abilities may be also subjects to change.

Detecting change in individual patient's neuropsychological performances requires the use of appropriate methods. There are two specific types of change over time one can focus on: rank-order change (i.e. change in an individual's cognitive performance relative to other individuals') and mean-level change (i.e. changes in average performance over time). The two are independent of each other. For example, perfect rank-order stability may characterize groups with substantial mean-level change, because individuals often change in the same way.

There is limited information available about the stability of the CANTAB cognitive battery tests for different groups of patients, and especially for patients with FEP.

In terms of mean-level trends, our results appeared to show that spatial recognition (PRM) and episodic memory (PAL) declined over a six month period. In contrast, mental flexibility (IED), executive functioning (SOC), manipulation with items in one's working memory (SWM), and information processing speed (RVP) seemed to improve. We did not detect any evidence for changes in pattern recognition memory (PRM) or working memory capacity (SSP). Our results tend to corroborate previous suggestions (Censits *et al.* 1997; Rund 1998; Heaton *et al.* 2001) that there is no broad progression of cognitive deficits during the initial stages of chronic psychotic disorders. This supports the hypothesis of a primary neurodevelopmental deficit (Weinberger 1987; Murray & Lewis 1988; Bora 2015).

Moreover, previous researchers have also demonstrated cognitive improvement in CSs and FEP patients (Nopoulos *et al.* 1994; Hoff *et al.* 2005;

Rodríguez-Sánchez *et al.* 2008). However, one should consider the cognitive process being measured and how this may change with repeated assessments (Heilbronner *et al.* 2010). Measures of executive functioning generally show lower mean-level consistency. Notably, tests of executive function (IED, SOC, SWM) rely considerably on novelty. Thus, cognitive improvements in FEP patients during the early course of the disease may be related to a practice effect, a common process shared by CSs, and therefore increased mean change levels may not reflect real cognitive improvement, but rather stability or deficit (Goldberg *et al.* 2007).

In terms of the paired association learning test (PAL), our results are in line with previous studies that showed a decline in this particular cognitive function during the early phases of chronic psychotic disorder (Bilder *et al.* 1992; Hoff *et al.* 1999). In contrast, studies of FEP patients that have used memory and learning subtests from the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Cognitive Consensus Battery (Nuechterlein *et al.* 2004) have detected improvements in the performance of visual learning and working memory tests over a six month period (Olivier *et al.* 2015) or stable mean-levels over a year (Benoit *et al.* 2014). We speculated that inconsistent findings between these studies could be owing to them having patient groups with different symptom severities, using a different cognitive functioning measurement methodology, and employing different statistical methods.

The results concerning our analyses of the rank-order coefficients revealed high stability (r = 0.80 to 0.94) in the rank ordering of patients over time. Former studies using subtests from CANTAB battery have reported moderate to high (r = 0.40–0.84) stability indices over four weeks to three years for patients' samples with schizophrenia or FEP (Leeson *et al.* 2009b; Barnett *et al.* 2010). However, it is important to remember that test-retest correlations can vary depending on the sample assessed, and the amount of time between test and retest (shorter retest intervals lead to higher reliability coefficients) (Duff 2012).

In longitudinal models, a high degree of rank-order stability of a characteristic indicates either that individuals did not change much over time or that individuals changed over time, but in more or less the same way (i.e. everyone decreased or increased to the same extent). Therefore, a high rank order stability limits our possibility to identify factors in which individuals differ and that could have an influence on the characteristics.

The rank-order stability estimates can be also seen as the lower-bound reliability estimates of the CANTAB subtests: their actual reliability can only be equal or higher, because the observed stability may have also reflected real change over time.

The magnitude of the observed stability estimates from our study supports the CANTAB as a reliable instrument to assess cognitive functioning in FEP patients.

In mental health care, both clinical and scientific decisions for patients' cognitive functioning are frequently based on within-subject comparisons of neuropsychological test scores of the same battery at different points in time. To

establish the validity of test score comparisons over time, longitudinal MI should be established.

To the best of our knowledge, this is the first report to investigate the structure of the CANTAB tests ICSs (i.e. deviations from individual's predicted scores at follow-up) among FEP patients over six-months period. In order to see which patterns would emerge, PCA was performed. The first dimension identified by the PCA was assumed to reflect an underlying broad cognitive ability trait.

The plausibility of the model was estimated using CFA, which confirmed that the empirical model in which measures of CANTAB subtests were loaded on one broad ability domain demonstrated an excellent fit for the data. The replicability of the cognitive traits structure between the two testing occasions was evaluated using multi-group (groups represented occasions) confirmatory factor analysis.

Employing CFA, we tested whether the parameters of the factor model are different across consecutive measurements, similarly to how MI was tested across FEP patients and CSs.

Inspection of the goodness-of-fit statistics for the one-factor model of FEP patients indicated the model was a reliable representation of the data at the two time points. These results are consistent with our previous study (Haring *et al.* 2015b), which examined the potential relationships of an identical set of variables between CSs and FEP patient samples. This suggested that, in contrast to CSs, a broad latent ability factor model was the most appropriate representation of the relationships between the neuropsychological variables among FEP patients. This is consistent with the findings in previous studies that used a different kind of neuropsychological tests (Censits *et al.* 1997; Dickinson *et al.* 2006) or the same test battery (Leeson *et al.* 2009a). The finding of invariance of the factor loadings, provides empirical evidence to support the assumption that test scores measured an invariant psychological trait, and that latent factors had the same meaning after six month among FEP patients. However, the observed scores' intercepts were not invariant between the two assessments, and misfit of scalar invariance suggests that comparisons of the factor means should be interpreted with caution.

Overall, these findings suggest that when the FEP patients' neuropsychological performance is compared on a timeline, CANTAB subtest scores should be used.

Although heterogeneity in terms of mean-level change and high rank-order stability emerged over a six month period, it is of theoretical, practical, and clinical importance to examine how individuals differed from each other, and what variables, if any, could explain such individual differences.

Of the demographic and other characteristics taken into account, age and education seemed to have by far the most important impact on cognitive performance. Furthermore, one of the most consistent finding is that men are younger than women at the onset of a chronic psychotic disorder (Eranti *et al.* 2013). In the present study, although men's mean age at onset was indeed lower

compared to women, the difference was not significant. According to our results, being younger had a significant correlation with the paired associate learning subtest change scores (PAL), which is consistent with previous results among healthy control subjects (desRosiers & Ivison 1988). A longer time in education had a correlation with performance change at the processing speed task (RVP).

Gender differences in cognitive functioning are well known among healthy individuals. In general, women tend to perform better than men at tasks measuring verbal abilities, whereas the opposite is the case regarding visuospatial skills (Halari *et al.* 2005). However, a recent review by Hyde (2016) suggests that males and females are quite similar in terms of most, but not all cognitive variables, and gender differences can vary substantially in magnitude with ages and the context in which the measurements occur. Gender differences in cognitive functioning among patients with FEP are a controversial issue (Albus *et al.* 1997; Hoff *et al.* 1998; Ittig *et al.* 2015). In this study, men made less reverse errors at the set-shifting task (IED), had better spatial executive functionality (SOC), higher spatial span length (SSP), and used strategies (SWM) more effectively than women. Regarding visual (PRM) and spatial (SRM) recognition memory and paired associate learning (PAL), as well as information processing (RVP), men and women performed equally. A similar trend in gender differences was traceable among the ICSs of the tests (that is, changes in scores over time as opposed to their levels at baseline). It is worth mentioning that we used computerized tests that measure performance based on visuospatial abilities, and our findings on gender differences are in accordance with previous reports of the generally better performance of male patients in these domains (Albus *et al.* 1997). Among patients with schizophrenia, Perlick *et al.* (1992) found that women had lower performance at attention tasks, and Roesch-Ely *et al.* (2009) demonstrated that women scored lower than men on executive functioning, and working memory tasks. However, some previous literature has reported lower overall cognitive performance among males with schizophrenia (Goldstein 1988; Seidman *et al.* 1997) or a lack of gender difference among schizophrenia, and FEP patients (Hoff *et al.* 1998; Ittig *et al.* 2015).

There may be several factors that contribute to the heterogeneity of the results of these studies. For example, men and women may vary in their symptoms of expression over the course of illness and in response to treatment, and differences may be related to the selected study sample (e.g. patients with chronic illness or FEP, and early- or late-onset schizophrenia patients) (Mendrek & Mancini-Marïe 2016).

In addition, we suspected that aspects of psychopathology might differentially account for any differences in cognitive functioning between the two test occasions.

The associations between illness-dependent symptom dimensions and cognitive functioning have been widely studied, and the relationship between symptom dimensions and cognitive domains varies across groups of symptoms. Studies have demonstrated that negative symptoms and disorganization are

associated with cognitive functions, with more severe symptoms related to poorer cognitive performance (Harvey 2013). Overall, findings suggest that cognition is more closely associated with negative than positive symptoms (Heinrichs & Zakzanis 1998; Nieuwenstein *et al.* 2001).

It is worth emphasizing that the levels of *changes* in symptom dimensions severity were calculated and used in the further analysis in our study. According to our results, patients' cognitive functioning change across consecutive measurements could not be attributed to changes in their negative symptoms. Consistent with our finding, Bell and Mishara (2006) demonstrated that changes in negative symptoms did not predict changes in cognition, and concluded that negative symptoms could not directly cause cognitive impairment or *vice versa*.

With regard to the relationships between positive symptoms and cognitive performance, the literature is less consistent. The meta-analytical review of Dominguez *et al.* (2009), suggested only a slight negative correlation occurs between processing speed and positive symptoms among patients with schizophrenia, whereas recent works by Olivier *et al.* (2015) and Trampush *et al.* (2015) found that a decline in the positive symptom dimension score of FEP patients was related to improvements in speed of processing, attention/ vigilance, working memory, verbal memory, verbal and visual learning, as well as reasoning and problem solving tasks. Our results revealed that improved performances at spatial working memory and processing speed tests, were associated with diminished positive symptom scores.

In addition, we demonstrated clinically meaningful and statistically significant correlations between AP dose and BPRS ratings. The results indicated that patients with more severe treatment-refractory symptoms, received higher doses during the both assessment. During the six month period as patients continued to recover, psychopathology scores decreased, and as such AP doses were gradually reduced. We found potential impact of changes to CPZ equivalent dosage on frontal lobe functionality: reduced doses appeared to mediate an improvement in working memory capacity (SSP span length), as well as change towards enhanced executive functioning (SOC problem solving). Previously, Sota and Heinrich (2003) also found that CPZ equivalent dose was negatively related to learning and recall abilities. For that reasons, the suggestion was made for clinicians to carefully consider changing drug doses in terms of quantity and or frequency it is taken, when psychopathology severity has declined, and use a lowest-dose strategy whenever possible. However, an individual approach is recommended whenever any antipsychotic dosage change is considered.

In addition, our data highlighted the need to evaluate additionally patients' subjective experiences of cognitive functioning to provide more comprehensive view about the clinically important dimension (i.e. cognitive impairment) of the disorder. There is little empirical information with respect to the subjective cognitive complaints in relation to objective neuropsychological test performance among healthy population compared to patients with chronic psychotic disorder. However, the relationship tends to be stronger for the CSs ($r = 0.31$,

$p = 0.05$), and nonsignificant for patients with schizophrenia (Medalia *et al.* 2008; Sellwood *et al.* 2013). Previous studies have demonstrated that self-assessed cognitive dysfunction is also prevalent among patients with FEP (Moritz *et al.* 2000; Homayoun *et al.* 2011). Results of the present study are in line with others (van den Bosch & Rombouts 1998; Zanello & Huguelet 2001; Chang *et al.* 2015), in supporting the hypothesis of the independence of self-perceived cognitive disturbances, from objectively measured cognitive impairments, among FEP patients.

In the literature, several explanations have been proposed for this discrepant finding, which is not unique for the FEP patients and which is often observed in clinical neuropsychology. Psychological factors (such as anxiety, depression, dysphoria, personality traits), as well as physical factors (such as fatigue, pain), can impact subjectively perceived cognitive functioning above and beyond neurolopsychologically determined cognitive status (Sweet 2000).

Moreover, the findings suggests that patients' subjective perceptions of their cognitive function have a different theoretical basis than objective indicators, as patients do not conceptualize their cognitive functioning in terms of distinct cognitive domains, as clinicians and neuropsychologists do (Stip *et al.* 2003). The domains assessed by neuropsychological tests may have little overlap with the everyday experience on which patients base their self-report. In the other words, the conditions under the neuropsychological tests are assessed may be different from real-life demands. During the neuropsychological testing patients are encouraged to do their best and cognitive tests attempt to assess subjects maximal level of functioning, whereas how subjects cope with daily life reflects their typical level of functioning (Salthouse 2012). Furthermore, patients may be able to perform well during a relatively short test period, but their daily functioning may be compromised and give rise to cognitive complaints. At the same time, neuropsychological tests may accentuate the existence of deficits, without affecting daily life functioning.

Furthermore, the discrepancy may occur owing to variations in methodology (differences in the subjective cognitive scales employed) and study design. We used the SWN-K-E "Cognitive Functioning" subscale that comprises four simple statements about self-perceived cognitive functioning. This subscale did not seem to appropriately correspond to the specific cognitive test scores obtained using the CANTAB. In addition, one possible explanation for the low inter-correlation between measurements might be the different nature of the evaluations. The CANTAB tests were all visually presented to subjects and high performance relied on visual information processing, whereas the subjectively perceived cognitive functioning items might refer to much broader indicators including among others verbal and arithmetical abilities, as well as semantic processing.

However, both methods (SWN-K and CANTAB subtests) have been validated among psychotic populations (Elliott *et al.* 1995; Naber *et al.* 2001; Joyce *et al.* 2005; Leeson *et al.* 2009a; Haring *et al.* 2013, 2015b).

It could also be argued that awareness of one's own cognitive deficits could be affected by awareness of one's condition as a mentally ill person, and schizophrenia is frequently accompanied by a lack of insight (Pini *et al.* 2001). However, the literature suggest that subjective and objective cognitive tests might have unique contributions, and thus both should be implemented to give a broader perspective about a patient's cognitive functioning to determine appropriate clinical practice regarding assessment and management of cognitive problems.

7.3. Brain morphological correlates to cognitive functioning (Paper III)

The third part of the thesis focused on brain MRI correlates of cognitive function in patients with FEP and CSs. Our aims were to investigate how the cognitive deficits of FEP patients compared to CSs are reflected in both CTh and CA morphological parameters.

To attain our main objective, we first replicated the earlier findings (Bilder *et al.* 2000) that cognitive impairment in FEP patients is substantial, amounting from moderate to high effect size, and cuts across various neuropsychological measures (i.e. set shifting, executive functioning, working memory, spatial working memory, and information processing tasks).

Thereafter, differences in CTh and CA morphological parameters were evaluated between the FEP patients and CSs, and our analysis revealed significant bilaterally reduced CTh in the middle- and superior-frontal and left anterior cingulate cortex areas of FEP patients. These findings are in line with studies by Narr *et al.* (2005) and Fornito *et al.* (2008). However, our finding of thickened clusters of cortex in the left temporal pole and right middle and inferior temporal cortex in FEP patients compared to CSs contradict previous research, which has found reductions in left and right temporal poles or no morphological changes at all in these brain regions (Vita *et al.* 2006; Roiz-Santiáñez *et al.* 2010). We suggest that variations in quantitative assessment techniques, as well as use of different covariates and significance thresholds might explain these inconsistencies, in addition to either finding reflecting type 1 error. Previously, Takayanagi *et al.* (2011) used the automated surface-based approach provided by FreeSurfer, and demonstrated CTh reduction in 52 FEP patients compared to 40 CSs which was most prominent in the prefrontal and temporal cortices (the between-group comparison consisted of the mean thickness of the region of interest). In our study, cortical reconstructions were performed using a similar methodological approach, except that we used an entire cortex surface-based cluster analysis. Using the same methodology (as we did), Ansell *et al.* (2015) demonstrated that a non-affective FEP patients group (*n* = 27) exhibited pronounced cortical thinning compared to CSs (*n* = 27) in frontal regions and did not find overlapping patterns of reduced cortical thickness in the left temporal pole or in the inferior temporal gyrus. Furthermore, they characterized the diffe-

rential effect of first and second generation antipsychotic (FGA and SGA) medication on CTh parameters and found that patients treated with SGA displayed increased CTh in frontoparietal regions compared to patients treated with FGA, and that the SGA group had higher CTh in the pre- and post-central sulcus than the CS group. Our notably larger study, in which all the patients (*n* = 63) were treated with SGA, also found increased thickness in the right precentral cluster.

The reasons for the increased cortex thickness clusters among the FEP patients found in our study are not entirely clear. One can assume that increased proinflammatory status might represent a compensatory effect during the early stage of the disease. Doorduin *et al.* (2009) and van Berckel *et al.* (2008) reported increased activation of microglia cells, especially in the temporal lobes, among patients with early-stage schizophrenia compared with CSs. Furthermore, astrocytes can be activated by proinflammatory cytokines (e.g. interleukins) and growth factors (e.g. epidermal growth factor) that may lead to cellular hypertrophy and astrocyte proliferation, which could increase cortical thickness (Liberto *et al.* 2004). We have demonstrated previously, using the partially same participants, that antipsychotic-naïve FEP patients exhibit alterations in cytokine and growth factor levels (Haring *et al.* 2015a). The CTh increase in the temporal region that we report in the current study, may be particularly relevant to the processes one can see during the very early stage of the disease.

Furthermore, our results suggesting enlarged surface area clusters in the left middlefrontal and right occipito-parietal areas, and thus did not replicate previous findings of surface area reduction or no change in these cortical parameters in FEP patients (Crespo-Facorro *et al.* 2011). Possible explanations for such heterogeneity among results are the differences in sample sizes and or composition; our sample was relatively large among the studies of the kind and it was also gender-balanced. For example, female patients with schizophrenia are underrepresented in the literature (Tamminga 1997), whereas males and females were equally represented in both groups of the present study.

Similarly to the present findings, previous structural MRI studies have suggested that FEP patients brain volume loss, although widespread, is not homogeneous (Keshavan *et al.* 2005; Vita *et al.* 2006), antipsychotic treatment may have impact on brain tissue (Keshavan *et al.* 1998) and chronic psychotic disorder itself demonstrate a non-static nature (Shenton *et al.* 2001). It has been argued that cortical thinning (Rimol *et al.* 2012) or surface area reduction (Sanabria-Diaz *et al.* 2010) is the most important factor in volume reduction, with some suggestion that cortical folding differences could account for the some of the regional differences (Palaniyappan *et al.* 2011). Neuropathological studies suggest that the cellular changes associated with these anatomical properties affect diverse tissue compartments in a regionally heterogeneous way. Cellular shrinkage, reduction in dendritic arborization, an increase in myelination of GM and decreased interneuronal neuropil in the prefrontal cortices, and disruptions in WM bundles connecting cortical association areas, are the

pathological mechanisms most likely related to cortical thinning and impaired connectivity and functionality (Selemon *et al.* 1998; Selemon & Goldman-Rakic 1999; Casanova *et al.* 2005).

Hence, it may be that the measurements of CA and CTh recorded in this study reflect structural aspects other than the columnar organization of the cortex. However, these findings may indicate that changes in the anatomical properties of the cortical mantle underlie the GM volume variations and that it is necessary to explore CTh and CA separately to better understand the neuro-biological mechanisms associated with brain abnormalities among FEP patients.

In addition, data presented in this thesis provide insight into the relationships similarities and differences of the FEP patients and CSs neurocognitive performance using the CANTAB tests scores with CTh and CA parameters. A number of studies have previously examined correlations between cognitive performance and cortical volume, CTh and or CA in FEP patients (Salgado-Pineda *et al.* 2003; Minatogawa-Chang *et al.* 2009; Gutiérrez-Galve *et al.* 2010; Crespo-Facorro *et al.* 2011; Hatton *et al.* 2012, 2013). With respect to the localized regions of the cerebral cortex where thickness or area correlates with cognitive performance, the findings of the present study are consistent with these of above-mentioned studies, indicating that a diffuse pattern of asymmetrically reduced CTh and CA (predominantly encompassing frontal, temporal, parietal and cingulate cortices) was correlated with lower attentional set-shifting (IED error score), a diminished capability to manipulate items in spatial working memory (SWM error score) and strategy usages (SWM ineffective strategy usage), and a thicker left cingulate cortex was correlated with better information processing (RVP score or sensitivity for detecting sequences) among the FEP patient group. In addition, in the current study, an inverse correlation between working memory capacity (SSP) and CA was observed for both groups in the pericalcarine/lingual/occipital region, with a thinner cortex being associated with better performance. Findings such as this require further investigation with larger samples of subjects.

In general terms, although the association patterns somewhat overlapped, there was some heterogeneity between the groups and bilateral asymmetry in both groups. Previous studies have also shown that some brain structure/neuro-cognitive associations tend to be specific to FEP patients (Toulopoulou *et al.* 2004; Cocchi *et al.* 2009; Minatogawa-Chang *et al.* 2009; Crespo-Facorro *et al.* 2011; Ehrlich *et al.* 2012; Hatton *et al.* 2013) and our study provides comple-mentary findings of neuropsychological function-brain structure association alterations in FEP patients compared to CSs which may be due to a mixture of genetic, neurodevelopmental and environmental effects. Alterations in structural measurements suggest disturbances in brain maturation, supporting the neuro-developmental hypothesis of schizophrenia pathophysiology (Weinberger 1987; Murray & Lewis 1988). Moreover, it has been argued that structural and functional changes seen in patients with chronic psychotic disorder may be a consequence of disturbed brain regenerative capacities (Falkai *et al.* 2015),

which may be incorporated with epigenetic dysregulation, which is involved in neuronal plasticity mechanisms (Hasan *et al.* 2013).

Our results agree with the suggestion that neuroanatomical/cognitive ability alterations are not limited to individual brain regions, but rather affect wider neural systems (Friston 1998) and that besides the prefrontal dysfunction, other brain regions may be invoked in a compensatory response to cognitive demands in FEP patients, which is similar to what has been suggested for schizophrenia patients (Tan *et al.* 2007).

However, there is a growing body of evidence suggesting that a disturbance in connectivity between different brain regions, rather than abnormalities within the separate regions themselves, are responsible for the clinical symptoms and cognitive dysfunctions observed in the pathophysiology of the disorder (Friston 1998; Bassett *et al.* 2008; Stephan *et al.* 2009), and according to the results of the current study, we hypothesize that the cortical parameters that contribute to variability in the functions of sustained attention, spatial working memory, spatial planning and set-shifting mental flexibility in healthy individuals may be abnormal in FEP patients.

Our study strengthens the evidence for an altered relationship between disease-related changes in brain morphology and clinically important cognitive difficulties in FEP patients.

7.4. Methodological issues and limitations

Before summarizing the results coming out of this thesis, the following methodological issues, participant samples characteristics and limitations should be considered.

First, the recruitment of subjects was based on opportunity rather than random sampling. The clinical sample was restricted to a group of patients that were clinically stable and willing to participate in the testing. Subjects in the control group came from a sub-population and results may not be extrapolatable to the general Estonian populace. Our findings may thus not reflect the overall cognitive characteristics of patients with FEP in Estonia or beyond. It must be noted, however, that the sample was relatively large in the context of typical sample sizes in the research area.

Second, the recruited patients were virtually heterogeneous in terms of diagnosis, medication, and duration of untreated illness – something which is difficult to avoid among any sample of FEP patients. Nevertheless, patients were at the early stage of the chronic psychotic disorder which allowed to diminish confounding effects of chronic condition and/or continuous treatment impact. Potentially, antipsychotic medications could be influencing cognitive function, although how and to which extent is still entirely unknown.

Whereas all atypical antipsychotics share serotonin/dopamine antagonism, they vary notably in their affinity at other receptors, including cholinergic, muscarinergic, serotonergic, adrenergic, and histaminergic receptors with a mix

of agonist and antagonist effects (Stahl 2013). As most neurotransmitter activity is regulated by multiple other systems, it is hard to distinctly estimate the specific effects of particular antipsychotic drugs. Furthermore, because of the naturalistic study design some of the patients received additionally mood stabilizers or antidepressants and patients were treated with various antipsychotic medications and when clinical need occured changes were made in doses or specific active substance selections. In addition, majority of the patients were engaged in psychotherapeutic intervention. These conditions were not taken under control in the analyses.

Moreover, we did not exclude participants with comorbid conditions, for example cannabis use in the previous anamnesis as attempt was made to investigate natural cohort of patients with FEP.

Third, to reliably identify the profile and pattern of cognitive deficit in FEP patients, it is essential to have a comprehensive battery of neuropsychological tests that is sensitive to specific as well as general cognitive impairment. However, the findings of differential deficits should be interpreted in the context of the psychometric limitations of the neuropsychological tests (i.e. their ability to measure specific cognitive processes) (Krabbendam & Jolles 2002). Nevertheless, the use of traditional clinical neuropsychological measures of cognition among patients with psychotic disorder has the advantages because of normative data and standardized administration, and remains the standard for cognitive assessment in clinical practice. In addition, when generalizing the findings over studies, one should be aware that different studies used different neuropsychological tests to assess the same cognitive function. It is noteworthy that there is a need to differentiate studies that used general ability scores versus individual neuropsychological test scores when comparing FEP patients to CSs, over time or to brain morphological parameters.

Forth, the current study did not assess the premorbid cognitive functioning of the patients as we lacked properly adapted existing instruments in Estonian. Of course, a proper assessment of pre-morbid cognitive abilities would require early testing of the general population as it is not known at that point who will develop a psychotic disorder.

Fifth, we did not control intra-individual factors that may influence testing or test-retest consistency, such as poor motivation, fatigue or cigarette smoking prior to the CANTAB test sessions.

Sixth, several statistical issues associated with conducted analysis should be mentioned. The limited (in absolute terms) sample size may have reduced statistical power for the analyses. We admit that patients were at the early stages of the illness when cognitive performance was evaluated, so results are not necessarily generalizable for different follow-up periods. In addition, we adopted the vertex by vertex whole brain analysis in order to assess group differences in the CTh and CA parameters and the extent to which cognitive performance scores were related to brain morphology across GM tissue. To establish significant differences cluster-defining threshold (thresholding criteria 0.05) and FDR criteria (i.e. correction for multiple comparisons, $p < 0.05$) were

implemented. However, it is important to note that above-mentioned statistical methods could not avoid entirely false positive results. In addition, as we correlated cognitive performance scores (which may have state-related nature) with brain structure parameters (which are rather trait-related variables) our findings might be inclined to false negative results, as cognitive performance is more dynamic than brain structural changes.

Finally, we reported linear correlations between the cortical morphological parameters and cognitive functioning, but it is important to acknowledge the possibility that such associations may not follow a linear relationship (Hartberg *et al.* 2010; Hatton *et al.* 2012). Furthermore, we should be aware of the inescapable fact that correlational research does not tell us that there is causality between variables, but rather that they are somehow related. It should also be emphasized that measurements of CTh or CA did not directly reflect functional activation during task performance. Nonetheless, if a set of cortical regions show significant thinning and it is known that those areas are interconnected within the particular brain cognitive network, it is reasonable to conclude that certain cortical layers and cell types are relevant for particular cognitive function (Makris *et al.* 2006).

Despite these limitations, our research has some strengths, mainly related to the natural FEP patients sample (we have gathered a well characterized study material on a group of patients that is challenging to include in research), the longitudinal design used to evaluate changes in cognitive functioning over time, and the low level of drop-outs by the follow-up period.

7.5. Clinical relevance

Despite the potential limitations discussed above, we believe the present thesis offers interesting results that are useful in everyday psychiatric practice.
Cognitive impairment is a core feature of schizophrenia, and the importance of neuropsychological assessment both in research and clinical practice cannot be overestimated. Our findings show, in line with earlier research, that there is evidence for a generalized cognitive deficit in FEP.

Our findings have practical significance for the broader use of neuropsychological tests for assessing cognition at the early stage of psychotic disorder. According to our results we recommend that assessments which use CANTAB could not compare individual FEP patient' and CSs in terms of their mean latent cognitive factors because the underlying structural relations among the cognitive tests were different between the groups (i.e. FEP patients *vs.* CSs) and within the group between two time point (i.e. baseline and follow-up testing occasion), the analyses should be restricted to differences in the subtests levels.

Although no specific „neurocognitive profile" exists for psychotic disorders (Mohamed *et al.* 1999; Bilder *et al.* 2000) and the assessment may not be helpful for the diagnosis, it has significant contributions to understanding individual patient' cognitive functioning and the course of the impairment, be-

cause it has been suggested that different patterns of neurocognitive dysfunction could contribute to the heterogeneity of the disease and its variable functional outcome (Holthausen *et al.* 2002).

Among FEP patient particular attention should be paid to cognitive impairment when defining the therapeutic strategy and rehabilitation programs.

The controversial cognitive benefit of typical and atypical antipsychotics (Keefe *et al.* 2007) has led to the search for alternative pharmacological mechanisms to enhance cognitive function (Keefe *et al.* 2013). Although potential pharmacological targets have been identified (i.e. cholinergic, dopaminergic, GABA-ergic, glutamatergic agents, alpha-7 nicotinic receptor agonists), to date, however, no drug has been approved for this indication (Harvey 2013).

In addition, cognitive remediation interventions have generated considerable interest as these methods are far less costly than pharmacologic treatment and are likely to be safer. This includes methods to train or restore cognitive function and compensatory techniques through modifying cognitive domains of attention, working memory, executive functioning as well as planning with the goal of durability and generalization (Wykes *et al.* 2011). Several studies and meta-analysis suggest that cognitive remediation produces small-to-medium effect size improvements in cognitive performance, and when combined with any psychiatric rehabilitation (e.g. supported employment, vocational rehabilitation and social skill training), also helps patients achieve better functional outcomes (McGurk *et al.* 2007b, 2007a; Wykes & Huddy 2009; Wykes *et al.* 2011).

7.6. Implications for further research

We believe that our work has drawn attention to the need for further validation of the CANTAB on larger populations, through more longitudinal period, between patients groups with different disease duration and to investigate the stability of the structure of cognitive functioning among patients with chronic psychotic disorder cross-culturally.

With regard to MRI study, our results support a viewpoint's that brain GM alterations are an early feature of the pathogenesis of the chronic psychotic disorder. The mechanisms that underlie these alterations, the nature of these alterations and causal relationships between the brain morphology and cognitive functioning require further research. Moreover, efforts should be made to translating MRI research results (i.e. detection and monitoring of brain morphometric alteration and progression) into clinical practice to provide more reliable identification of patients individual-specific quantification of affected brain regions.

Our future investigations will be associated with the ongoing longitudinal project related to our FEP patients group. Additionally, attempts are made to recruit a sample of long term schizophrenia patients and individuals with at genetic risk for psychosis/schizophrenia or any prodromal signs to investigate in

a comprehensive manner their cognitive functioning (dis-)similarities. Furthermore, disease related whole-body biomarker level alterations, particularly characteristics of inflammatory, oxidative stress and metabolism state as well as links between biomarker levels and cognitive functioning are of our interest.

The real challenge for clinical psychiatry and neuroscience will be to use comprehensive advances in genetics, biochemistry, imaging and cognitive science in conjunction with symptom descriptions to provide a cognitive- and biomarkers based approach that would supplement the symptom-driven diagnostic process and help defining the therapeutic strategy for individual patient.

CONCLUSIONS

This dissertation presents a comprehensive investigation into the cognitive impairments among the FEP patients. The results suggest the following conclusions:

1) FEP patients differed from healthy individuals in qualitative and quantitative aspects of their cognitive functioning, exhibiting widespread cognitive impairments. In particular, results indicated that although cognitive assessments could be carried out in the same way in controls and patients, the nature of the relationships between observed test scores and their purported underlying constructs tended to be dissimilar. Higher inter-correlations of cognitive domains emerged for patients compared to control subjects. Patients' cognitive profile tended to be more homogeneous. At the group level, patients demonstrated impairments in visual (i.e. pattern and spatial) recognition memory capacity, learning, set shifting, executive functioning, working memory (including storage and manipulation) as well as in the ability to rapidly process new information.

2) There is variability in the type, direction, and size of the changes of different cognitive functions among FEP patients over time, and researchers, clinicians and neuropsychologists should consider measurement invariance, as well as patients' demographic and clinical characteristics, when assessing neuropsychological change over time. Subjectively perceived and objectively measured cognitive deficits among FEP patients are two independent but likely complementary constructs, and should be measured separately in order to attain a more comprehensive assessment of each patient's day-to-day functioning.

3) Morphological changes in the frontal, temporal, cingulate and parietal cortices may be related to altered cognitive performance in FEP patients and that brain structure-function relationships may be dissimilar for FEP patients compared to CSs, when metrics of the CTh and CA – obtained by using MRI scanner – and cognitive performance – measured by the CANTAB tests – are linked.

In general, our findings acknowledge the need for continued efforts to investigate cognitive dysfunction and its underlying alterations in specific brain morphology as the biological feature of the early stage of schizophrenia.

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SUMMARY IN ESTONIAN

Esmase psühhoosiepisoodiga patsientide kognitiivne funktsionaalsus

Psühhoos tähistab kliinilist sündroomi, mille puhul võivad ilmneda erinevad psühhopatoloogilised ilmingud: häired tajumises, mõtlemises, tunde- ja tahteelus, mis põhjustavad probleeme sotsiaalses toimimises. Psühhootilised häired on bioloogiliste põhjustega aju toimimise häired. Enamlevinud krooniline psühhootiline häire on skisofreenia, mille puhul eelpoolnimetatud kliinilised tunnused indiviiditi ja haiguse erinevatel ajaperioodidel varieeruvad suurel määral. Üha suuremat kliinilist ja teadusuuringute põhist tähelepanu pööratakse häire esmasele psühhootilisele episoodile, mis avaldub enamasti noores täiskasvanueas ja omab olulist prognostilist tähendust haigestunud isiku edasisele toimetulekule ühiskonnas.

Alates XIX sajandi lõpust, mil Emil Kraepelin (Kraepelin, 1896) määratles skisofreenia *dementia praecox*'ina ehk enneaegse dementsusena, on häirele omase tuumsümptomina kirjeldatud ka patsientide kognitiivse funktsionaalsuse omapära.

Kognitiivsed ehk tunnetusprotsessid tuginevad ajutasandi närvivõrgustiku toimimisele ning võimaldavad omandada uusi teadmisi, analüüsida informatsiooni ning tagada ümbruses toimuvast arusaamise ja inimese toimimise teda ümbritsevas keskkonnas. Kognitiivsed ehk neuropsühholoogilised funktsioonid hõlmavad muuhulgas taju, mälu ja tähelepanu funktsioone, probleemilahendusoskuseid, infotöötluskiirust, otsustusvõimekust, keele ja varasemalt omandatud teadmiste kasutust.

Kliiniliselt olulise kognitiivsete funktsioonide langusena käsitletakse olukorda, kus isiku sooritus ühe või enama testi põhiselt on taustagrupiga võrreldes üks või enam standardskoori madalam. Taustagrupi moodustavad enamasti terved eakaaslased, kes omavad uuritavatega sarnast haridustee pikkust. Skisofreeniahaigete grupis on leitud mitmete neuropsühholoogilisi funktsioone mõõtvate testide sooritamise raskuseid. Grupi tasandil ilmnevad neil haigetel (spetsiifiliselt muude probleemsete haigusele omaste valdkondade hulgas) nt. töömälu vähene maht, raskused kiires infotöötlemises, tähelepanu säilitamises/ ümberlülitumises ja uue info omandamises, probleemide lahendamises, järelduste tegemises ja tegevuse planeerimises ning olulise ja ebaolulise info eristamises. Teisalt, kuna antud häire puhul on tegemist väga erinevaid kognitiivseid funktsioone hõlmavate probleemidega, on käsitlemist leidnud ka üldise ehk laiapõhjalise kognitiivse funktsioneerimisvõime häirumise vaatenurk (Dickinson *et al.* 2008).

Kognitiivsete funktsioonide ebatõhusus mõjutab tugevalt haigete elukvaliteeti ja sotsiaalset toimimist (Goldberg *et al.* 1993), mistõttu antud valdkonna uurimine on haiguse olemuse mõistmise ja ravistrateegiate planeerimise seisukohalt väga oluline.

Uurimustöö eesmärgid:

1) Iseloomustada esmase psühhootilise episoodiga patsientide kognitiivsete funktsioonide struktuuri, profiili ja sooritussuutlikkuse eripärasid võrreldes kontrollgruppi kuuluvate eakaaslastega, kasutades mõõtmisvahendina ala-teste arvutipõhisest neuropsühholoogilisest testikogumikust *Cambridge Neuropsychological Test Automated Battery* (CANTAB).

2) Hinnata esmasest psühhoosiepisoodist taastumise järgselt ehk kuue kuu möödudes patsientide kognitiivse funktsiooni struktuuri püsivust ajas ning sooritussuutlikkuse stabiilsust individuaalsel ja kogu grupi tasandil. Järg-nevalt, uurida demograafiliste ja kliiniliste tegurite (vanus, sugu, haridustase, psühhopatoloogia raskusaste, antipsühhootilise ravimi annus) mõju sooritus-suutlikkuse muutusele. Lisaks, võrrelda objektiivselt neuropsühholoogiliste testide abil mõõdetud ja patsientide subjektiivsete hinnangute kokkulange-vust kognitiivsele sooritussuutlikkusele.

3) Tuvastada aju funktsionaalse toimimise (hinnatuna CANTAB testipatareid kasutades) ja aju morfoloogiliste parameetrite (ajukoore paksuse ja ajukoore pindala – mõõdetuna magnetresonantsuuringut kasutades) vahelisi korrela-tiivseid seoseid ning määratleda antud seoste erinevused esmase psühhoosi-episoodiga patsientide grupis võrrelduna kontrollgruppi kuuluvate isikutega.

Uuritavad ja meetodid

Uurimistöö on läbi viidud Tartu Ülikooli Inimuuringute Eetikakomitee loa alu-sel ning kõik uuritavad andsid kirjaliku informeeritud nõusoleku uuringus osale-miseks. Uuritavateks olid valdavalt Sihtasutus Tartu Ülikooli Kliinikumi (SA TÜK) ja osaliselt Põhja-Eesti Regionaalhaigla psühhiaatriakliinikutesse krooni-lise psühhootilise häire esmase psühhoosiepisoodi avaldumise järgselt ravile pöördunud patsiendid, vanuses 18–45 aastat ning terved, eakaaslastest vaba-tahtlikud. Uuringus osales kokku 109 patsienti ja 96 kontrollgruppi kuuluvat isikut, kes valdasid eesti keelt ning kellel ei esinenud rasket kehalist haigust, aju orgaanilist haigust, vaimses arengus mahajäämust, väljendunud nägemis- ja kuulmislangust. Kontrollgruppi kuulumist välistas lisaks psühhootilise häire diagnoosi olemasolu lähisugulasel.

Kognitiivsete funktsioonide objektiivseks hindamiseks kasutati arvutipro-grammil põhinevat testipatareid CANTAB (Robbins & Sahakian 1994). Kasu-tati alateste, mis võimaldasid hinnata uuritavate visuaalset ja ruumilist äratund-mismälu, episoodilist mälu ja õppimisvõimet, tähelepanu ümberlülitumisvõi-met, tegevuse planeerimis- ja täidesaatmisvõimekust, töömälu mahtu, töömälus oleva infoga toimetamisvõimekust ning infotöötluse kiirust. Antud alatestide tõhus sooritus toetub valdavalt närvivõrgustikele, mis hõlmavad eesajukoore, oimu- ja kiirusagara, vöökääru ning juttkeha vahelisi ühendusi. On täheldatud, et kroonilise psühhootilise häirega patsientide grupi tasandil ilmnevad raskused nimetatud testide teostamises ning see peegeldab häirele omast ulatuslikku kognitiivset düsfunktsionaalsust.

Patsientide psühhopatoloogia väljendusastme määratlemiseks oli kasutusel „Psühhiaatriline lühiskaala" (*Brief Psychiatric Rating Scale*, BPRS) (Overall, 1962).

Subjektiivselt tajutud kognitiivset funktsionaalsust hinnati nelja enesekohase väite põhjal, mis pärinesid eesti keelde adapteeritud "Subjektiivse heaolu küsimustiku" lühikesest versioonist (*Subjective Well-Being under Neuroleptics-Short Form* (SWN-K, Naber *et al.*, 2001) *Estonian version* (SWN-K-E, Haring *et al.* 2013).

Ajukuvamisuuringud teostati SA TÜK radioloogiakliinikus, kasutades magnetresonantstomograafi ning tugeva magnetvälja abil saadud kujutisi ajukoore paksusest ja ajukoore pindalast. Vastavate parameetrite seoseid neuropsühholoogiliste testide tulemustega analüüsiti FreeSurfer v5.1.0 (http://surfer.nmr. mgh.harvard.edu) programmi abil.

Uurimistöö peamised tulemused ja arutelu

Uurimistöö esimeses etapis analüüsisime patsientide ja kontrollisikute gruppide tasanditel CANTAB alatestide skooride koondumiste eripärasid latentsete tunnuste koosseisu. Tunnuste grupeerimiseks kasutasime peakomponentide meetodit ning ilmnenud konstruktide psühhomeetrilistele omadustele hinnangu andmiseks kinnitavat faktoranalüüsi. Leidsime, et nii patsientide kui ka kontrollisikute grupis oli tunnuste koosvarieerumist võimalik teatavatele erinevustele vaatamata kirjeldada ühe- ja kahe-faktorilise mudeli abil. Edasise kinnitava faktoranalüüsi (hindamaks gruppide siseselt mõõdetud tunnuste kovariatsioonimaatriksite psühhomeetrilisi omadusi) viisime läbi ühe-faktorilise mudeli (kõik mõõdetud tunnused koondusid ühe latentse faktori ehk „Laiaulatusliku võimekuse faktori" koosseisu) ning kahe-faktorilise mudeli (visuaalset-, ruumilist-, ja episoodilist mälu ning töömälus olevate infoühikute mahtu kajastavad tunnused koondusid „Tähelepanu/mälu faktori" koosseisu ning töömälus oleva infoga manipuleerimist, tähelepanu ümberlülitumise ja tegevuse planeerimise efektiivsust peegeldavad tunnused laadusid „Täidesaatva funktsiooni faktori") alla. Tulemused kinnitasid, et CANTAB testide abil hinnatud kognitiivset funktsionaalsust kirjeldavate tunnuste (testiskooride) kovariatsioonimaatriksite struktuurid on mõlemas grupis defineeritavad ühe- ja kahe-faktorilise mudeli kaudu. Samas ilmnes oluline gruppide põhine erinevus kahe-faktorilise mudeli latentsete tunnuste vahelise korrelatsiooni tugevuses. Kontrollisikute grupis oli täheldatav teineteisest suhteliselt eristuvate faktorite („Tähelepanu/mälu faktori" ja „Täidesaatva funktsiooni faktori") profiil (korrelatsioon faktorite vahel $r = 0.31$). Patsientide grupis antud latentsed faktorid omasid märkimisväärselt kõrgemat omavahelist korrelatsiooni suurust ($r = 0.83$). See viitas asjaolule, et patsientide grupis tugineb kognitiivsete funktsioonide realiseerumine oluliselt vähem modaalsusspetsiifilisele sooritusele ning pigem toetuvad patsiendid erinevat tüüpi soorituste puhul laiaulatusliku vaimse võimekuse faktori kaasatusele. Teisisõnu viitab enam homogeenne kognitiivne profiil (kui sooritus oli

probleemsem ühe testi puhul, siis ilmnesid suure tõenäosusega raskused ka teiste alatestide teostamisel) patsientide grupis funktsionaalsuse ebaökonoomsusele ning see võib peegeldada haigusega seonduvaid ja haigussümptomeid esile kutsuvaid protsesse. Meie tulemused on kooskõlas varasemate uuringutega (Leeson *et al.* 2009; Dickinson *et al.* 2008), mis samuti on näidanud kognitiivsete funktsioonide suuremat koherentsust psühhoosihaigete grupis võrreldu-na kontrollgruppi kuuluvate isikutega ning asjaolu, et patsientide grupi kognitiivse funktsiooni kovariatsioonimaatriksi kirjeldamiseks sobib pigem ühe-faktoriline („Laiaulatusliku võimekuse faktori") mudel.

Gruppide vaheline kinnitav faktoranalüüs võimaldas samaaegselt uurida kognitiivsete funktsioonide mõõtmistulemuste alusel loodud hüpoteetiliste faktor-struktuuride sobivust psühhootilise häirega isikute ja kontrollgrupis. Tegemist on mõõtmistulemuste struktuuri sarnasusele hinnangute andmisega erinevatel tasanditel.

Kahe-faktorilise mudeli puhul leidsid kinnitust: gruppide vaheline faktor-struktuuri 'konfiguraalne sarnasus' (mõlemas grupis olid latentsed tunnused defineeritavad sarnaste algtunnuste poolt) ja 'nõrk struktuuri sarnasus' (ilmnes faktorlaadungite sarnasus gruppides). Gruppide vaheline 'tugev struktuuri sarnasus' eeldab, et nii faktorlaadungid kui ka indikaatortunnuste keskmised väärtused on mudelites sarnased. Meie tulemused näitasid, et antud tasemel eristusid mudelid teineteisest. See viitas asjaolule, et sarnased CANTAB ala-testide skoorid defineerisid erinevates vaadeldud gruppides erinevaid latentseid tunnuseid. Kuna viimati nimetatud tasemel ilmnes mudelite faktorstruktuuri sarnasuse lahknevus, siis edasiste, enam piiranguid arvesse võtvate mudelite testimine ei olnud otstarbekas.

Gruppide vahelise ühe-faktorilise mudeli struktuuri sarnasuse hindamisel leidis kinnitust üksnes 'konfiguraalne sarnasus'.

Seega osutasid tulemused, et CANTAB testide mõõtmistulemuste kovariat-sioonimaatriksite põhiselt loodud mudelite latentsete tunnuste skooride võrdlus ei ole asjakohane ning sooritussuutlikkusele hinnangu andmine gruppide tasan-dil (psühhootilise häirega patsiendid võrreldes tervete kontrollisikutega) peaks toetuma alatestide põhjal saadud tulemustele.

Lisaks ilmnes tulemuste põhjal, et enam iseloomustas patsientide kognitiivse kahjustuse profiili infotöötluskiiruse langus, raskus tegevuse planeerimisel ja täidesaatmisel, tähelepanu ümberlülitumisel ja töömälus oleva infoga toime-tamisel. Patsientide grupis ilmnes tervete eakaaslastega võrreldes soorituse ebatõhusus ka visuaalse ja ruumilise äratundmise testide, episoodilise mälu ja õppimisvõime ülesande ning töömälu mahtu hindava testi osas. Antud tule-mused kinnitasid varasemalt teostatud uuringuid (Gold & Harvey 1993; Hein-richs & Zakzanis 1998), mille kohaselt juba kroonilise psühhootilise häire varajases staadiumis ilmneb patsientidel spetsiifiliste kognitiivsete funktsioo-nide kahjustus, mis on oma olemuselt laiaulatuslik (Dickinson *et al.* 2008).

Uurimistöö teises etapis analüüsisime patsientide grupis CANTAB testide põhiselt leitud kognitiivse sooritussuutlikkuse stabiilsust ajalises dünaamikas. Eristatakse kahte, teineteisest sõltumatut stabiilsust või ka muutuse ulatust kir-

jeldavat tunnust: muutust individuaalses soorituses võrreldes teiste gruppi kuuluvate liikmetega ja grupi tasandil ilmnenud keskmise sooritussuutlikkuse muutust ajas. Tulemuste põhjal ilmnes kuuekuulise ajaintervalli järel langus ruumilise äratundmismälu ja episoodilise mälu/õppimisvõime testide skooride osas. Samas, tähelepanu ümberlülitumisvõime/vaimne paindlikkus, tegevusi täidesaatev funktsionaalsus, töömälus oleva infoga toimetamine ja informatsiooni töötluskiirus ajas tõhustusid. Töömälu mahu ja visuaalse äratundmismälu osas muutuseid ei ilmnenud. Seega kinnitasid meie tulemused varasemaid uuringuid (Censits *et al.* 1997; Rund 1998; Heaton *et al.* 2001), mille kohaselt kroonilise psühhootilise häire varajases staadiumis ei esine laiaulatuslikku kognitiivse funktsionaalsuse langust.

Lisaks säilitasid patsiendid kahel erineval testimiskorral saadud testiskooride põhiselt kõrge stabiilsuse grupi-siseses järjestuses (isikud, kes said kõrgemaid testiskoore algsel testimisel, said kõrgemaid skoore ka järgneval testimisel). Seega kaldusid kogu grupi tasandil saadud keskmiste testiskooride muutuste hinnangud iseloomustama enamikku patsientidest sarnasel viisil.

Järgnevalt uurisime, kas kahe järjestikuse testimise käigus saadud testiskooride kovariatsioonimaatriksid esindavad sarnaseid struktuurimudeleid. Varasemalt näitasime, et patsientide grupi andmete puhul töötab paremini ühefaktoriline lahend. Kinnitav faktoranalüüs näitas, et sarnasus ajas antud faktorlahendi osas püsis 'konfiguraalsel' ja 'nõrgal struktuuri sarnasuse' tasemel. Tulemused pakkusid empiirilist tõendust hüpoteesile, et testiskoorid mõõtsid sarnast psühholoogilist tunnust ja latentsed faktorid omasid sarnast tähendust erinevatel ajahetkedel. Kuna aga edasistel faktorstruktuuri analüüsitasemetel sarnasus puudus, tuleks ka ajalises dünaamikas esmaste psühhoosihaigete grupis CANTAB testide skooridele/skooride muutustele hinnangute andmisel piirduda alatestide põhiselt saadud väärtustega.

Edasine analüüs tõi esile, et võrreldes naispatsientidega osutus meeste sooritussuutlikkus tähelepanu ümberlülitusvõimet, eksekutiivset funktsionaalsust, töömälu mahtu ja töömälus oleva infoga manipuleerimisvõimekust hindavate testide sooritamisel stabiilselt tõhusamaks. Meie tulemused kattusid osaliselt varasemate tulemustega (Albus *et al.* 1997, Perlick *et al.* 1992, Roesch-Ely *et al.* 2009), kuid on ka viiteid vastupidistest tulemustest (Seidman *et al.* 1997; Goldstein *et al.* 1998) ning sooliste erinevuste puudumisest psühhoosihaigete valimi puhul (Hoff *et al.* 1998; Ittig *et al.* 2015).

Tulemuste osas väärib tähelepanu asjaolu, et patsientide seisundi paranemine (hinnatuna psühhopatoloogiliste avalduste esinemismäära põhjal) jätkus peale haiglaravi, kuuekuulise jälgimisperioodi jooksul. Sümptomite taandumine ja kontrolli all püsimine võimaldas langetada antipsühhootilise raviannuse suurust, mis omakorda seondus tõhustunud eksekutiivse funktsionaalsuse ja suurenenud võimekusega hoida infot töömälus. Seetõttu oleks soovituslik ajalises dünaamikas kliinilises töös kaaluda psühhopatoloogiliste avalduste taandumisega ja sümptomite kontrolli all püsimisega kooskõlaliselt antipsühhootilise raviannuse langetamise võimalust, mis grupi tasandilt vaadatuna võib soodustada kognitiivset funktsioneerimisvõimekust.

Patsientide subjektiivselt tajutud hinnangud kognitiivsele funktsionaalsusele meie uuringus ei ühtinud objektiivselt, neuropsühholoogilise uuringu alusel saadud kognitiivse funktsionaalsuse hinnangutega. Ka varasemad uuringud (Zanello & Huguelet 2001, Stip *et al.* 2003) on tõdenud, et tegemist on kahe erineva konstruktiga, mis teineteist täiendavad.

Kolmandas etapis keskendusime patsientide ja kontrollisikute aju morfoloogiliste parameetrite (ajukoore paksuse ja ajukoore pindala) ning kognitiivse funktsionaalsuse (töömälu mahu, töömälus oleva infoga manipuleerimisvõime, vaimse paindlikkuse, tegevuse planeerimise ja informatsiooni töötluskiiruse) korrelatiivsete seoste uurimisele. Meie tulemused kinnitasid varasemaid uuringutulemusi (Salgado-Pineda *et al.* 2003; Minatogawa-Chang *et al.* 2009; Gutiérrez-Galve *et al.* 2010; Crespo-Facorro *et al.* 2011), mille kohaselt difuusne asümmeetriliselt väiksem ajukoore paksus ja ajukoore pindala (eeskätt eesaju, oimu-, kiirusagarate piirkonnas, vöökäärus) omasid korrelatiivseid seoseid vähese vaimse paindlikkuse ning madalama võimekusega toimetada töömälus oleva informatsiooniga ja strateegiate ebaefektiivsema kasutamisega töömälu ülesande sooritamisel. Lisaks, paksem vöökäär vasemal oli seotud tõhusama informatsioonitöötlusega ehk võimekusega eristada olulist informatsiooni ebaoluliselt. Lisaks ilmnes seos ajukoore väiksema (kukla- ja oimusagara alade) pindala ja efektiivsema võimekusega hoida töömälus informatsiooniühikuid. Seostemustrid osaliselt haigete ja tervete isikute rühmades kattusid. Eelnevad uurijad (Toulopoulou *et al.* 2004; Cocchi *et al.* 2009; Minatogawa-Chang *et al.* 2009; Crespo-Facorro *et al.* 2011; Ehrlich *et al.* 2012; Hatton *et al.* 2013) on näidanud, et esmase psühhootilise häirega patsientidele on omased teatavad aju struktuuride ja kognitiivse funktsionaalsuse seostemustrid. Ka meie uuring pakkus antud tõdemusele kinnitust. Psühhoosihaigete aju strukturaalseid ja funktsionaalsuse erisusi on seostatud aju arenguliste omapäradega (Weinberger 1987; Murray & Lewis 1988) ja/või häirunud regeneratiivsete protsessidega (Falkai *et al.* 2015), mis omakorda seonduvad epigeneetiliste ja aju plastilisuse düsregulatsiooni mehhanismidega (Hasan *et al.* 2013). Lisaks toetab meie uurimus oletust, et psühhoosihaigete neuroanatoomilised/kognitiivse funktsionaalsuse eripärad ei seondu spetsiifiliste ajupiirkondadega, vaid pigem on haigusprotsessi ja/või haiguse kompensatoorsetesse mehhanismidesse kaasatud erinevad ajupiirkonnad.

Antud uurimistöö läbiviimine on aidanud kaasa esmase psühhoosiepisoodiga patsientide kliinilise uurimise tõenduspõhise käsitluse juurdumisele SA TÜK psühhiaatriakliinikus.

Meie edasiste uurimissuundade eesmärgid seonduvad esmase psühhoosiepisoodiga patsientide metabolismi, põletiku- ja oksüdatiivse stressi markerite eripärade kaardistamisega ning biomarkerite ja kognitiivse funktsiooni seoste uurimisega. Lisaks on plaanis kaasata uuringusse haiguse kroonilises staadiumis olevaid patsiente ja psühhootilise häire suhtes riskigruppi kuuluvaid isikuid, et kirjeldada laiapõhjaliselt kroonilise psühhootilise häire erinevates faasides

ilmnevaid patofüsioloogilisi muutusi, mis võivad realiseeruda kliinilisel tasandil haigustunnustena ning mõjutada seeläbi patsientide igapäevast toimetulekut.

Uurimistöö järeldused

1) Uurimistöö tulemused viitasid, et võrreldes tervete eakaaslastega ilmneb esmase psühhoosiepisoodi järgselt patsientide grupi tasandil laiaulatuslik kvantitatiivne ja kvalitatiivne kognitiivne düsfunktsionaalsus. Probleemsed valdkonnad patsientide kognitiivsete funktsioonide sooritussuutlikkuses avaldusid: infotöötluskiirust, tegevuse planeerimist ja täidesaatmist, tähelepanu ümberlülitumist ja töömälus oleva infoga toimetamisvõimekust ning visuaalse ja ruumilise äratundmismälu käepärasust, õppimisvõimekust ja töömälu mahtu hindavate testide läbimisel. Lisaks ilmnes, et sarnased CANTAB alatestide skoorid võisid defineerida erinevates vaadeldud gruppides sarnaseid latentseid tunnuseid, kuid mudelite aluseks olevad konstruktid olid struktuurilt erinevad. Kahefaktorilise lahendi puhul avaldus patsientide grupis oluliselt kõrgem latentsete tunnuste omavaheline korrelatiivsus, mis peegeldas enam homogeense faktorstruktuuri olemasolu.

2) Selgitasime, et patsientide grupis hinnatud kognitiivsete funktsioonide sooritussuutlikkuse muutused ajas võivad ilmneda määra, viisi ja suuna erinevustes. Hinnates kliinilises töös või teadusuuringute kontekstis ajalises dünaamikas patsientide objektiivset kognitiivset funktsioneerimisvõimekust strukturaalsel ja sooritussuutlikkuse stabiilsuse tasandil, tuleks mõõtmistulemuste kokkulangevustele hinnangute andmisel arvesse võtta patsientide demograafilisi ja kliinilisi eripärasid ning mõõtmisvahendi korduvast kasutamisest tulenevaid tegureid. Lisaks kinnitas uurimus, et patsientide poolt subjektiivselt tajutud kognitiivse kahjustuse määr ja objektiivselt neuropsühholoogiliste testide abil mõõdetud kognitiivne funktsionaalsus on eraldiseisvad konstruktid ning antud hinnangud pakuvad teineteisele täiendust, kirjeldamaks patsiendi igapäevast toimetulekuvõimekust.

3) Tuvastasime, et morfoloogilised eripärad eesajukoores, oimu-, kiirusagarates ja vöökäärus omavad korrelatiivseid seoseid kognitiivse sooritussuutlikkusega. Lisaks kinnitasime, et esmase psühhoosiepisoodiga patsientide aju struktuuri (ajukoore paksus ja ajukoore pindala) ning funktsionaalsuse (mõõdetud CANTAB alatestide abil) korrelatiivsed seosed on erinevad tervete eakaaslastega võrreldes.

Kokkuvõtvalt kinnitasid meie uuringutulemused, et kroonilise psühhootilise häire varajases staadiumis esineb patsientidel laiaulatuslik ja ajas suhteliselt püsiv kognitiivsete funktsioonide kahjustus, mis omab seoslikkust aju neurobioloogiliste parameetritega.

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Tables A1−A3.

Table A1. Results of the between-group (first-episode psychotic (FEP) patients ($n = 63$) compared to control subjects (CSs) ($n = 30$)) differences within cortical thickness (CTh) and surface area (CA). Only statistically significant differences in CTh and CA clusters (may span more than one anatomical region), clusters sizes, and corresponding anatomical region names are reported. Standard *FreeSurfer* atlases were used to determine anatomical nomenclature.

		Cluster	Brain region	Size	P_{cw}*	P_{cw} Low to High	FEP patients Mean (S.D.)	CSs Mean (S.D.)
Thickness	**LH**	Superior frontal		1283	0.0019	0.0014 − 0.0025	3.02 (0.23)	3.22 (0.18)
			Caudal anterior cingulate					
		Superior frontal		1193	0.0039	0.0031 − 0.0047	2.59 (0.21)	2.77 (0.19)
			Rostral middlefrontal					
		Temporal pole		1051	0.0093	0.0081 − 0.0011	3.44 (0.34)	3.14 (0.39)
			Fusiform					
			Entorhinal					
			Superior temporal					
			Insula					
	RH	Rostral middlefrontal		5158	0.0001	0 − 0.0002	2.81 (0.19)	3.01 (0.22)
			Caudal middlefontal					
			Superior frontal					
		Precentral		1371	0.0012	0.0008 − 0.0017	2.53 (0.26)	2.30 (0.42)
		Middle temporal		1107	0.0084	0.0072 − 0.0096	3.03 (0.26)	2.73 (0.38)
			Inferior temporal					
Area	**LH**	Rostral middlefrontal		1055	0.0095	0.0083 − 0.0108	1.04 (0.10)	0.94 (0.11)
			Pars triangularis					
	RH	Lateral occipital		2359	0.0001	0 − 0.00002	0.92 (0.08)	0.85 (0.07)
			Inferior parietal					
			Superior parietal					

*The p-values are expressed as cluster-wise probability (P_{cw}), and P_{cw} is equivalent to the overall alpha significance level. LH – left hemisphere; RH – right hemisphere. Surface area is expressed in mm^2, cortical thickness is expressed in mm. All comparisons were made controlling for the effects of age and gender. Significance was set at $p < 0.05$ (FDR corrected).

Table A2. Cortical grey matter thickness and area correlations with neurocognitive performance in FEP patients ($n = 63$) and CS group ($n = 30$). Standard *FreeSurfer* atlases were used to determine anatomical nomenclature.

FEP patients							
		Cluster	Brain region	Size	P_{cw}*	P_{cw} Low to High	Mean (S.D.)
IED							
Thickness	**LH**	Fusiform		2932	0.0001	0 – 0.0002	2.23 (0.14)
			Inferior temporal				
			Lateral occipital				
			Lingual				
			Pericalcarine				
			Cuneus				
			Precuneus				
		Superior frontal		2919	0.0001	0 – 0.0002	2.97 (0.21)
			Lateral orbitofrontal				
			Medial orbitofrontal				
			Rostral anterior cingulate				
			Caudal anterior cingulate				
		Isthmus cinguli		2330	0.0001	0 – 0.0002	2.72 (0.16)
			Precuneus				
			Lingual				
			Posterior cingulate				
			Paracentral				
			Superior frontal				
			Caudal anterior cingulate				
		Rostral middlefrontal		2778	0.0001	0 – 0.0002	2.65 (0.18)
			Pars opercularis				
			Pars triangularis				
			Precentral				
	RH	Superior frontal		6649	0.0001	0 – 0.0002	2.97 (0.21)
			Medial orbitofrontal				
			Rostral middlefrontal				
			Pars triangularis				
			Pars opercularis				
			Precentral				
			Caudal middlefrontal				
		Posterior cingulate		3470	0.0001	0 −0.0002	2.54 (0.16)
			Paracentral				
			Superior frontal				
			Isthmus cingulate				
			Lingual				
			Parahippocampal				
			Cuneus				
			Pericalcarine				
			Precuneus				
			Superior parietal				
Area	**LH**	Pars triangularis		1038	0.0088	0.0076 – 0.01	1.09 (0.11)
			Pars orbitalis				
			Rostral middlefrontal				
	RH	No					

		Cluster	Brain region	Size	P_{cw}*	P_{cw} Low to High	Mean (S.D.)
FEP patients							
SOC							
Thickness	**LH**	No					
	RH	No					
Area	**LH**	No					
	RH	No					
SSP							
Thickness	**LH**	No					
	RH	No					
Area	**LH**	No					
	RH	Lingual		1133	0.007	0.0059 – 0.0081	0.88 (0.09)
			Pericalcarine				
			Lateral occipital				
			Fusiform				
			Lateral occipital				
SWM strategy							
Thickness	**LH**	Rostral middlefrontal		8658	0.0001	0 – 0.0002	2.79 (0.19)
			Caudal middlefrontal				
			Superior frontal				
			Posterior cingulate				
			Caudal anterior cingulate				
			Medial orbitofrontal				
			Rostral anterior cingulate				
			Lateral orbitofrontal				
		Pars opercularis		1836	0.0015	0.001 – 0.002	2.90 (0.16)
			Pars triangularis				
			Insula				
			Precentral				
			Postcentral				
		Inferior parietal		1777	0.0021	0.0015 – 0.0027	2.49 (0.20)
			Supramarginal				
			Superior parietal				
		Fusiform		1533	0.0079	0.0068 – 0.009	2.32 (0.16)
			Lingual				
			Lateral occipital				
	RH	Rostral middlefrontal		10520	0.0001	0 – 0.0002	2.76 (0.16)
			Caudal middlefrontal				
			Precentral				
			Pars opercularis				
			Pars triangularis				
			Medial orbitofrontal				
			Superior frontal				
			Rostral middlefrontal				
		Precuneus		4146	0.0001	0 – 0.0002	2.54 (0.15)
			Parahippocamapal				
			Lingual				

			FEP patients				
		Cluster	Brain region	Size	P_{cw}*	P_{cw} Low to High	Mean (S.D.)
			Isthmus cingulate				
			Posterior cingulate				
			Superior frontal				
		Inferior parietal		2800	0.0001	0 – 0.0002	2.61 (0.16)
			Supramarginal				
			Superior temporal				
			Inferior parietal				
Area	**LH**	Superior frontal		1890	0.0001	0 – 0.0002	1.12 (0.09)
			Rostral middlefrontal				
			Frontal pole				
			Lateral orbitofrontal				
			Pars triangularis				
		Temporal pole		1780	0.0001	0 – 0.0002	1.31 (0.13)
			Inferior temporal				
			Fusiform				
			Superior temporal				
			Middle temporal				
	RH	Superior temporal		2274	0.0001	0 – 0.0002	1.20 (0.11)
			Middle temporal				
			Inferior temporal				
			Fusiform				
			Entorhinal				
SWM errors							
Thikness	**LH**	Superior frontal		15140	0.0001	0 – 0.0002	0.94 (0.05)
			Caudal anterior cingulate				
			Paracentral				
			Rostral anterior cingulate				
			Medial orbitofrontal				
			Rostral middlefrontal				
			Lateral orbitofrontal				
			Caudal middlefrontal				
			Pars orbitalis				
			Pars triangularis				
			Insula				
			Precentral				
		Fusiform		1955	0.0007	0.0004 – 0.001	0.88 (0.05)
			Lingual				
			Lateral occipital				
		Pericalcarine		1952	0.0007	0.0004 – 0.001	0.90 (0.06)
			Precuneus				
			Superior parietal				
			Cuneus				
	RH	Precentral		15953	0.0001	0 – 0.0002	0.91 (0.04)
			Superior frontal				
			Caudal middlefrontal				
			Rostral middlefrontal				
			Pars opercularis				
			Pars trinagularis				

FEP patients							
		Cluster	Brain region	Size	P_{cw}*	P_{cw} Low to High	Mean (S.D.)
			Postcentral				
			Supramarginal				
			Inferior parietal				
			Middle temporal				
			Medial orbitofrontal				
			Caudal anterior cingulate				
		Precuneus		3595	0.0001	0 – 0.0002	0.87 (0.03)
			Isthmus cingulate				
			Posterior cingulate				
			Lingual				
			Paracentral				
Area	**LH**	Inferior temporal		1356	0.0014	0.0009 – 0.0019	1.12 (0.10)
			Middle temporal				
			Temporal pole				
			Superior temporal				
		Pars orbitalis		1290	0.0019	0.0014 – 0.0025	1.10 (0.11)
			Lateral orbitofrontal				
			Pars triangularis				
			Rostral middlefrontal				
	RH	Superior temporal		1724	0.0002	0 – 0.0004	1.07 (0.09)
			Middletemporal				
			Inferior temporal				
			Temporal pole				
		Medial orbitofrontal		1128	0.0073	0.0062 – 0.0084	1.30 (0.13)
			Superior orbital				
			Rostral middlefrontal				
RVP							
Thickness	**LH**	Superior frontal		1840	0.0018	0.0013 – 0.0024	2.87 (0.21)
			Posterior cingulate				
			Caudal anterior cingulate				
			Rostral anterior cingulate				
	RH	No					
Area	**LH**	No					
	RH	No					

CSs							
		Cluster	Brain region	Size	P_{cw}*	P_{cw} Low to High	Mean (S.D.)
IED							
Thickness	**LH**	No					
	RH	No					
Area	**LH**	No					
	RH	No					

CSs							
		Cluster	Brain region	Size	P_{cw}*	P_{cw} Low to High	Mean (S.D.)
SOC							
Thickness	**LH**	Middle temporal		3409	0.001	0 – 0.002	2.51 (0.22)
			Inferior temporal				
			Fusiform				
			Lingual				
			Pericalcarine				
			Cuneus				
	RH	Temporal pole		1893	0.001	0.001 – 0.002	2.97 (0.35)
			Entorhinal				
			Inferior temporal				
			Fusiform				
			Parahippocampal				
			Middle temporal				
		Superior temporal		1724	0.0033	0.0026 – 0.004	2.83 (0.23)
			Insula				
			Transverse temporal				
			Middle temporal				
Area	**LH**	No					
	RH	No					
SSP							
Thickness	**LH**	No					
	RH	No					
Area	**LH**	No					
	RH	Pericalcarine		1341	0.0015	0.001 – 0.002	0.88 (0.17)
			Cuneus				
			Lingual				
SWM strategy							
Thickness	**LH**	Lateral orbitofrontal		2260	0.0001	0 – 0.0002	2.88 (0.22)
			Pars opercularis				
			Pars triangularis				
			Insula				
	RH	Pars triangularis		1787	0.0043	0.0035 – 0.0051	2.78 (0.22)
			Rostral middlefrontal				
			Pars orbitalis				
		Fusiform		1988	0.0023	0.0017 – 0.0029	2.51 (0.21)
			Lingual				
			Lateral occipital				
			Inferior temporal				
			Middle temporal				
		Precentral		1777	0.0045	0.0037 – 0.0054	2.53 (0.40)
			Paracentral				
			Superior frontal				
		Precuneus		1938	0.0026	0.002 – 0.0033	2.58 (0.26)
			Cuneus				

| | | | | | | P_{cw} | Mean |
		Cluster	Brain region	Size	P_{cw}*	Low to High	(S.D.)
			Pericalcarine				
			Superior parietal				
			Isthmus cingulate				
			Posterior cingulate				
Area	**LH**	No					
	RH	No					
SWM errors							
Thikness	**LH**	Superior frontal		1765	0.0023	0.0023 – 0.0029	2.56 (0.29)
			Precentral				
			Paracentral				
		Precentral		7153	0.0001	0 – 0.0002	2.69 (0.20)
			Lateral orbitofrontal				
			Caudal middlefrontal				
			Insula				
			Pars opercularis				
			Pars triangularis				
			Rostral middlefrontal				
			Postcentral				
		Precuneus		3565	0.0001	0 – 0.0002	2.41 (0.20)
			Isthmus cingulate				
			Cuneus				
			Pericalcarine				
			Superior parietal				
			Inferior parietal				
	RH	Precentral		4018	0.0001	0 – 0.0002	2.57 (0.33)
			Superiorfrontal				
			Caudal middlefrontal				
			Paracentral				
		Fusiform		1980	0.0012	0.0008 – 0.0017	2.36 (0.18)
			Lateral occipital				
			Lingual				
		Precuneus		3977	0.0001	0.0001 – 0.0002	2.49 (0.23)
			Isthmus cingulate				
			Posterior cingulate				
			Cuneus				
			Pericalcarine				
			Superior parietal				
		Lateral occipital		2971	0.0001	0 – 0.0002	2.53 (0.23)
			Inferior parietal				
			Superior parietal				
		Pars triangularis		2927	0.0001	0 – 0.0002	2.76 (0.21)
			Pars opercularis				
			Pars orbitalis				

CSs							
		Cluster	Brain region	Size	P_{cw}*	P_{cw} Low to High	Mean (S.D.)
			Rostral middlefrontal				
			Lateral orbitofrontal				
		Superior temporal		2726	0.0001	0 – 0.0002	2.91 (0.25)
			Fusiform				
			Inferior temporal				
			Middletemporal				
			Banks of the superior temporal sulcus				
			Inferior parietal				
			Supramarginal				
Area	**LH**	Precentral		2250	0.0001	0 – 0. 0002	0.88 (0.09)
			Superior frontal				
			Caudal middlefrontal				
			Rostral middlefrontal				
		Precuneus		1167	0.0037	0.0029 – 0.0045	1.00 (0.10)
			Superior parietal				
	RH	Pars triangularis		2029	0.0001	0.0001 – 0.0002	1.04 (0.08)
			Precentral				
			Pars opercularis				
			Pars orbitalis				
			Insula				
			Lateral orbitofrontal				
		Rostral middlefrontal		1389	0.0009	0.0005 – 0.0013	1.07 (0.10)
			Superior frontal				
			Medial orbitofrontal				
RVP							
Thickness	**LH**	No					
	RH	No					
Area	**LH**	No					
	RH	No					

*The *p*-values are expressed as cluster-wise probability (P_{cw}) and P_{cw} is equivalent to the overall alpha significance level. LH – left hemisphere, RH – right hemisphere.

Surface area is expressed in mm^2, cortical thickness is expressed in mm.

IED – intra/extradimensional shift; SOC – Stockings of Cambridge; SSP – spatial span; SWM error and strategy – spatial working memory errors and strategy scores; RVP – rapid visual information processing.

All comparisons were made controlling for the effects of age and gender.

Significance was set at *p* < 0.05 (FDR corrected).

Table A3. Significant relationship differences between cortical thickness/area and neuropsychological measures between the FEP patients ($n = 63$) and control subjects ($n = 30$). Standard *FreeSurfer* atlases were used to determine anatomical nomenclature.

		Cluster	Brain region	Size	P_{cw}*	P_{cw} Low to High
IED						
Thickness	**LH**	No				
	RH	No				
Area	**LH**	Pars triagularis		964	0.0015	0.001 – 0.002
			Pars orbitalis			
			Rostral middlefrontal			
	RH	No				
SOC						
Thickness	**LH**	Entorhinal		1546	0.0001	0 – 0.0002
			Inferior temporal			
			Fusiform			
			Lingual			
	RH	Middle temporal		1709	0.0001	0 – 0.0002
			Superior temporal			
			Transverse temporal			
			Insula			
		Temporal pole		1434	0.0008	0.0005 – 0.0012
			Inferior temporal			
			Middle temporal			
			Entorhinal			
			Fusiform			
		Inferior parietal		1278	0.0026	0.002 – 0.0033
			Middle temporal			
Area	**LH**	No				
	RH	Lateral occipital		1106	0.0003	0.0001 – 0.0005
			Cuneus			
			Pericalcarine			
			Lingual			
SSP						
Thickness	**LH**	No				
	RH	No				
Area	**LH**	No				
	RH	No				
SWM strategy						
Thickness	**LH**	No				
	RH	Supramarginal		1196	0.0047	0.0038 – 0.0056
			Superior temporal			
			Inferior parietal			
Area	**LH**	No				
	RH	No				
SWM errors						
Thickness	**LH**	No				
	RH	Paracentral		1959	0.0001	0 – 0.0002
			Precntral			
			Postcentral			

		Cluster	Brain region	Size	P_{cw}*	P_{cw} Low to High
Area	**LH**	No				
	RH	No				
RVP						
Thickness	**LH**	No				
	RH	Lingual		1297	0.0024	0.0018 – 0.003
			Fusiform			
			Lateral occipital			
			Cuneus			
			Pericalcarine			
Area	**LH**	No				
	RH	No				

*The *p*-values are expressed as cluster-wise probability (P_{cw}), and P_{cw} is equivalent to the overall alpha significance level. LH – left hemisphere, RH – right hemisphere.

Surface area is expressed in mm^2, cortical thickness is expressed in mm.

IED – intra/extradimensional shift; SOC – Stockings of Cambridge; SSP – spatial span; SWM error and strategy – spatial working memory errors and strategy scores; RVP – rapid visual information processing.

All comparisons were made controlling for the effects of age and gender.

Significance was set at $p < 0.05$ (FDR corrected).

Note: Paper III comprises Supplementary materials in relation to MRI results (i.e. statistical maps of cortical parameters and their associations with cognitive functioning as well as descriptions of particular clusters, corresponding anatomical region names, cluster sizes, and statistical significance values). The same information is provided in the dissertation under the Figure 6 – 9 and in the Table A1 – A3, and is not added extra to the manuscript.

ORIGINAL PUBLICATIONS

CURRICULUM VITAE

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2008–	University of Tartu, Faculty of medicine, doctoral studies in neurosciences
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2001–2005	University of Tartu, Faculty of medicine, residency in psychiatry
1998–2001	University of Tartu, Faculty of medicine, internship
1991–1998	University of Tartu, Faculty of medicine
1988–1991	Tartu High School No.12

Professional employment:

2005–	Psychiatry Clinic of Tartu University Hospital, psychiatrist (1.0)

Scientific work and professional organizations:

Field of research:	Cognitive neuroscience, biomarkers of psychotic disorders
Publications:	8 international
Membership:	Estonian Psychiatric Association, member
	Schizophrenia International Research Society, member

Supervised dissertation:

Maret Trei, MA/MSc student, 2015, (sup) Liina Haring, Liina Vahter, Cognitive functioning in first-episode psychosis: a six month follow-up study, University of Tartu, Faculty of social sciences, institute of psychology

Dissertations under supervision:

Jaana Mägi, MA/MSc student, (sup) Liina Haring, Karin Täht, Personal and Social Performance Scale (PSP): reliability and validity in an Estonian speaking sample, University of Tartu, Faculty of social sciences, institute of psychology

Siim Jakobsoo, MA/MSc student, (sup) Liina Haring, Karin Täht, Adaptation of the psychosis risk assessment instruments into Estonian, University of Tartu, Faculty of social sciences, institute of psychology

Kirti-Ly Jaanson, MA/MSc student, (sup) Liina Haring, Karin Täht, Risk of developing psychotic disorder: relationship with genetic predisposition, general functioning and cannabis abuse, University of Tartu, Faculty of social sciences, institute of psychology

Publications:

Haring L, Mõttus R, Kajalaid K, Koch K, Uppin K, Maron E, & Vasar E (2017). The course of cognitive functioning after first-episode of psychosis: A six month follow-up study. *Schizophrenia Research* 182, 31–41.

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Haring L, Mõttus R, Jaanson P, Pilli R, Mägi K, & Maron E (2013). Subjective Well-Being Under Neuroleptics Scale short form (SWN-K): reliability and validity in an Estonian speaking sample. *Annals Of General Psychiatry* 12:28.

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2005–   SA TÜK Psühhiaatriakliinik, arst-õppejõud psühhiaatria erialal (1.0)

Teadus ja erialaline tegevus:
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Publikatsioonid: 8 rahvusvahelistes meditsiiniajakirjades
Liikmelisus: Eesti Psühhiaatrite Selts, liige
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Juhendatud väitekirjad:
Maret Trei, magistrikraad, 2015, (juh) Liina Haring, Liina Vahter, Esmase psühhoosiepisoodiga patsientide kognitiivne sooritus ajalises dünaamikas, Tartu Ülikool, sotsiaalteaduste valdkond, psühholoogia instituut.

Juhendamisel väitekirjad:
Jaana Mägi, magistrant (teaduskraad), (juh) Liina Haring, Karin Täht, Isikliku ja sotsiaalse toimetuleku skaala kohandamine eesti keelde, Tartu Ülikool, sotsiaalteaduste valdkond, psühholoogia instituut.
Siim Jakobsoo, magistrant (teaduskraad), (juh) Liina Haring, Karin Täht, Psühhoosiriski hindavate mõõdikute adapteerimine eesti keelde, Tartu Ülikool, sotsiaalteaduste valdkond, psühholoogia instituut.

Kirti-Ly Jaanson, magistrant (teaduskraad), (juh) Liina Haring, Karin Täht, Psühhoosiriski seosed kanepi kuritarvitamise ja päriliku eelsoodumusega, Tartu Ülikool, sotsiaalteaduste valdkond, psühholoogia instituut.

Publikatsioonid:

Haring L, Mõttus R, Kajalaid K, Koch K, Uppin K, Maron E, & Vasar E (2017). The course of cognitive functioning after first-episode of psychosis: A six month follow-up study. *Schizophrenia Research* 182, 31–41.

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Koido K, Innos J, **Haring L**, Zilmer M, Ottas A, & Vasar E (2016). Taurine and Epidermal Growth Factor Belong to the Signature of First-Episode Psychosis. *Frontiers in Neuroscience* Vol.10, pp. 331.

Kriisa K, **Haring L**, Vasar E, Koido K, Janno S, Vasar V, Zilmer K, & Zilmer M (2016). Antipsychotic Treatment Reduces Indices of Oxidative Stress in First-Episode Psychosis Patients. *Oxidative Medicine and Cellular Longevity* 2016, 1–7.

Haring L, Mõttus R, Koch K, Trei M, & Maron E (2015). Factorial validity, measurement equivalence and cognitive performance of the Cambridge Neuropsychological Test Automated Battery (CANTAB) between patients with first-episode psychosis and healthy volunteers. *Psychological Medicine* 45, 1919–1929.

Haring L, Koido K, Vasar V, Leping V, Zilmer K, Zilmer M, & Vasar E (2015). Antipsychotic treatment reduces psychotic symptoms and markers of low-grade inflammation in first-episode psychosis patients, but increases their body mass index. *Schizophrenia Research* 169, 22–29.

Haring L, Mõttus R, Jaanson P, Pilli R, Mägi K, & Maron E (2013). Subjective Well-Being Under Neuroleptics Scale short form (SWN-K): reliability and validity in an Estonian speaking sample. *Annals Of General Psychiatry* 12:28.

DISSERTATIONES NEUROSCIENTIAE
UNIVERSITATIS TARTUENSIS

1. **Sirli Raud.** Cholecystokinin$_2$ receptor deficient mice: changes in function of GABA-ergic system. Tartu, 2005.
2. **Kati Koido.** Single-nucleotide polymorphism profiling of 22 candidate genes in mood and anxiety disorders. Tartu, 2005.
3. **Dzhamilja Safiulina.** The studies of mitochondria in cultured cerebellar granule neurons: characterization of mitochondrial function, volume homeostasis and interaction with neurosteroids. Tartu, 2006.
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6. **Annika Vaarmann**. The studies on cystatin B deficient mice: neuro-chemical and behavioural alterations in animal model of progressive myo-clonus epilepsy of Unverricht-Lundborg type. Tartu, 2007.
7. **Urho Abramov.** Sex and environmental factors determine the behavioural phenotype of mice lacking CCK$_2$ receptors: implications for the beha-vioural studies in transgenic lines. Tartu, 2008.
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