The outcome of psychosis

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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE

This thesis focuses on several aspects of schizophrenia and related psychotic disorder outcomes. The main goal is to examine factors related to mental health outcomes (i.e. symptomatic and global (or general) functioning) and physical outcomes (metabolic and olfactory functioning) in psychosis. Understanding which factors are related to the outcome of psychosis (and schizophrenia) could clarify some of its complexity and might ameliorate prognostic estimations. Furthermore, it potentially will help mitigate the pathological course, which is often present in schizophrenia. An important related question is: why are some patients more resilient than others?

1. PSYCHOSIS

Schizophrenia spectrum disorders, classified as psychotic disorders, are considered one of the most serious life shortening, burdening mental illnesses worldwide, at a personal, familial and societal level (Charlson et al., 2018; Chong et al., 2016; Global Burden of Disease, 2016), with approximately a 2– to 3–fold mortality risk compared to the general population (Crump et al., 2013; Olfsen et al., 2015). Besides a higher chance of an unnatural death (e.g. a high suicide rate; Reininghaus et al., 2015; Simon et al., 2018), this is mainly caused by the unhealthy lifestyles and a greater (genetic) chance of physical comorbidities associated with psychosis (Das–Munshi et. al., 2017; de Hert et al., 2011; van Welie et al., 2013). Up to sixty percent of excess death in serious mental illnesses is associated with mostly preventable physical comorbidities, such as diabetes mellitus type 2, obesity, dyslipidemia and hypertension (Parks et al., 2006).

The lifetime prevalence rate of psychosis is estimated at approximately 0.7%, with higher rates in developed countries compared to less developed ones (McGrath et al., 2008), and no apparent lifetime prevalence difference between sexes (Charlson et al., 2018). However, men tend to have a younger age of illness onset as compared to women (Barajas et al., 2015). Schizophrenia is a heterogeneous illness, with a clinical presentation characterized by either a chronic, recurrent or a single episode of psychotic positive symptoms, negative symptoms and/or cognitive deficits (for formal diagnostic classification see DSM–5; APA, 2013). Positive symptoms comprise hallucinations, delusions, catatonia, and disorganized thinking. Negative symptoms, implying the absence of normal functioning, include anhedonia, lack of motivation and social withdrawal. Especially the negative symptoms are associated with the inability to function independently (Marder and Galderisi, 2017), and are, in contrast to positive symptoms, more chronic and resistant against psychotropic medication (Miyamoto et al., 2012; Remington et al., 2016). Cognitive deficits are argued to be a core characteristic of schizophrenia as well (Kahn and Keefe, 2013), although not formally described in the classification criteria for schizophrenia (DSM–5; APA, 2013).

The symptoms associated with psychosis tend to have devastating effects on global, social, occupational and daily functioning, and quality of life (Suttajit et al., 2015 a, b).

While the development of schizophrenia is thought to have its origins prenatally, diagnosis of the illness tends to take place between the ages of 16 and 30 years old, and on average peaks between the ages of 20 and 25 (Mueser and Mcgurk, 2004). To date, the exact causes of psychosis are still unknown, but research indicates that risk factors include genetic vulnerability (Hilker et al., 2017; Ripke et al., 2014), (pre– and perinatal) environmental and social disturbances (Davis et al., 2016; Meli et al., 2012) and substance abuse (Verweij et al., 2017). In addition, lower socioeconomic status and housing instability may increase the likelihood of onset of the illness (Murray et al., 2017; van Os et al., 2010), as well as having a minority status (Kirkbride et al., 2017; Murray et al., 2017) and a high level of urbanicity (Krabbendam and van Os, 2005).

2. PREMORBID AND PRODROMAL MANIFESTATION

Although schizophrenia's overt symptoms are mostly expressed in the late adolescent or early adulthood phase of life, precursors of the illness in the premorbid phase include behavioural abnormalities in childhood, the presence of motor deficits, aberrant development of speech, language and cognition (Mollon et al., 2018; Welham et al., 2009), low school performance (Fuller et al., 2002; Kendler et al., 2016) and school dropout (Goulding et al., 2010). In prospective studies it was found that children who eventually develop schizophrenia in adulthood have lower cognitive abilities of approximately –0.5 standard deviation compared to their peers, present as early as seven years of age (Keefe and Fenton, 2007; Seidman et al., 2006). Moreover, social deficits related to the development of schizophrenia include impairment in sociability and social difficulties with peers in childhood (Cannon et al., 2001; Horton et al., 2015), preference for solitary play at four years of age (Jones et al., 1994), lower teacher ratings of childhood social and peer related functioning (Tsuji et al., 2013). These early signs suggest that schizophrenia is a disorder with neurodevelopmental disturbances (Murray et al., 2017). Further supporting the neurodevelopmental hypotheses of schizophrenia are structural brain abnormalities typically present in schizophrenia (i.e. enlarged ventricles), which are found to be associated with poor premorbid functioning in childhood (DeLisi et al., 1998). Other brain abnormalities associated with schizophrenia (i.e. reduced intracranial volume, grey matter and white matter) are also thought to have its origins in childhood (Pantelis et al., 2005; Smieskova et al., 2010), and may thus reflect a neurodevelopmental vulnerability, inducing schizophrenia's overt symptoms later in life. Interestingly, up to 90 % of the brain's volume is reached at the age of five (Sgouros et al., 1999), thus deficits found in brain volume at the age

when schizophrenia is diagnosed (Haijma et al., 2013) reflect a deficit originating from childhood.

In the period directly preceding the illness onset, prodromal signs are mostly recognized by a functional deterioration (i.e. academic, occupational and social problems), and non–specific psychiatric symptoms (i.e. depression and anxiety), which in a later phase is followed by attenuated psychotic symptoms, which gradually become worse (Keshevan et al., 2011).

3. MATERIALS

THE GENETIC RISK AND OUTCOME OF PSYCHOSIS STUDY

The studies presented in this thesis utilized data collected in the Genetic Risk and Outcome of Psychosis (GROUP) project. The GROUP project is a longitudinal naturalistic cohort study that conducted baseline, three–year and six–year follow–up measurements, and is designed to register vulnerability and resilience factors for illness course and outcomes of psychosis. GROUP is set up by a consortium of four universities in the Netherlands, in Amsterdam, Groningen, Maastricht and Utrecht.

Cases include those with first episode psychosis (schizophrenia and schizophrenia spectrum disorders) or more chronic patients. Patients assessment of GROUP includes elaborate records of demographic factors (e.g. age, gender, education, socioeconomic status, urbanicity), symptom assessment (lifetime and present state), medication use, comorbidities (e.g. substance use, depression, extrapyramidal symptoms), need of care, neuroimaging (fractional anisotropy (FA)/ diffusion tensor imaging (DTI), structural magnetic resonance imaging (sMRI)), elaborate (premorbid and social) neurocognitive assessment, genetic assessment, quality of life and a physical examination (blood samples, weight, height, waist circumference and blood pressure measurements). Procedure and detailed instrument description of the project has been written down by Korver and colleagues (2012).

4. OUTLINE

The overall aim of the research presented in this thesis is to identify determinants (in childhood, adolescence and after illness onset) of psychosis outcomes at a mental health and physical level. The thesis is divided in two parts. In the first part, we present studies exploring premorbid and baseline factors related to mental health outcomes–short–term at group level, and long–term at an individual level. In the second part, the

focus will be on cognitive and structural imaging measurements and the relation to physical outcomes of the metabolic syndrome (MetS) and olfactory identification (OI), with longitudinal retrospective and cross–sectional designs.

PART I: MENTAL HEALTH OUTCOMES

Besides heterogeneity in etiology and clinical presentation, outcomes for schizophrenia are heterogeneous as well. Outcomes can differ from full recovery to chronic severe symptomatology. Although psychosis has a high tendency to show relapse, (re) hospitalization and chronicity (Alvarez–Jimenez et al., 2012; Emsley et al., 2013), it is estimated that after having had a first psychosis approximately half of the patients have fairly good outcomes (low or of free symptoms and minimal functional disabilities) in the long term after illness onset (Lambert et al., 2010). A small number of patients remit clinically and recover functionally (13%; the latter meaning returning to former level of social and daily functioning; Albert et al., 2011; Jääskeläinen et al., 2013; White et al., 2009). Contrary, approximately three quarters of schizophrenia patients have relapses after a first psychosis (Capite et al., 2016; White et al., 2009) and (re)hospitalization is frequent (Strålin and Hetta 2018).

Multiple attempts have been made to find predictors of mental health outcomes (Lambert et al., 2010), since this is an important step in prognostic estimations of psychosis. For example, the degree of psychotic symptomatology is strongly related to symptomatic outcome (Chang et al., 2013; Díaz–Caneja et al., 2015; Koutsouleris et al., 2016). Predictors for symptomatic and global functioning outcomes have also been found to include demographic and illness related variables (e.g. gender, educational and occupational attainment, psychiatric comorbidities, degree of need of care; Koutsouleris et al., 2016; Lambert et al., 2010; Díaz–Caneja et al., 2015; Tsang et al., 2010), environmental factors (e.g. substance use; Weibell et al., 2017; living in deprived neighbourhoods; Heslin et al., 2018), (premorbid) neurocognitive (Chang et al., 2013; Torgalsbøen et al., 2014; Tsang et al., 2010) and social cognitive functioning (Maat et al., 2015).

The studies investigating cognitive predictors of psychosis outcome only investigated very short–term outcome (six months–one year), are small, lack a consensus definition of outcome, and/or do not include social cognition. In **chapter 2** we will explore predictors of three–year outcomes of remission, defined by consensus (Andreasen et al., 2005), and compulsory hospitalization, investigated at group level. Predictors include a comprehensive test–battery of cognitive and social cognitive domains, demographic and clinical information and comorbid substance abuse.

Many studies have shown that mental health outcomes are associated with aforementioned predictive factors at the level of correlations. Research on mental health long–term outcomes (>5 years follow–up) is sparse and despite this abundance of outcome predictors found at group level (Díaz–Caneja et al., 2015; Lambert et al., 2010), no clinical prediction model for long–term outcomes of schizophrenia is currently available at an individual patient level (Millan et al., 2016). Therefore we will provide in **chapter 3** research on the development of prediction models using machine learning. In this study we aim to predict individual medium– and long–term symptomatic and global functioning outcome (after three and six years respectively) based on patterns that are present in a broad range of predictors at baseline (i.e. demographic, clinical, genetic, environmental, premorbid and present state cognitive, premorbid and present social cognitive and extrapyramidal predictors).

In psychosis outcome research attempts have also been made using brain imaging measures (endophenotypes) to predict outcomes. Reduced grey matter volumes in the frontal cortex were found to predict worse functional short– and long–term outcomes (Behere, 2013; Prasad et al., 2005) and more negative symptoms (Behere, 2013) after approximately six years. Besides grey matter volumes, aberrant brain network connectivity (white matter pathways wiring), which also reflects a neurodevelopmental vulnerability of schizophrenia (Collin and van den Heuvel, 2013), is suggested to be related to increased symptomatology (Wang et al., 2012; Yu et al., 2011). However, studies on predictive power of network organization for mental health outcomes are missing. In **chapter 4** we will address the question whether, and if so how, changes over time in global, symptomatic and intellectual functioning are predicted by macroscale connectome organization.

PART II: PHYSICAL OUTCOMES

Outcomes in schizophrenia have usually been categorized in terms of mental well–being, such as symptomatology, and global functioning. In this thesis the focus will also be on physical outcomes in relation to cognition and MRI measurements. Neurodevelopmental disturbances of (premorbid) cognitive deficits and brain abnormalities may provide a valuable contribution for explaining disadvantageous physical outcomes, such as metabolic and olfactory disturbances.

Olfactory identification (OI) deficit are very well established in schizophrenia and are thought to be a consequence of structural brain abnormalities. OI deficit is also argued to be a marker of aberrant prenatal neurodevelopment (Turetsky, 2009; Nguyen et al., 2011; Takahashi et al., 2013), and it was found to be predictive of transition to psychosis (Woodberry et al., 2010). OI deficit is strongly related to impairment in other cognitive

functions, since OI and cognitive/social functioning share similar neural substrates, in particular of the frontotemporal structures in schizophrenia (Aleman, 2014; Nguyen et al., 2010; Turetsky et al., 2009). However, performed studies thus far investigating the association between OI and other cognitive domains include a limited range of cognitive domains, and are hampered because they lack the use of a range of possible confounders such as age, gender, smoking and the use of antipsychotics, potentially associated with OI (Moberg et al., 2014). Furthermore, no studies have been performed investigating the relationship of OI deficit with premorbid (social) cognitive abnormalities, which both are proximities of early aberrant neurodevelopment in schizophrenia. In **chapter 5**, we will investigate olfaction as an outcome of interest in relation to cognitive course, because it potentially sheds light on schizophrenia etiology. We focus on the lifetime cognitive course of premorbid cognition and premorbid social functioning in childhood and adolescence and a broad range of present state cognitive domains in association with present state OI functioning.

Metabolic complications and related cardiovascular risk are widespread in schizophrenia and contribute to the reduced life expectancy of about 15–20 years in patients (Nordentoft et al., 2013). The incidence of metabolic syndrome (MetS), which a cluster of metabolic risk factors (i.e. abdominal adiposity, hypertension, dyslipidemia and hyperglycemia), is still highly alarming in schizophrenia, despite the awareness of the necessity to prevent and treat MetS in schizophrenia to improve life expectancy. Prevalence rates of 30% to 50% are reported, with a risk ratio of two– to three–fold compared to the general population (de Hert et al., 2009; Mitchell et al., 2013; Papanastasiou 2013). MetS leads to a two– to three–fold increase in cardiovascular mortality and diabetes mellitus type two (Ford et al., 2005; Sung et al., 2015), two of the six leading death causes worldwide (WHO, 2016).

Besides a genetic vulnerability for developing metabolic disorders in schizophrenia (Malan–Müller et al., 2016; van Welie et al., 2013; Liu et al.,2013; Risselada et al., 2012), this high prevalence may be partly due to individual lifestyle choices, based upon the fact that the majority of the patients does not meet minimal physical activity recommendations (Stubbes et al., 2016). Other behavioural factors include a sedentary lifestyle (Vancampfort et. al. 2012a), a reduced nutritional status due to an unhealthy diet low in fiber (Dipasquale et al., 2013) and a lessened intake of unsaturated fatty acids (Dipasquale et al., 2013; Strassnig et al., 2005), in combination with the fact that schizophrenia patients tend to eat more (Kouidrat et al., 2014). Furthermore, approximately 60% of the patients smoke (Myles et al., 2012). Also, putative causes are disease related factors. First, psychotropic medication can induce and worsen weight gain (Bak et al., 2014). Second, a lack of motivation to be physically active (Farholm et

al., 2017), together with sedative effects of medication (Vancampfort et al., 2012b) and lack of a social support system to adopt a healthy lifestyle (Soundy et al., 2014) may result in inactivity. All these behaviours will induce the onset of MetS and proneness to developing diabetes mellitus type 2 and cardiovascular diseases.

High prevalence of MetS is a very disadvantageous outcome of schizophrenia for various reasons. Besides the increased mortality risk associated with the syndrome, brain abnormalities (i.e. reduced hippocampal volume, increased cerebrospinal fluid, and reduced frontal lobe volume) are well established in people with MetS (Yau et al., 2012; Yates et al., 2012). Also, MetS has been related to an increase in anxiety, depression (Nousen et al., 2013) and to cognitive deficits (McEvoy et al., 2012). Previous research has focused on the association between decreased brain integrity/cognitive deficits and metabolic comorbidities in the general population (Yaffe et al., 2004; Yau et al., 2012; Cavalieri et al., 2010; Yates et al., 2012; Smith et al., 2011). Studies of non–psychiatric samples describe MetS to cause high neuroinflammation (Yaffe et al., 2004) and brain infarction vulnerability (Kwon et al., 2006). Also, MetS has been associated with vascular abnormalities and oxidative stress (Yates et al., 2012). These devastating effects of MetS on the brain could be causing cognitive dysfunction. Treating and attenuating metabolic complication might thus be an important treatment target for cognitive deficits.

A role of cognitive deficit in the development of metabolic complications has also been suggested (Smith et al., 2011; Boyer et al., 2014; Kenny, 2012). Cognitive impairment, for example, in executive functioning or reward related functions, is a core characteristic of schizophrenia and may play an important role in the adoption of health–promoting lifestyles. The cognitive course might thus be of importance to the development of metabolic complications. Since cognitive dysfunction in schizophrenia has its origins in childhood, premorbid cognition might also be associated with MetS prevalence. However, no studies have been performed to investigate this long–term course of (premorbid and present state) cognitive functioning in relation to MetS in schizophrenia. In **chapter 6** we will investigate whether schizophrenia patients with and without MetS differ in premorbid (social) cognitive functioning. Furthermore, no structural MRI studies have been performed to examine the association between MetS and brain volumes in schizophrenia– neither in global measures, nor in specific reward related brain structure volumes. In **chapter 7** we will investigate whether grey and white matter brain volumes and ventricular volume are related to MetS prevalence. Especially, we investigate reward related grey matter brain areas, since they play a major role in regulating health behaviour, which is a major risk factor for the development of MetS.

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PART I

MENTAL HEALTH OUTCOMES

CHAPTER 2

THE ASSOCIATION BETWEEN COGNITIVE DEFICITS AND DIFFERENT OUTCOMES OF SCHIZOPHRENIA

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ABSTRACT

Background: Schizophrenia is a disorder with different outcomes. Besides the positive and negative symptoms, cognitive impairment is an important core feature of schizophrenia and often pre–dates the disorder. Cognition has consistently been related to outcome in schizophrenia. Given this finding and the fact that diagnosing and treating schizophrenia as early as possible has better outcome chances, the current study investigated the hypothesis that cognitive performance is associated with two seemingly opposite outcomes: clinical remission and forced hospitalization three years after first assessment.

Methods: Subjects in the current study were schizophrenia patients not in an active psychosis during cognitive testing (N=321). The results of the cognitive tests were used as predictor variables for the status of remission or the occurrence of a forced hospitalization in the three years following the cognitive testing. The cognitive tests included were WAIS–III subtests (Digit symbol, Information, Arithmetic, Block Design), Benton Facial Recognition task, Hinting task and the Rey Auditory Verbal Learning task. Besides these cognitive predictors, several relevant covariates (gender, age, education, number of psychotic episodes, duration of illness and amphetamine, cannabis or cocaine intoxication) were analysed. Two multinomial logistic regression analyses were conducted with the cognitive tests as independent variables and remission and forced hospitalization as dependent variables in separate models.

Results: The results showed that better performance on the verbal tasks (WAIS–III arithmetic score (b=0.17) and the WAIS–III information score (b=0.22)) and less psychotic episodes (b=–0.64) was associated with remission status. Worse performance on the memory task (b=–0.20) and more psychotic episodes (b=0.85) was related to forced hospitalization.

Conclusion: this three–year longitudinal study showed that higher verbal IQ is a protective factor and poor memory and higher number of psychotic episodes are risk factors of the outcome of schizophrenia. This suggests that future research on prediction tools for the outcome of schizophrenia should include assessment of (verbal) IQ and verbal memory.

Keywords: schizophrenia, outcome, remission, forced hospitalization, cognition

1. INTRODUCTION

The course of schizophrenia shows considerable heterogeneity and a great amount of variability exists in the etiology, symptomology and outcome of the illness. Within the defined prodromal, acute and the residual stage of schizophrenia (Barnett and Levitt, 2007), diversity in progression of the illness can be specified. One of the first and most influential longitudinal studies of Manfred Bleuler (1978) on the course of schizophrenia described eight course types, wherein variation existed concerning onset (abrupt versus insidious), symptom presentation (continuous versus intermittent) and outcome (poor versus non–poor). Only approximately 20 percent had the stereotypical insidious onset, continuous symptoms, and poor outcome.

Other influential longitudinal studies of schizophrenia demonstrate that the course of schizophrenia is not uniform (Harding et al., 1987; Hopper et al., 2007). The DSM–V has specified several course components that can be used one year after the diagnosis for describing the longitudinal course; continuous symptoms, multiple episodes in full remission, multiple episodes in partial remission, multiple episodes– currently in an acute episode, first episode in partial remission, first episode in full remission and an unspecified pattern (APA, 2000; Tandon et al., 2013).

Some patients experience only one psychotic episode. However, it is more common for patients with schizophrenia to experience multiple psychotic episodes with potential recurrent hospitalizations (Emsley et al., 2013; Alvarez–Jimenez et al., 2012). The description of the different outcomes as stated above, does not contain recovery; an ill–defined construct in schizophrenia. Several studies (Robinson et al., 2004; Harrison et al., 2001) have concluded that recovery is rare and currently there are no accepted scales to measure recovery (Bellack, 2006). A more clinically useful concept may be remission of schizophrenia (Fischer 2008). In remission, the individual has no or minimal symptoms that do not interfere with functioning for a period of six months (Andreasen et al., 2005). The Worldwide Schizophrenia Outpatient Health Outcomes study (Haro et al., 2011), in which 11.078 patients were analysed from 37 different countries, found a mean rate of 66.1% (range: 60.1% in North Europe to 84.4% in East Asia) for schizophrenia patients to reach remission after three years follow–up.

Cognitive deficits have been related to disadvantageous functional outcomes of independent living, social functioning, and vocational functioning in schizophrenia (Green 2004) and to adverse symptomatic/clinical outcomes (Lepage et al., 2014). Traditionally, cognitive impairment was thought to be evident only in elderly patients with schizophrenia. However, over the past decades, accumulating evidence has challenged this view (O'Connor, 2000; Reichenberg and Harvey, 2007; Green et al.,

2000). It has even been suggested that the diagnostic criteria of schizophrenia should include specific reference to cognitive impairments characterizing the disorder (Bora et al., 2010; Kahn and Keefe, 2013). People with schizophrenia have been shown to have a wide range of cognitive deficits which is reflected by impairments in intelligence, memory, speed of processing, attention and executive functioning (Bowie and Harvey, 2006; Mueser and McGurk, 2004; van Os and Kapur, 2009). Furthermore, cognitive deficits may predict non–remission status (Chang et al., 2013; Helldin et al., 2006), impede occupational rehabilitation (Bell and Bryson, 2001), or deteriorate insight (i.e. unawareness of illness).

This current longitudinal study investigates whether baseline cognitive deficits in schizophrenia are related to two seemingly opposite outcomes– clinical remission and forced hospitalizations– after three years.

2. METHODS

2.1. STUDY POPULATION

This trial was part of the Dutch longitudinal Genetic Risk and Outcome of Psychosis study (GROUP–project), a collaboration between academic institutions in Amsterdam, Groningen, Maastricht and Utrecht and a great amount of attached healthcare centres. The study focused on the interaction between various vulnerability and protective factors as well as genetic variation associated with the development of psychosis (Korver et al., 2012). Subjects were invited to several diagnostic interviews, neuropsychological tasks, blood and urine sampling as well as MRI. After both three and six year time intervals, participants were again invited for testing. Measurement inclusion criteria for patients were as follows: 1) age range between 16 and 50 years old 2) diagnosis of non–affective psychotic disorder and 3) good command of the Dutch language. The study protocol was approved by the Ethical review Board of the University Medical Center of Utrecht and each participating centre. Before participating, all subjects obtained a written informed consent.

For our patient sample, two extra criteria were added in the current study (see flow chart figure 1). The first extra inclusion criterion is a diagnosis of schizophrenia (DSM–IV diagnosis of 295.xx) during the first assessment and the three years follow–up measurement as assessed by the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) or the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990). Not all schizophrenia patients in the GROUP project had a diagnosis of schizophrenic disorder during both measurements. This

could be due subtle diagnostic and/or symptomatology changes between initial and subsequent inclusion. The second extra criterion was an exclusion criterion; patients who were in an active psychosis according to the definition of Evensen et al. (2012) during the cognitive tests, were excluded.

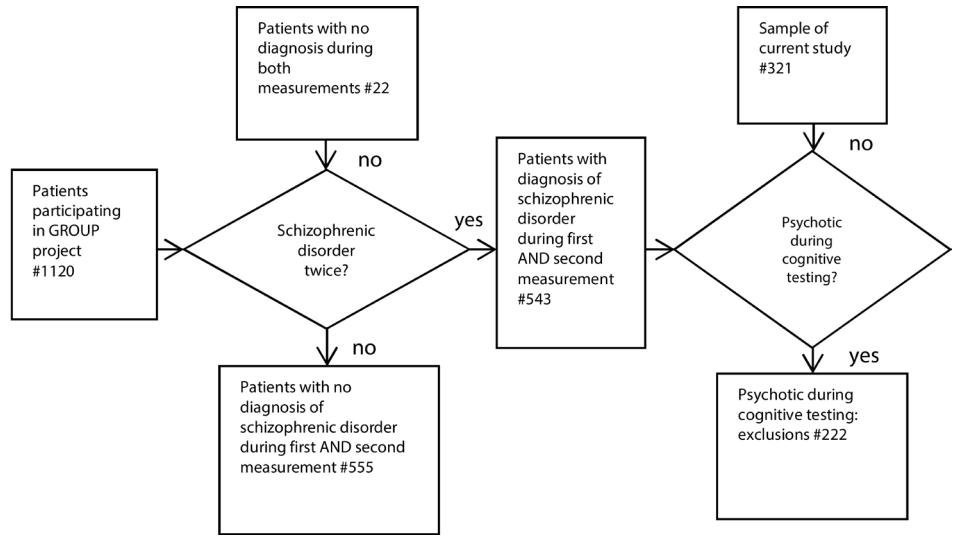

FIGURE 1. Flow chart demonstrating the formation of the sample used in this study.

2.2. CLINICAL MEASURES

All relevant demographic information including age, educational degree, age of onset of psychosis, duration of the illness as well as number of psychotic episodes and medication use was obtained by diagnostic interview. The cumulative number of psychotic episodes was obtained through self–report at inclusion and at follow–up. As the number of episodes may be dependent on duration of illness, we added separately duration of illness and total number of episodes (per year) since illness onset as covariates. This did not change any of the results.

Additionally, besides CASH and SCAN, basic clinical characteristics were assessed. The variety of positive and negative symptoms of schizophrenia as well as the general psychopathology during the past week was obtained via the Positive and Negative Syndrome Scale (Kay et al., 1987).

Cognitive assessment was done using an extensive neuropsychological test battery which is summarized in table 1. The tests were administered in a fixed order. A short version of the Wechsler Adult Intelligence Scale– Third Edition short form (WAIS–III SF) (Wechsler, 1997; Christensen et al., 2007) was used to assess patients Intelligence

TABLE 1. Explanation of the Cognitive Tests used in the GROUP Project

Task (reference)	Neurocognitive domain	Measurements	Reliability and validity of test
Word Learning Task (Brand and Jolles, 1985) [a]	Verbal learning and memory	– Total (of 3 trials) correct immediate recall – Total (of 3 trials) incorrect immediate recall – Total (of 3 trials) perseverations immediate recall – Total correct delayed recall (after 20 minutes) – Total incorrect delayed recall – Total perseverations delayed recall	Reported reliability: 0.70 for List A (Snow et al., 1988). Test–retest reliability for a one– year interval between test administration was reported moderate, 0.55 (Snow et al., 1988). Correlations ratings of 0.50 to 0.65 with other factor grouping and other learning tools (Macartney–Filgnate and Vriezen, 1988) supports RAVLT validity.
Digit symbol (WAIS–III; Wechsler, 1997) [b]	Processing speed	Number of correct items in 120 seconds. The four WAIS–III tasks are summed up; a total scaled score is calculated by (score *11/4). The IQ score is derived from this score	The test–retest reliability is for the different constructs (Niolon, 2005): Full Scale: 0.96; Verbal IQ: 0.96; Performance IQ: 0.91; Verbal Comprehension: 0.95; Perceptual Organization: 0.88; Working Memory: 0.89 Processing Speed: 0.89. Content Validity was established by expert judges who reviewed the items. Criterion Validity was established by correlating WAIS–R and WAIS–III. The numbers are good. Construct Validity was established using a factor analysis. g Was supported, and verbal subtests correlated better with each other than performance subtests. (Niolon, 2005).
Block design (WAIS–III; Wechsler, 1997)	Reasoning and problem solving	Score is dependent on solving speed. The four WAIS–III tasks are summed up; a total scaled score is calculated by (score *11/4). The IQ score is derived from this score	
Information (WAIS–III; Wechsler, 1997)	Acquired knowledge	Number of Items correct. The four WAIS–III tasks are summed up; a total scaled score is calculated by (score *11/4). The IQ score is derived from this score	
Arithmetic (WAIS–III; Wechsler, 1997)	Working memory	Score is dependent on solving speed. The four WAIS–III tasks are summed up; a total scaled score is calculated by (score *11/4). The IQ score is derived from this score	
Benton Facial Recognition Task (Benton et al., 1983)	Visuospatial discrimination of unfamiliar faces	Total correct score (maximum score=27)	Reliability for this test is 0.73. The validity numbers are good (Bradley et al., 2003)
Hinting Task (Corcoran et al., 1995)	Theory of mind (social cognition)	Total correct score (maximum score=20)	Reliability for this test is 0.65 (Roberts and Penn, 2009)

[a] Computerized assessment using E–prime 1.3.
[b] WAIS–III: Wechsler Adult Intelligence Scale.

Quotient (IQ) as measured with the following subtasks: Arithmetic (which measures working memory), Information (which measures general knowledge and long–term memory), Digit–Symbol Coding (as a measure of processing speed) and Block Design (as a measure of problem solving). Together, Arithmetic and Information subtasks measure the verbal IQ. Symbol Coding and Block Design measure the performance IQ. This method proved to be a reliable method for calculating the total IQ score for patients diagnosed with schizophrenia (Velthorst et al., 2013).

Recent cannabis, amphetamine and cocaine use was established by urinalysis by the Jellinek Clinic Laboratory. Cutoff level was 50 ng/ml, 1000 ng/ml and 300 ng/ml respectively.

2.3. MEASUREMENT OF REMISSION AND FORCED HOSPITALIZATION

The status of remission was determined by the remission tool (Andreasen et al., 2005), which is based on the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987). This tool defines remission as a period of at least six months in which the main symptoms are maintained on a low level. This means they have to be scored on PANSS as mild (score 3) or lower. The main PANSS symptoms are delusions (P1), conceptual disorganization (P2), hallucinatory behaviour (P3), blunted affect (N1), social withdrawal (N4) and lack of spontaneity (N6), mannerism and posturing (G5) and unusual thoughts (G9). During interview the number of forced hospitalizations so far is enquired by self–report.

2.4. SELECTION OF NON–PSYCHOTIC GROUP

To determine whether a patient was psychotic during the cognitive assessment, the method of Evensen et al. (2012) was applied. They state that a score of 4 or higher (out of 7) on one the following items defines a psychosis: Delusions, Hallucinations, Grandiosity, Suspiciousness/ Persecution or Unusual thought content.

2.5. STATISTICAL ANALYSIS

The cognitive tests as shown in table 1 (Brand and Jolles, 1985; Snow et al., 1988; Macartney–Filgate and Vrieze, 1988; Niolon, 2005; Benton et al., 1983; Bradley et al., 2003; Corcoran et al., 1995; Roberts and Penn, 2009) were administered to assess neurocognitive functioning of the participants during the first measurement. The scores on these tests were used as the independent variables. The outcome variables consisted of remission tool scores and the self–report regarding the forced hospitalizations during the follow–up measurement approximately three years later.

Because the main focus of this study targets a potential association between cognitive predictors and two different outcomes of schizophrenia, while taking into account several covariates, multinomial logistic regressions were used. In separate analyses, the association between cognitive factors (the four subscale WAIS–III scores, the Benton Facial score, the Hinting score and the number of correct items on the immediate recall of the verbal learning task and covariates) and the different outcomes (remission status and forced hospitalization) was tested. All tests were two–tailed at a significance level of p=0.05. Data were analysed using the IBM Statistical Package for the Social Sciences (SPSS) version 20.0.0.

3. RESULTS

3.1. OUTCOME AT 3 YEARS FOLLOW–UP

Table 2 shows the demographic characteristics of the sample as well as the results on the cognitive tests.

TABLE 2. Characteristics of the Sample

	In remission three years later		
	Yes	**No**	**Unknown**
	N=207	**N=100**	**N=14**
Forced hospitalization in 3 years to follow			
Yes	13	17	1
No	194	83	13
Demographic variables			
Sex. M/F	148/59	77/23	12/2
	Mean (sd)	Mean (sd)	Mean (sd)
Age at first inclusion	27.6 (6.5)	29.2 (8.0)	23.4 (4.9)
Duration of illness	4.7 (3.7)	4.9 (4.1)	4.7 (3.0)
Education	4.6 (1.9)	3.9 (2.3)	3.1 (1.9)
PANSS total	43.5 (9.6)	50.3 (11.8)	50.0 (14.8)
Positive symptoms	9.2 (2.4)	10.0 (2.4)	10.3 (2.6)
Negative symptoms	11.3 (4.8)	14.4 (5.9)	13.5 (6.2)
Cognitive tests results			

TABLE 2. Continued

	In remission three years later		
	Yes	**No**	**Unknown**
	N=207	**N=100**	**N=14**
IQ score	99.5 (15.2)	94.5 (17.6)	90.6 (14.8)
WAIS–III block score	10.2 (3.3)	9.5 (3.5)	10.3 (2.8)
WAIS–III calculation score	10.3 (3.2)	9.1 (3.2)	8.6 (3.8)
WAIS–III digit score	7.9 (2.9)	7.05 (2.8)	5.8 (3.0)
WAIS–III information score	11.4 (2.9)	10.7 (3.4)	9.7 (2.9)
Benton score	23.0 (2.1)	22.5 (2.4)	23.3 (1.6)
Hints score	17.6 (2.7)	17.3 (2.9)	16.9 (3.6)
RAVLT immediate correct	24.1 (5.7)	22.2 (6.9)	23.8 (7.7)

RAVLT: Rey Auditory Verbal Learning Test.

3.2. REMISSION

The first multinomial logistic regression analysis was conducted with the four subscale WAIS–III scores, the Benton score, the Hinting score and the number of correct items on the immediate recall of the RAVLT as predictors for the status of remission. The following covariates were also included in this analysis; gender, age, education, number of psychotic episodes, duration of illness and amphetamine, cannabis or cocaine intoxication (during the cognitive assessment with the result of the urine sample analysis).

Additional to the number of psychotic episodes, higher information and arithmetic subscales of the WAIS–III were significantly associated with remission (see table 3). The p–values were as follows: number of psychotic episodes (p=0.004), information score (p=0.017), arithmetic score (p=0.019). Additional to the logistic regression analyses, ROC curves were made to show the cutoff points for the predictors for remission (see figure 2, 3 and 4). The ROC curves show that 2 or less psychotic episodes in a lifetime so far predict the status of remission. A WAIS–III arithmetic score of 10 or more predicts remission, as well as a WAIS–III information score of 11 or more.

TABLE 3. Results of Multinomial Logistic Regression Analysis with cognitive predictors for Remission

		95% CI for Odds Ratio		
	b (SE)	**Lower**	**Odds ratio**	**Upper**
Intercept	1.38 (2.56)			
Age	−0.04 (0.03)	0.90	0.96	1.03
Education	0.14 (0.10)	0.94	1.16	1.41
Duration of illness	0.08 (0.06)	0.97	1.09	1.22
Number of psychotic episodes	−0.64 (0.22)*	0.34	0.53	0.82
Benton score	0.03 (0.08)	0.88	1.03	1.21
Hinting score	−0.04 (0.07)	0.84	0.96	1.10
Correct immediate RAVLT	0.40 (0.04)	0.97	1.04	1.12
WAIS–III Block design score	−0.04 (0.07)	0.84	0.96	1.09
WAIS–III Arithmetic score	0.17 (0.07)*	1.03	1.19	1.37
WAIS–III Digit symbol score	0.01 (0.07)	0.88	1.01	1.17
WAIS–III Information score	0.22 (0.09)*	0.67	0.81	0.97
Drug during tests	0.53 (1.67)	0.06	1.71	45.26
Gender	−0.04 (1.70)	0.04	0.97	26.91
Drugs × Gender	−0.09 (1.75)	0.03	0.92	28.07

Note: R^2=0.14 (Cox and Snell); 0.20 (Nagelkerke); Model χ^2 (14)=215.16.
*p<0.05.

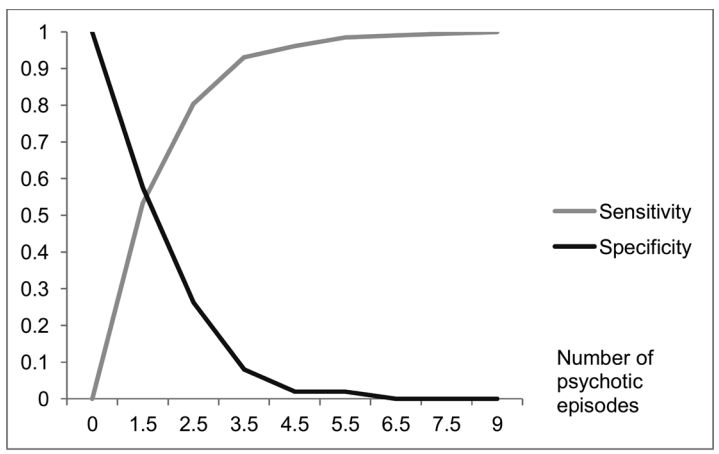

FIGURE 2. ROC curve for cutoff point number of psychotic episodes for the association with remission.

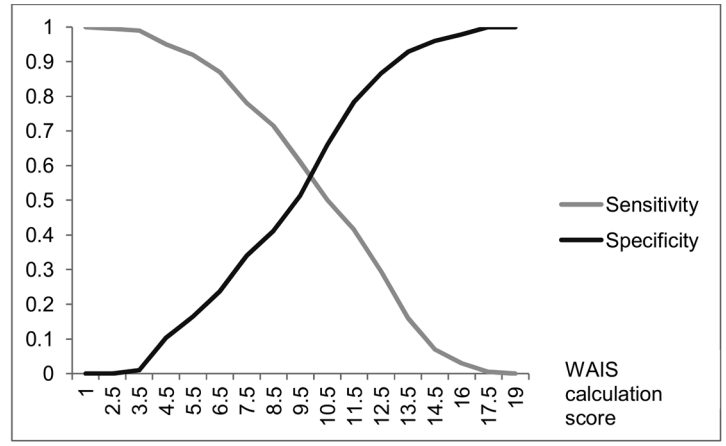

FIGURE 3. ROC curve for cutoff point WAIS arithmetic score for the association with remission.

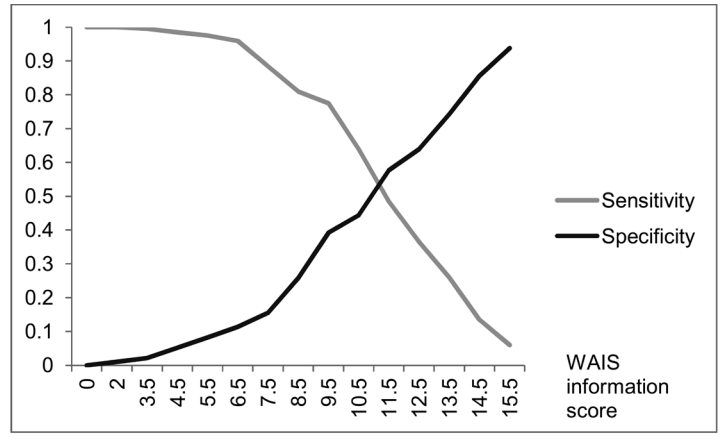

FIGURE 4. ROC curve for cutoff point WAIS information score for the association with remission.

3.3. FORCED HOSPITALIZATION

The second multinomial logistic regression analysis was conducted with the four subscale WAIS–III scores, the Benton score, the Hinting score and the number of correct items on the immediate recall of the RAVLT as predictors for forced hospitalization. The following covariates were included in this analysis; gender, age, education, number of psychotic episodes, duration of illness and amphetamine, cannabis or cocaine intoxication. Since negative symptoms predict poor outcome (Herbener and Harrow,

2004), the mean baseline score on the negative symptoms subscale of the PANNS was also added as a covariate.

The result of this multinomial logistic regression (see table 4) shows that less correct items on the immediate recall of the RAVLT (p=0.021), and more psychotic episodes (p=0.024) was associated with a forced hospitalization. ROC–curves (figure 5 and 6) show that two or more psychotic episodes was associated with a forced hospitalization and 22 or less correct items on the immediate recall was related to a forced hospitalization.

TABLE 4. Results of Multinomial Logistic Regression Analysis with cognitive predictors for Forced Hospitalization

		95% CI for Odds Ratio		
	b (SE)	**Lower**	**Odds ratio**	**Upper**
Intercept	–0.39 (4.09)			
Age	–0.05 (.07)	0.83	0.95	1.10
Education	–0.25 (.19)	0.53	0.78	1.13
Duration of illness	–0.17 (.15)	0.63	0.85	1.14
Number of psychotic episodes	0.85 (0.38)*	1.12	2.33	4.87
Negative symptoms PANSS	0.05 (0.07)	0.91	1.05	1.21
Benton score	0.26 (0.18)	0.92	1.30	1.83
Hinting score	–0.05 (0.11)	0.76	0.96	1.19
Correct immediate RAVLT	–0.20 (0.09)*	0.69	0.82	0.97
WAIS–III Block design score	–0.09 (0.13)	0.71	0.92	1.19
WAIS–III Arithmetic score	0.21 (0.16)	0.91	1.23	1.68
WAIS–III Digit symbol score	–0.13 (0.18)	0.62	0.88	1.24
WAIS–III Information score	0.15 (0.18)	0.81	1.16	1.65
Drug during tests	–3.55 (2.03)	0.00	0.03	1.52
Gender	–4.56 (2.14)	0.00	0.01	0.70
Drugs × Gender	4.18 (2.28)	0.74	65.08	5690.70

Note: R^2=0.11 (Cox and Snell); 0.28 (Nagelkerke); Model χ^2 (14)=86.90.
*p <0.05.

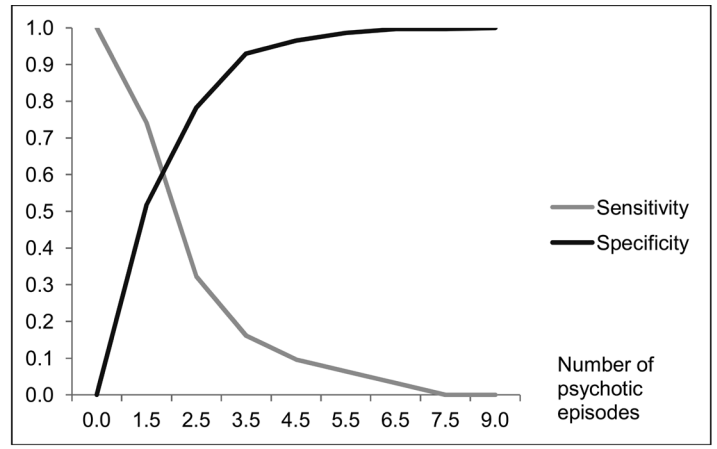

FIGURE 5. ROC curve for cutoff point number of psychotic episodes for the association with forced hospitalization.

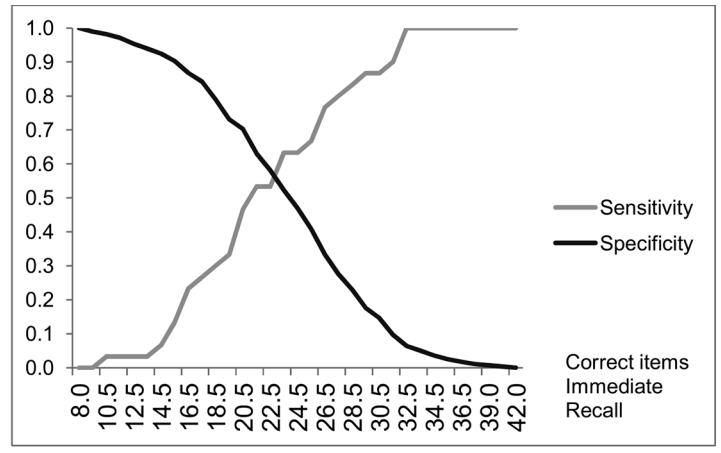

FIGURE 6. ROC curve for cutoff point number of correct items on immediate recall on the RAVLT for the association with forced hospitalization.

4. DISCUSSION

The aim of this study was to investigate the association of cognitive deficits at baseline with two opposite outcomes in schizophrenia: clinical remission and forced hospitalization, which were measured after three years. A variety of cognitive tests were used to test this hypothesis.

Higher baseline verbal IQ (WAIS–III arithmetic scores and WAIS–III information scores), but not performance intelligence, was related to a greater chance of remission after three years. This suggests that patients with an average (or above) verbal intelligence, in a non–active phase of the illness are more likely to reach the status of clinical remission in schizophrenia. Jones et al. showed already in 1994 that verbal skills are impaired in those children who later develop schizophrenia (Jones et al., 1994). This current study found that verbal intelligence, besides being associated with the development of schizophrenia, is also a related to schizophrenia outcome. In addition, number of psychotic episodes was associated with remission status. This is in line with studies showing that relapse and greater severity of schizophrenia is associated with the number of psychotic episodes (Chabungbam, 2007; Seok Jeong et al., 2005).

Forced hospitalization was associated with worse memory, in particular the encoding and learning skills, as measured by the number of correct items on the immediate recall of the RAVLT. Others also found deficits in memory functioning to be associated with the outcome of schizophrenia (Lepage et al., 2014), with moderate to high effect sizes ranging from Cohen's d value of 0.45 to 0.71. Despite this being a robust finding, some studies examining the relationship between verbal memory and outcome did not find a better memory performance for remitted patients (Hofer et al., 2011; Brissos et al., 2011). Lepage et al. (2014) stated that these studies used a somewhat less pure memory task, which also tapped into executive functioning. Furthermore, Diaz et al. (2013) and Buckley et al. (2007) did not find an association between RAVLT memory task and remission status. The discrepancy with our results may be due to sample selection. These studies did not exclude schizophrenia patients who were in an active psychosis, which is known to influence cognitive functioning.

Impaired memory may impede outcome in schizophrenia in various ways. For example, it has been found that worse memory functioning is associated with poorer treatment decisions, such as medication adherence and therapy compliance, (i.e. forgetting to take medication or go to mental health service appointments) (Donohoe et al., 2001; Prouteau et al., 2005). Worse memory has also been associated with a deterioration of insight, or unawareness of illness (Mysore et al., 2007; Aleman et al., 2006), which in turn may worsen outcome (Mintz et al., 2007).

Moreover, forced hospitalization was also related to the number of psychotic episodes during the three year follow–up. This is consistent with Chabungbam et al. (2007) showing patients in remission to retrospectively have an average of 2.9 psychotic episodes as compared to relapsed patients, who had an average of 4.4 psychotic episodes. In our study we showed that two or more psychotic episodes is associated with (non)remission status and forced hospitalization during three years of follow up with a sensitivity rate of 57 and 60 percent and a specificity rate of 40 and 43 percent respectively.

The results of this study might have some clinical implications. An important issue put forward by Kahn and Keefe (2013) is that in schizophrenia "the treatment of cognitive deficits should be central to any guidelines, which now it is not" (p.1110). Our results are proof of this important role of cognition in outcome of schizophrenia. To predict outcome, neuropsychological functioning could be used. In particular the two WAIS–III verbal tasks and the RAVLT task. A score of 22 or less on the immediate recall of the RAVLT and two or more psychotic episodes were related to a forced hospitalization in the future. It might be useful to integrate (verbal) IQ measurements, verbal memory RAVLT and previous psychotic episodes into a prediction tool to measure schizophrenia outcomes. If a patient is at high risk for forced hospitalization one should monitor the patient more closely. Furthermore, to achieve remission status and to prevent forced hospitalization in schizophrenia cognitive remediation, aiming to improve verbal and memory skills, might be of help. Cognitive remediation has shown moderate improvements on cognitive outcomes in schizophrenia (Wykes et al., 2011).

Nevertheless, there are several limitations to this study. First, although various cognitive domains have been examined, no information was gathered on executive functioning. Second, information on forced admission was gathered through patients' interviews, which might not be as accurate as gathering the information through medical notes. Third, the selection of patients in the non–active phase of the illness, which might have resulted into prediction to be more difficult for the entire group of patients with schizophrenia. Lastly, because of relatively small sensitivity and specificity rates, caution is warranted for generalizability of the results. Before implementing a valid outcome prediction tool in the clinical practice more research is recommended.

In conclusion, this three year longitudinal study in schizophrenia showed that higher verbal IQ is a protective factor and poor memory and higher number of psychotic episodes are risk factors in the outcome of schizophrenia. This suggests that future research on prediction tools for the outcome of schizophrenia should include assessment of (verbal) IQ and memory.

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CHAPTER 3

INDIVIDUALIZED PREDICTION OF THREE AND SIX YEAR OUTCOMES OF PSYCHOSIS IN A LONGITUDINAL MULTICENTRE STUDY: A MACHINE LEARNING APPROACH

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In preparation

ABSTRACT

Background: Schizophrenia and related disorders have heterogeneous outcomes. Predicting long–term outcome of psychosis may help improve treatment decision. We hypothesized that, using machine learning, it is possible to predict individual long–term outcome based on patterns present in baseline symptoms, demographic, clinical, cognitive, genetic and environmental factors.

Methods: 523 patients (mean (SD) age = 27.6 (7.4) year) were included and extensively assessed at baseline, 3– and 6–year follow–up. Outcome was defined as 1) being in remission or not in remission, according to a consensus definition; and 2) poor and good global functioning, using Global Assessment of Functioning (GAF) scale. A support vector machine was trained to predict outcome based on sets of features from a number of clinical instruments; and variables that were recently found to be predictive of short–term outcome (European First Episode Schizophrenia Trial). We tested performance of prediction models using recursive feature elimination, nested cross–validated, i.e. predicting outcome in patients not part of the training set.

Findings: For symptomatic outcome at follow–up, classification accuracies ranged from 62.2%–64.7%. For global outcome this ranged from 63.5%–67.6%. Important predictors included baseline GAF symptoms and GAF disabilities, quality of life, the use of antipsychotics, present state symptoms, social needs, education and schizophrenia diagnosis. Replication using the best scoring predictors of short–term outcome resulted in accuracies up to 66%.

Interpretation: Predicting long–term symptomatic and global outcome can be done with reasonable accuracies. We also showed that short–term outcome predictors are predictive of long–term outcome. Our study is a promising step in pursuit of personalized medicine applicability in mental care institutes. Our models need replication in independent samples.

Keywords: psychosis, symptomatic outcome, global outcome, individualized prediction, machine learning

1. INTRODUCTION

Schizophrenia is a heterogeneous illness and long–term outcomes in schizophrenia are highly variable (Volavka and Vevera, 2018; Morgan et al. 2014). Attempts to provide a prognosis for long–term outcome, such as Rumke's "praecox feeling", have appeared throughout medical history (Parnas, 2011). Despite an abundance of outcome predictors at group level, such as sociodemographic characteristics, clinical, and neurocognitive markers (Lambert et al., 2010; Díaz–Caneja et al., 2015), no clinically meaningful prediction model for long term outcome of schizophrenia is available at a patient level (Millan et al., 2016). This complicates clinical decision making, for example when considering an early switch to clozapine (Leucht et al., 2015), or dose reduction/ discontinuation strategies for antipsychotic medication (Wunderink et al., 2013). From a public health perspective, reliable long–term outcome prediction and the resulting treatment stratification are important as demands usually outweigh the capacity of institutions, even in countries with high expenses on mental healthcare (van Os and Delespaul, 2018).

Machine learning presents a way to reliable individual outcome prediction for multifactorial and heterogeneous illnesses, such as schizophrenia (Noble and Street, 2006; Koutsouleris et al., 2016, 2018; Kessler et al. 2016, Gifford et al., 2017, Janssen et al. 2018). In clinical research, machine learning, or pattern recognition, refers to an algorithm that is able to learn from a large multivariate dataset to make an adequate prediction for a patient, for example concerning future clinical outcome (Huys et al., 2016). Modern prospective multicentre studies facilitate the development of outcome prediction models based on machine learning. They provide well–established outcome measures and a large number of potential predictors (i.e. "features"), in study samples large enough to cover the heterogeneity of the target population (Dwyer et al., 2018). A landmark study by Koutsouleris et al. (2016) demonstrated recently the potential of machine learning for individual outcome prediction in psychosis. They used pre–treatment data from a multicentre clinical trial to predict global outcome after four weeks and one year of treatment in first episode psychosis. The predictive accuracy of their models was found significant above chance, with accuracies of approximately 75%. Furthermore, it retained its accuracy when the geographic sites were left out of the model training procedure, which is suggestive of its validity for other samples. Unemployment, lower education, functional deficits, and unmet psychosocial needs were found most useful in predicting four week outcome and one–year outcome.

In this present study, we extend the paradigm of machine learning prediction models based on patient reportable data to long–term (three and six year) outcome of a heterogeneous population of schizophrenia spectrum patients in a care–as–usual

setting. This implies including patients with variable durations of illness, and both good and poor baseline clinical status. We aim for concise sets of features from a number of clinical instruments, selected from a wide range of clinical characteristics, and assess their generalizability by testing our models on study sites left out of model development. Additionally, we investigate the external validity of patient reportable measures found to predict four–week and one–year outcomes of first episode psychosis (Koutsouleris et al., 2016) for long–term outcome. To this end, we use baseline characteristics and three– and six–year symptomatic and global outcomes of patients from the Genetic Risk and Outcome in Psychosis (GROUP) prospective longitudinal cohort study (Korver et al., 2012).

2. METHODS

2.1. STUDY SAMPLE AND DATA SELECTION

The GROUP prospective longitudinal cohort study has been described elsewhere in more detail (Korver et al., 2012). In short, in– and out–patients presenting consecutively at selected representative services in representative geographical areas in the Netherlands and Belgium from January 8th, 2004–February 6, 2008 were asked to participate. Inclusion criteria were (1) diagnosis of a psychotic disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria; (2) age 16–50 years (extremes included); (3) Dutch language proficiency; (4) ability to provide informed consent. Genetic data, cognitive profile, environmental characteristics and outcome were collected at baseline (T_0), at three–year (T_3) and six–year (T_6) follow–up. The full GROUP sample at baseline consists of 1100 patients with recent onset psychosis, as well as a longer illness duration. For this study, we used data of 523 participants with a schizophrenia spectrum or schizoaffective disorder (i.e. schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, psychosis NOS), assessed with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992) or the Schedules for Clinical Assessment for Neuropsychiatry version 2.1 (SCAN; Wing et al., 1990) for whom outcome assessments at T_3 and T_6 were available. A selection process flow chart is provided supplementary (figure S1). We assessed selection bias by comparing our study sample on demographic and clinical characteristics to GROUP patients who were not included in this study.

The GROUP study protocol was approved by the Medical Ethical Review Board of the University Medical Centre Utrecht and by local review boards of participating institutes. All participants signed informed consent in accordance with the Medical Ethics Review Committee guidelines.

2.2. LONG–TERM OUTCOMES AND BASELINE PREDICTORS

A classification approach to outcome prediction was chosen. Four outcomes – i.e., symptomatic remission and global functioning at T_3 and T_6 – were selected to express long term outcome. Symptomatic outcome was selected as it traditionally is a mainstay of clinical care. We followed the consensus definition of symptomatic remission, operationalized as a mild (score 3) or less (≤3) score, measured by the positive and negative syndrome scale (PANSS) on selected items of positive, negative and disorganized psychopathological dimensions, maintained for at least six months (Andreasen et al., 2005). Patients were divided into two groups, based on good symptomatic outcome; i.e. symptomatic remission or poor symptomatic outcome; i.e. non–remission status. For global outcome we followed Koutsouleris et al. (2016) in operationalizing global outcome with a dichotomization of the Global Assessment of Functioning (GAF; American Psychiatric Association, 2000) scale, considering a score of <65 poor global outcome, and ≥65 good global outcome.

Available candidate baseline predictors were clustered in modalities according to information type: 1) demographic variables, including age, gender and socioeconomic status; 2) illness related variables, such as diagnosis, comorbidities, illness course and medication use; 3) clinician–rated, present state symptoms, measured by the PANSS; 4) substance use characteristics (i.e. illicit drug use, alcohol use and smoking) indicated by urine analysis and the Composite International Diagnostic Interview; 5) neurocognitive task scores, i.e. IQ, memory, processing speed, attention and executive functioning; 6) social cognitive task scores, i.e. theory of mind, facial and affect recognition; 7) Premorbid Adjustment Scale items, comprising social and cognitive functioning in childhood and adolescence; 8) need of care items, measured with the Camberwell Assessment scale of Need Short Appraisal Schedule (CANSAS); 9) self–rated lifetime psychotic experiences, consisting of Community Assessment of Psychic Experiences (CAPE) questionnaire items; 10) extrapyramidal symptoms, comprising akathisia, dyskinesia and Parkinsonian symptoms measurement; 11) genetic features: polygenic risk score and familial loading and 12) environmental variables of urbanicity and living situation. Global content of, and features within the modalities are provided in the supplement, with psychometric instrument references (section S1 and table S1). Within each modality, we selected predictors and subjects with ≤20% missing values, imputed and scaled the data (see supplement paragraph S2).

For reporting of the prediction models this study made use of the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD; Collins et al., 2015) statement.

2.3. CREATION OF INDIVIDUAL PREDICTION MODELS

2.3.1. MACHINE LEARNING STRATEGY

We trained a linear support vector machine (SVM) to find the optimal separating hyperplane to separate the patients into the two outcome classes (Vapnik, 1999). For a given training dataset, each patient is represented by a labelled datapoint in an m–dimensional feature space. The position of the datapoint is determined by the patient's score on the m baseline predictors (input features) and its binary label is the patient's outcome. SVM returns features weights, reflecting the influence of predictors on the outcome prediction. We used class weighting to account for unbalance between outcome group sizes. Internal validation was performed with three–layer, k–fold cross–validation, where the inner cross validation layer optimized the cost parameter, representing the penalty imposed on the cases violating the margin of the decision boundary of the model. The middle layer used recursive feature elimination (RFE) to select the smallest predictor set with performance within 10% of the best performing set. The outer layer provided performance estimates, reflecting the accuracy of the ensemble of k models taken together. This validation procedure was repeated 50 times to reduce dependency on the choice of train–test partitions. All models were trained using the open source library for machine learning in R; the caret package for R was used for RFE (http://topepo.github.io/caret; Kuhn, 2018).

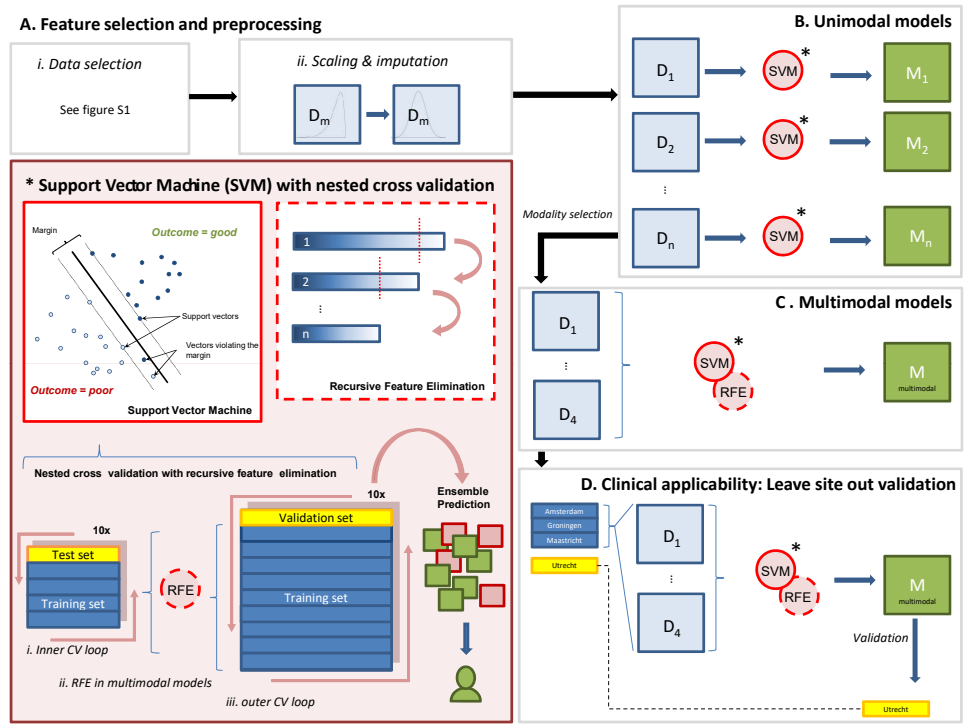


FIGURE 1. Machine learning pipeline. D = modality; M = Model; training sets in dark blue, test/validation sets in yellow. (A) data selection and preprocessing; (i) see supplementary figure S1 for details on feature selection; (ii) scaling and imputation (B) Unimodal models, to identify the most informative modalities; (C) Multimodal models consisting of 2–4 modalities, including recursive feature elimination (RFE); (D) external validation of multimodal models using Leave–Site–Out (LSO) validation, where one of the four geographic sites is held out of model training and used for external validation. LSO validation was performed once on each of four geographic sites (Amsterdam, Groningen, Maastricht and Utrecht); (*) Support Vector Machine (SVM). RFE is part of the SVM–pipeline. (i) The inner CV loop is used to find the optimal value for C from 38 points equidistant in ^{2}log, starting at 0.0001 and ending at 37.07. C sets a penalty for violating the margin of the hyperplane.; (ii) the middle layer is RFE, which is a feature selection algorithm which running inside the outer CV loop. It starts by including all available features in the model and iteratively eliminates the least informative features from it until the stopping criterion is met; (iii) the outer CV loop is used to define feature weights in the training set (9/10th of the data) and test the accuracy of the model in the validation set (1/10th of the data). Repetition of this procedure yields 10 models, which is repeated 50 times to reduce dependency on the choice of train–test partitions. The final ensemble prediction for a patient constitutes the average of the 10 resultant models operating on its features, repeated 50 times.

2.3.2. TRAINING AND VALIDATION DESIGN

For each outcome, we first trained uni–modal outcome prediction models, each based on a single modality of predictors (see table S3). Then, the best performing modalities were entered together into the SVM to train multi–modal prediction models. We employed this data–driven, modality–wise learning pipeline with the aim to automatically identify a concise set of measures from a limited number of clinical instruments (see figure 1). Our approach facilitates a comparison of performance between established theoretical constructs represented by modalities in model selection. This theoretically leads to models that more closely adhere to causal pathways and retain accuracy in other clinical samples (Cheng et al., 2013).

Model performance was assessed by calculating sensitivity, specificity, balanced accuracy (BAC; the average of sensitivity and specificity), positive predictive value (PPV; true positive / (true positive + false positive)) and negative predictive value (NPV; true negative / (true negative + false negative)).

As is best practice in machine learning analyses (Dwyer et al., 2018), we employed a three–step validation setup to test generalizability of the models: A. Internal validation using cross–validation (see section 2.3.1.). B. Leave–site–out (LSO) validation. Each of the four geographical sites of the GROUP study was held out once, and the prediction model was trained on the patients from the remaining three sites. This model is then tested on the hold–out site. To estimate the predictive power in unseen data, the average prediction accuracy from the four left–out sites was calculated. C. External validation of the value of short–term outcome predictors for long–term outcome prediction. We selected GROUP predictors matching the top–10% four–week and one–year global outcome predictors from the European First Episode Schizophrenia Trial (EUFEST; Koutsouleris et al., 2016; see list in supplementary table S1) and trained the SVM to test their capability of predicting long–term outcome.

To test model significance we randomly permuted the outcome labels and built the models for these permuted outcomes. The p–value was based on the proportion of tests permutations with accuracies that exceeded the observed accuracy.

3. RESULTS

3.1. SAMPLE CHARACTERISTICS

Demographic and clinical baseline characteristics of the study sample and comparisons to study dropouts are given in table 1. Patients with unfavourable baseline characteristics were more likely to be lost to follow up.

Symptomatic and global outcome status at baseline, T_3 and T_6 are shown in figure 2. At baseline 49% of patients were in symptomatic remission (note that at baseline only the symptom–based criterion of remission was included), and 31% had good global functioning status.

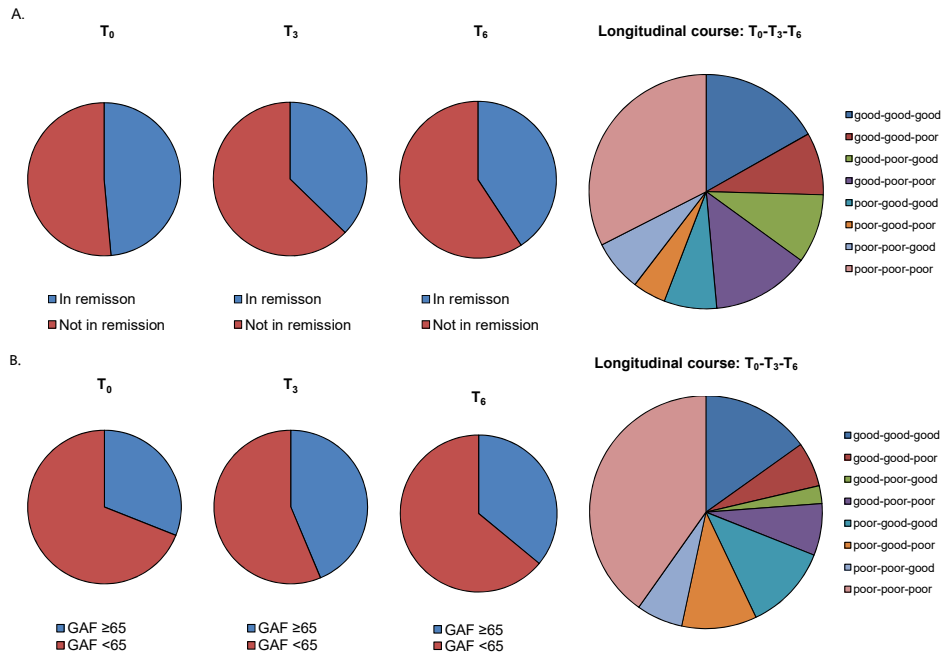


FIGURE 2. A. Symptomatic outcome ratios and longitudinal course of remission during baseline and follow–up. T_0 remission was only available without time component, thus solely based on PANSS symptoms. **B.** Global outcome ratios and changes in global outcome during baseline and follow–up.

TABLE 1. Baseline demographic and clinical characteristics of patients who completed baseline and follow–up (N=523), and those who were not included in the study (N=577).

	Included patients	Excluded patients	Statistic	p–value
Age (years; mean±sd)	27.62±7.44	26.57±6.97	t=2.374	0.018
Gender (% male)	76.86	77.60	χ2=.0081	0.775
Ethnicity (% white)	85.85	72.6	χ2=27.416	<0.001
WAIS IQ (mean±sd)	97.38±16.06	92.13±15.6	t=5.061	<0.001
Education patient (mean±sd)	4.27±1.97	3.75±2.12	t=4.134	<0.001
SES education father (mean±sd)	5.12±2.45	4.71±2.61	t=2.458	0.014
SES education mother (mean±sd)	4.44±2.36	4.13±2.53	t=1.927	0.054
Employment/student (% yes)	46.08	41.16	χ2=2.367	0.124
Illness duration (years; mean±sd)	4.58±4.16	3.85±3.37	t=3.066	0.002
DSM–IV schizophrenia diagnosis (% 295.1,2,3)	65.39	62.45	χ2=0.999	0.317
APD use present state (% yes)	91.57	99.31	χ2=30.525	<0.001
Current clozapine use (% yes)	12.24	14.75	χ2=1.451	0.228
Cannabis abuse/dependency present state (% yes)	30.59	32.60	χ2=0.501	0.479
Other illicit drug use in the past (% yes)	62.91	69.52	χ2=5.082	0.024
PANSS positive symptoms (mean±sd)	12.17±5.12	13.34±5.52	t=–3.464	0.001
PANSS negative symptoms (mean±sd)	13.30±5.52	14.74±6.30	t=–3.842	<0.001
PANSS general symptoms (mean±sd)	26.97±7.81	29.01±8.78	t=–3.845	<0.001
PANSS total	52.37±15.71	56.93±17.51	t=–4.227	<0.001
Global Assessment of Functioning; global functioning	57.91±16.02	53.53±15.30	t=4.331	<0.001
Global Assessment of Functioning; degree of disabilities	57.04±15.56	51.28±15.80	t=5.710	<0.001
Ratio GAF score ≥65/ GAF score <65	33.08/66.92	21.17/78.83	χ2=17.034	<0.001
CAPE frequency symptoms	0.92±0.47	0.88±0.46	t=1.110	0.267
CANSAS number of needs	6.71±3.83	7.76±3.85	t=–4.253	<0.001

Abbreviations: WAIS IQ is Wechsler Adult Intelligence Scale Intelligence Quotient; SES is socioeconomic status; DSM–IV is Diagnostic and Statistical Manual of Mental Disorders 4th edition; APD is antipsychotic drugs; PANSS is Positive and Negative Syndrome Scale; GAF is Global Assessment of Functioning; CAPE is Community Assessment of Psychic Experiences; CANSAS is Camberwell Assessment scale of Need Short Appraisal Schedule.

A summary of the number of features in the models, sample sizes per model and per outcome, and distributions of good versus poor symptomatic and functional outcome is provided in table 2 for our multimodal models and EUFEST replication models (for unimodal models see supplementary table S2).

3.2. CLASSIFICATION OF GOOD VERSUS POOR SYMPTOMATIC AND GLOBAL OUTCOME AT T3 AND T6

Based on the unimodal modeling results (shown in table S3), we included demographic information, illness related variables, PANSS (present state clinician–rated symptomatology), and CANSAS (clinician–rated and self–reported need of care) or CAPE (self–reported lifetime psychotic experiences) data for multimodal modeling. (Because combining all five aforementioned modalities resulted in a small sample (N=172), we did not train this model).

A. INTERNAL VALIDATION

All the full–set multimodal models were significant. For symptomatic outcome at T_3 and T_6, cross–validated classification accuracies (BACs) ranged from 62.2% to 64.7%. For global outcome at T_3 and T_6 accuracies ranged from 63.5% to 67.6% (table 3). The average prediction accuracies of T_3 or T_6 were similar (64.4% and 65.5%, respectively). Including CANSAS or CAPE predictors in the multimodal prediction models also made a small difference (64.5% and 65.4% accuracy, respectively).

The 10% most frequently selected predictors per model (and corresponding selection chance and betas (sd)) are given in supplementary tables S4–S11. The most influential features for global as well as symptomatic outcome based on weight and frequency of selection included PANSS items, illness related, demographic features and need of care items. Frequency of inclusion of a feature against its average weight is shown in figure 3 for symptomatic outcome models, and in figure 4 for global outcome models.

Worse GAF symptoms and GAF disabilities, worse scores on judgement and insight, hallucinatory behaviour, flat affect, unusual thought content, motor retardation of the PANSS, worse score on (health related) quality of life and the use of antipsychotics were associated with multiple poor outcome endpoints, supplemented by lower number of no needs and lower number of met needs, together with housing and food need in models including CANSAS items. No features of general importance were found in models including the CAPE. Important items, albeit selected in less outcome models included lower education (of the patient and of the parents), schizophrenia diagnosis and higher level of present state delusions, suspiciousness/persecution, grandiosity, stereotyped thinking, lack of spontaneity, difficulty in abstract thinking, emotional withdrawal, depressive symptoms and tension of the PANSS, associated with poor outcome.

TABLE 2. Summary of the total number of features in the predictor modalities, sample sizes per model, and distributions of good versus poor symptomatic and functional outcome.

Modalities (T_0)	No of features	N Rem T_3	% good/poor symptomatic outcome T_3	N Rem T_6	% good/poor symptomatic outcome T_6	N GAF T_3	% good/ poor global outcome T_3	N GAF T_6	% good/ poor global outcome T_6
PANSS, ill, demo, CANSAS	119	332	38/62	332	40/60	274	46/54	313	38/62
PANSS, ill, demo, CAPE	152	445	37/63	445	42/58	377	44/56	414	35/65
EUFEST 4 weeks	24	332	38/62	332	40/60	274	46/54	313	35/65
EUFEST 52 weeks	22	332	38/62	332	40/60	274	46/54	313	35/65

Abbreviations: T_0 is baseline measurement; T_3 is follow–up at 3 years interval after the baseline; T_6 is follow–up at 6 years interval after the baseline; rem is remission; GAF is Global Assessment of Functioning; PANSS is positive and negative syndrome scale; ill is illness related; demo is demographic; CANSAS is Camberwell assessment of need short appraisal; CAPE is Community Assessment of Psychic Experiences; EUFEST 4 weeks is set of 10% best performing features of 4–week outcome prediction of the European First Episode Schizophrenia Trial; EUFEST 52 weeks is set of 10% best performing features of 52–week outcome prediction of the European First Episode Schizophrenia Trial.

TABLE 3. Results of recursive feature elimination (RFE) and RFE leave–site–out (LSO; average of four sites left out once) performance of multimodal models, predicting symptomatic (i.e. remission) and global outcome (i.e. GAF) at T_3 and T_6.

Predictor (outcome)	BAC	Sens/Spec	PPV/NPV	LSO BAC	LSO Sens/spec	LSO PPV/NPV
PANSS, ill, demo, CANSAS (remission T_3)	62.2	77.9/42.6	68.9/54.1	61.3	59.7/62.9	73.1/47.7
PANSS, ill, demo, CAPE (remission T_3)	64.4	76.0/50.0	72.2/54.8	63.8	62.9/64.7	75.8/48.5
PANSS, ill, demo, CANSAS (remission T_6)	64.7	78.7/46.5	69.0/59.0	62.5	68.5/56.5	74.3/49.3
PANSS , ill, demo, CAPE (remission T_6)	62.3	75.4/46.5	66.2/57.6	59.9	64.2/55.6	69.3/49.1
PANSS, ill, demo, CANSAS (GAF T_3)	63.5	66.3/59.7	65.6/60.5	63.5	66.1/60.8	68.5/59.6
PANSS, ill, demo, CAPE (GAF T_3)	67.6	74.9/58.4	70.1/64.2	64.8	65.8/63.8	72.7/56.5
PANSS, ill, demo, CANSAS (GAF T_6)	67.6	81.8/47.7	71.8/61.6	64.0	71.8/56.1	73.2/55.3
PANSS, ill, demo, CAPE (GAF T_6)	67.3	84.3/43.3	73.4/59.8	61.2	65.9/56.5	76.8/45.5
EUFEST 4 weeks (remission T_3)	62.7	61.3/64.0	69.0/45.1	–	–	–
EUFEST 52weeks (remission T_3)	59.0	60.9/57.1	70.5/47.4	–	–	–
EUFEST 4 weeks (remission T_6)	62.4	58.1/66.7	72.0/50.9	–	–	–
EUFEST 52weeks (remission T_6)	61.0	60.2/61.8	69.8/50.0	–	–	–
EUFEST 4 weeks (GAF T_3)	60.4	61.7/59.1	64.5/57.9	–	–	–
EUFEST 52weeks (GAF T_3)	56.5	58.5/54.6	60.3/53.4	–	–	–
EUFEST 4 weeks (GAF T_6)	62.0	61.4/62.7	73.2/50.3	–	–	–
EUFEST 52weeks (GAF T_6)	66.4	70.0/62.8	76.1/57.1	–	–	–

Abbreviations: BAC is balanced accuracy; sens is sensitivity; spec is specificity; PPV is positive predictive value; NPV is negative predictive value; T3 is follow–up at 3–years interval after the baseline; T6 is follow–up at 6–years interval after the baseline; PANSS is positive and negative syndrome scale; ill is illness related, demo is demographic; CANSAS is Camberwell assessment of need short appraisal, CAPE is Community Assessment of Psychic Experiences; GAF is Global Assessment of Functioning; EUFEST 4 weeks is set of 10% best performing features of 4–week outcome prediction of the European First Episode Schizophrenia Trial; EUFEST 52 weeks set of 10% best performing features of 52–week outcome prediction of the European First Episode Schizophrenia Trial.

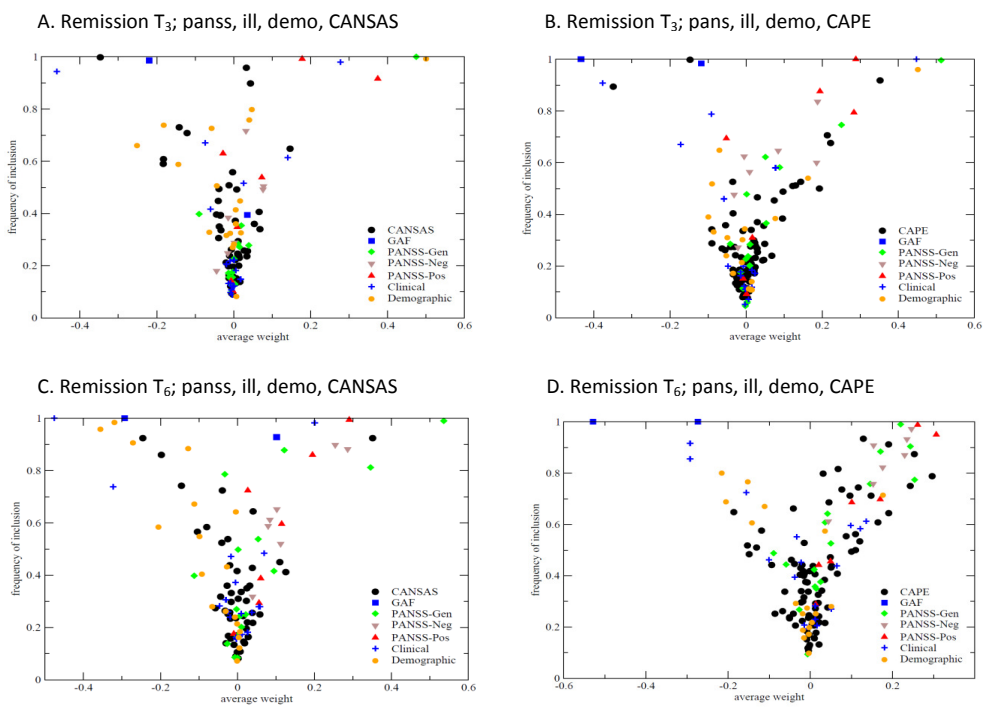


FIGURE 3. Frequency of inclusion of a feature against its (average) weight in the model; for symptomatic outcome models at T3 (A and B) and T6 (C and D), containing PANSS, demographic, illness and need of care related features (A and C) or PANSS, demographic, illness and lifetime psychotic experiences related features (B and D).

B. LEAVE–SITE–OUT VALIDATION

The leave–site–out (LSO) validated models also performed above chance, but had (slightly) lower accuracies than the full–set models (table 3). The range of the average prediction accuracies for symptomatic outcome at T_3 and T_6 was 59.9%–63.8% (site specific BACs ranged from 56.4% to 69.7%; table 4). For global outcome the range was 61.2%–64.8% (BACs of the different sites ranged from 53.0% to 68.9%) (table 3 and 4). The difference between T_3 and T_6 prediction accuracy was small (64.7% and 66.4%, respectively). There was, again, a small difference between CANSAS–based and CAPE–based models (62.8% and 62.4% accuracy, respectively).

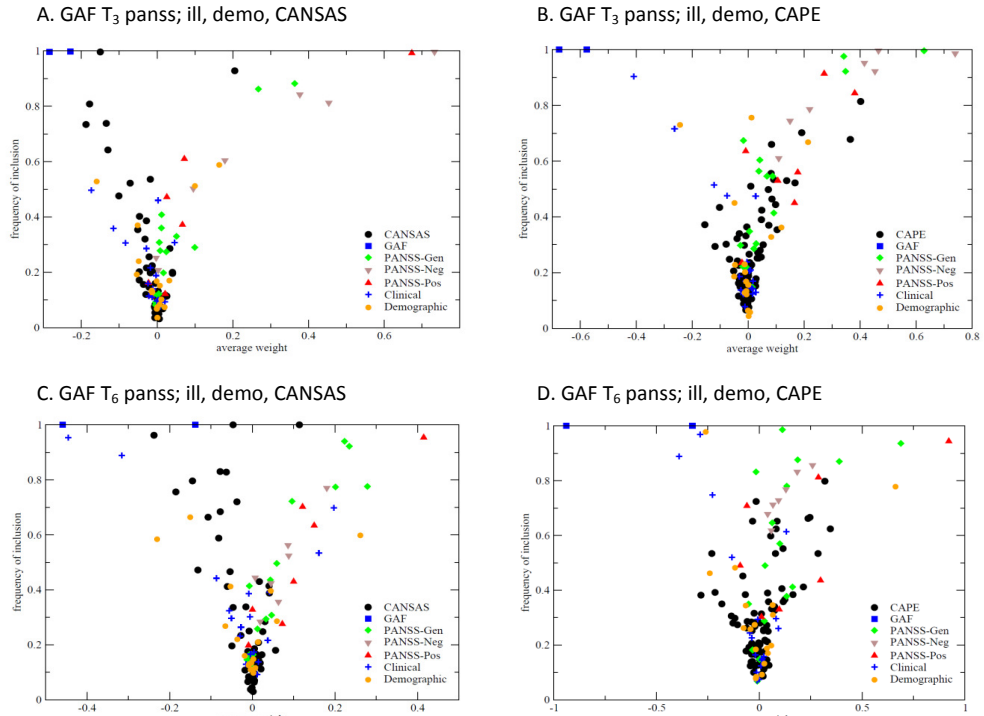


FIGURE 4. Frequency of inclusion of a feature against its (average) weight in the model; for global outcome models at T3 (A and B) and T6 (C and D), containing PANSS, demographic, illness and need of care related features (A and C) or PANSS, demographic, illness and lifetime psychotic experiences related features (B and D).

C. EXTERNAL VALIDATION OF EUFEST PREDICTORS

Predicting long–term outcome based on the top 10% most predictive features for short–term outcome (EUFEST study) resulted in accuracies of 59.0% to 62.7% for symptomatic outcome. For global outcome, we obtained accuracies of 56.5% to 66.4%. All but one of these prediction accuracies were significant (table 3).

TABLE 4. Leave–site–out cross–validation site performance, predicting symptomatic and global outcome at T_3 and T_6.

	N	BAC Remission T_3 [a]	N	BAC Remission T_3 [b]	N	BAC Remission T_6 [a]	N	BAC Remission T_6 [b]
Amsterdam	81	60.8	104	69.5	81	69.3	104	60.1
Groningen	73	62.4	132	63.1	73	62.3	132	57.2
Maastricht	124	56.4	139	53.0	124	63.8	139	61.5
Utrecht	54	65.5	70	69.7	54	54.4	70	60.6
	N	BAC GAF T_3 [a]	N	BAC GAF T_3 [b]	N	BAC GAF T_6 [a]	N	BAC GAF T_6 [b]
Amsterdam	80	66.4	100	68.1	77	63.9	98	65.4
Groningen	65	61.5	118	64.4	58	62.5	107	64.2
Maastricht	81	68.0	93	68.9	124	66.3	139	62.1
Utrecht	48	58.0	66	57.9	54	63.1	70	53.0

Abbreviations: BAC is balanced accuracy; GAF is global assessment of functioning; T_3 is follow–up at 3–years interval after the baseline; T_6 is follow–up at 6–years interval after the baseline.

[a] Models contained PANSS, demographic, illness and need of care related features.

[b] Models contained PANSS, demographic, illness and lifetime psychotic experiences related features.

4. DISCUSSION

Using a rigorous machine learning approach in a multicentre sample of 523 schizophrenia spectrum patients, we developed models to predict three– and six–year symptomatic and global outcomes for a heterogeneous population of schizophrenia spectrum patients in a care–as–usual setting based on patient–reportable data. To our knowledge, no prognostic model for long–term outcome of psychosis is available at present. We report cross–validated prediction accuracies of 62.2–64.7% for good versus poor symptomatic outcome, and 63.5%–67.6% for global outcome. Generalization of the models to other geographical sites was tested using leave–site–out cross–validation. This led to a minor drop in accuracy, to 59.9%–63.8%, and 61.2%–64.8% for symptomatic and global outcome, respectively. This retainment of significant predictive capacities in other samples suggests our long–term outcome prediction models may potentially enhance clinical decision–making. We also validated the use of short–term outcome predictors (Koutsouleris et al, 2016) for long–term outcome prediction, with up to 66.4% accuracy.

Model performance is similar to an experimental prognostic model in psychiatry based on machine learning that predict long–term clinical outcome of depression based on patient reportable data (Dinga et al., 2018; Kessler et al., 2016). Predictive accuracy did not reach the leave–site–out cross–validated accuracy of 71% in a model on one year outcome of first episode psychosis (Koutsouleris et al., 2016), presumably due to the uncertainty introduced by time, care–as–usual setting, and the heterogeneity of baseline clinical status and duration of illness within our target population. Nevertheless, given all these factors, the results of the current study are promising.

PREDICTORS OF THE MULTIMODAL MODELS

Through a modality–wise learning strategy, a combination of baseline sociodemographic features and clinician–rated symptoms, complemented by self–rated lifetime psychotic experiences or psychosocial needs was selected in the models, highlighting the importance of measures closely related to symptomatic and global outcome. Notably, important items in the top 10% best performing predictors included GAF symptoms and GAF disabilities, (health related) quality of life, the use of antipsychotics and present state symptoms of poor judgement and insight, hallucinatory behaviour, motor retardation, flat affect and unusual thought content, delusions, suspiciousness/persecution, grandiosity, stereotyped thinking, lack of spontaneity, difficulty in abstract thinking, emotional withdrawal, depressive symptoms, tension and the core

social need of housing and food, together with number of met needs, number of no need, education (of the patient and of the parents) and schizophrenia diagnosis.

The utility of measures that offer an integration of the clinical picture is highlighted by the prominence of features with a broad underlying construct in our models (e.g. quality of life; schizophrenia diagnosis; depression; GAF; summed no need/met need items; education; insight). We also suggest a complementary value of including both of lifetime and present state clinical information as exemplified by the similarity of predictive accuracies in models including CAPE or CANSAS.

Global functioning, positive symptoms and psychosocial needs are found in both one–year outcome in first episode psychosis (Koutsouleris et al, 2016) and long–term outcome prediction in a heterogeneous sample, suggesting a lasting predictive value of these predictors. We also note differences: symptom severity and particularly, lack of insight are relatively important for our long–term outcome compared to short–term outcome of Koutsouleris et al., 2016. Furthermore, we speculate that differences in importance between social needs in our models and those for short–term outcome depend on relatively higher social functioning in first episode psychosis patients relative to our heterogeneous cohort (Landolt et al., 2012).

TRANSLATIONAL CHALLENGES FOR CLINICAL PRACTICE AND FUTURE RESEARCH

Our models have the following limitations. Although we present the largest machine learning study to date on outcome in psychosis, which is based on patient–reportable data, the sample size may not be sufficient to account for the heterogeneity of the population with a schizophrenia spectrum disorder (Schnack, 2017). This is illustrated by the, albeit small, drop in performance when the models were applied to patients from sites that were not part of the training sample. A small amount of overfitting caused by the use of cross–validation procedures may play a part in the observed drop in predictive accuracy (Varoquaux, 2017).

Although a naturalistic cohort might represent the clinical population better than a clinical trial sample, the GROUP study sample is known to be relatively well functioning. Generalization to other study samples might be hindered by exclusion of the most severely affected patients, either by study drop–out, or incompetence to study consent (Ruissen et al. 2012). External validation should provide a true measure of transportability of this model (see 'TRIPOD' guidelines; Collins et al., 2015).

We used baseline data for outcome prediction, whereas in clinical practice, decisions are typically based on longitudinal, rather than single, examinations. Longitudinally informed models are expected to result in better prediction accuracies. Furthermore,

we suggest that contextual factors, such as family support status, and psychosocial treatment status could further enhance model performance. The addition of biomarker modalities, including imaging data and genetic data derived from the genome wide association studies holds the same promise (Koutsouleris et al., 2018), however, all additions come at the expense of clinical time investment, model interpretability and the requirement of larger training datasets (Janssen et al., 2018).

The use of large, multi–centre samples dedicated to prognostic model development or models based on national registry data, as has been successfully done to predict psychosis with machine learning from high–risk mental states and suicidal behaviour, might be needed to deliver reliable predictions (Schnack and Kahn 2016; Kessler et al., 2017; Koutsouleris et al. 2018).

Accurate individual outcome prediction does not present the clinician with a straightforward guideline to stratify treatment. The significance of an outcome predicted might differ per patient. Moreover, pharmacological and behavioural interventions present differing benefits, risks and availability. Models on an array of outcome dimensions with accessible features might best fuel the clinician–patient dialogue on intervention (Leamy et al., 2011; Fusar–Poli and Van Os 2013). Predictions of longitudinal patterns, or adverse events, such as readmission to a psychiatric hospital (Sullivan et al., 2017) may also add clinical relevance, especially for long–term outcome.

To estimate the potential clinical applicability of our models is a challenge, since we are not aware of any studies that have assessed the net benefit in outcome prediction of psychotic disorders. It is thus unknown how patient and clinician weigh benefit and harm due to treatment choices based on predictive models (Vickers et al., 2016). For future research and translation of prognostic models on psychosis into clinical practice, consensus on their scope, minimum predictive capacities and clinical consequences is needed (Vickers, 2015; First et al., 2012). Guidance on what kind of predictions are important for clinicians and patients, should steer future research on, and development of new, improved, prediction tools. Clinical guidance on when and how to use such tools might prove essential for successful dissemination of prognostic models based on machine learning in psychiatry. These future models should be developed in larger training samples, and external validation as well as field–testing is needed before clinical implementation.

In conclusion, we demonstrate the feasibility of long–term outcome prediction based on patient reportable data for a heterogeneous target population of schizophrenia spectrum patients. Individual outcome prediction based on machine learning may inform the treatment stratification needed both from a patient and a public health perspective.

SUPPLEMENT

S1. DESCRIPTION OF PREDICTORS

Below, we describe the global content of different modalities of predictors; i.e. sets of variables assessed at baseline, which will be used to predict outcome at T_3 and T_6. See supplementary table 1 for a specification of predictors per block.

S1.1. SOCIO–DEMOGRAPHIC VARIABLES

Baseline demographic characteristics of the patients, i.e. gender, age, ethnicity, (parental) education, living/family situation, employment and number of lifetime moves were assessed, which were self–reported. Number of staying backs and whether a patient had received special education were recorded. In the Dutch educational system special education constitutes schools for disabled children, children with behavioural and / or psychiatric disorders and for children with cognitive problems. Educational level and degree ranged from 0 to 8 (0: no education, 1: primary school, 2, 3: secondary school, 4: high school, 5, 6 vocational education, 8: university degree. Educational level and degree of both mother and father of the patient constituted the parental SES. Scoring regarding ethnicity was dichotomized: score could either be white or non–white/mixed. If the country of origin of three or more grandparents of the subject was similar, the subject's ethnicity was equal to this. In all other cases, the ethnicity was mixed. Lifetime postal codes were registered, thus the number of lifetime moves could also be extracted from the database. Living situation/household was either scored 'independent living' or 'dependent living'. Independent living included subjects with a single–person household, or those living with their partner and/or own family. Dependent living was defined as either sheltered living, living with parents, or 'other' (i.e. hospital admission, homelessness, living with sibling). Living with parents was considered as deviant from the norm as subjects were on average 27.6 (±7.4 sd) years old. Whether the patient lost a parent/parents and whether they have children was also registered.

Patients were asked whether they had any occupation. Employment was defined as having a paid job. Volunteer work, as a consequence, did not constitute employment in this study. Besides employment, occupation also included whether the participant was currently a fulltime student.

S1.2. ILLNESS RELATED VARIABLES

Baseline illness related characteristics of the patients were registered, and included information on course of illness, duration of untreated psychosis, diagnostics, quality of life, comorbidity of lifetime depression and suicide attempt, antipsychotic drug use, degree of functioning and disabilities. Diagnostic subtypes (disorganized, catatonic, paranoid, residual, undifferentiated types of schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, psychosis NOS) were converted into a binary variable: schizophrenia or other than schizophrenia within the schizophrenia spectrum. In a composite questionnaire the following illness related information was acquired: age of psychosis onset (AOP; which was categorized in: early AOP 0–19, normal AOP 20–30, late AOP >30), duration of illness, whether the illness onset was recent (i.e. in the past year and in the past two years), duration of untreated psychosis (i.e. age when first treated with antipsychotic drugs and age of first contact with a mental care institute subtracted by the AOP) and course of illness (having had one episode, episodic (i.e. having had multiple episodes), chronic course and cases of recent onset in the past year and past two years). Level of functioning and disabilities was assessed with the Global Assessment of Functioning scale (GAF; APA, 2000). Also information on whether or not patients currently used clozapine was assessed. Quality of life and quality of health were assessed on a 5–point scale with the World Health Organization Quality of Life– short version (WHOQOL–BREF; The WHOQOL group 1998).

S1.3. PANSS

In the GROUP project, current severity of symptoms was measured with the PANSS (Kay et al., 1987), which consists of 30 items. Each item is scored on a 7–point scale ranging from 1 (absent) to 7 (extreme), with item rating incorporating the behavioural effect of symptoms severity and frequency. The PANSS consists of three subscales, measuring positive, negative or general symptoms.

S1.4. SUBSTANCE USE

Current and lifetime use of tobacco (section B), alcohol (section J) and illicit drug (section L) was assessed with the Composite International Diagnostic Interview (CIDI; World Health Organization 1990). Urinalysis by an external laboratory revealed recent cannabis use. Cutoff level was 50 ng/ml. These substance use related features were dichotomized in 'using' or 'not using'.

S1.5. (SOCIAL) COGNITIVE TESTING

Neurocognitive and social cognitive functioning was assessed with a test battery with a duration of 90–120 minutes. In short, the domains tested were IQ, immediate and delayed recall, processing speed, attention, executive functioning, face recognition, emotion recognition and theory of mind. For an elaborate description of the (social) cognitive domains assessed and the neuropsychological tests used in the GROUP test battery see Korver et al. (2012).

S1.6. PREMORBID ADJUSTMENT SCALE

Premorbid academic and social assessment was assessed with the Premorbid Adjustment Scale (PAS; Cannon–Spoor et al., 1982). It was designed to retrospectively evaluate the degree of achievement of academic and social goals in three distinct age epochs: in childhood (0 to 12 years), early adolescence (12 to 16 years) and late adolescence (16 to 19 years). Academic adjustment consisted of school performance and school adaptation subscales and social adjustment consisted of social behaviour, peer relations and social–sexual aspect subscales (i.e. social sexual aspects 12 to16 years, social sexual aspects 16 to19 years and from 16 to 19 year: independence, highest level of functioning, social personal adaptation, interest in life and energy level). Premorbid adjustment is scored on a 7–point scale ranging from 0 (best functioning) to 6 (worst functioning). Informants were either a parent, a family member of the patient or patients themselves.

S1.7. CANSAS

The Camberwell Assessment scale of Need Short Appraisal Schedule (CANSAS; Phelan et al., 1995; Andresen et al., 2000) was used to assess need of care of a patient in the past three months and whether the need is met or unmet. It comprises the question whether there is a need in 24 different clinical and social domains, and whether it is met or unmet according to the patient as well as the clinician. Assessment of need is scored on a 3–point scale (0: no problem, no need; 1: need, but resolved by care; 2: need but unmet by care) or rated as 9: unknown. If a need is established more information is gathered concerning the adequateness of the effect of the care received. If there is no consensus between the patient and the clinician whether there is a need the item is always scored either 1 or 2. If there is no consensus between the patient and the clinician whether the need is met or unmet, a 1 is scored only when the patient has unrealistic expectations about the care, and a 2 is scored when either the patient or the clinician considers the care met. Also the amount of no need items, met need items and unmet items were calculated.

S1.8. CAPE

The Community Assessment of Psychic Experiences (CAPE; Stefanis et al, 2002) assesses lifetime frequency and amount of distress of psychotic experiences. It is a self–reported 42–item questionnaire. The CAPE is rated on a 4–point Likert scale, ranging from 0 (less frequent/distress) to 3 (most frequent/distress).

S1.9. EPS

Extrapyramidal symptom assessment consisted of global clinical assessment of akathisia and diagnosis of dystonia. Dyskinesia was measured with items one to seven of the Abnormal Involuntary Movement rating Scale. With the unified Parkinson's disease rating scale Parkinsonian symptoms such as bradykinesia, rigidity and tremor were measured (for detailed explanation and references of the variables described in this paragraph see Korver et al., 2012).

S1.10. GENETIC CONTRIBUTION

For calculation of familial loading score of bipolar disorder, psychotic disorder and drug abuse, we used the method described by Derks et al. (2009). In short, the absence or presence of affected relatives of the patient was assessed. An algorithm by the authors was developed, taking into account the amount of affected relatives, the age and gender of the relatives and the degree of relatedness. A polygenic risk score for schizophrenia was calculated. The methods of this calculation are described by McLaughlin et al. (2017). We used a threshold of p=.1, including 121958 single nucleotide polymorphisms.

S1.11. ENVIRONMENTAL CONTRIBUTION

The environmental modality of predictors consists of the level of urbanicity– at birth and present state, the number of people living with the patient and whether or not there was any experience of maltreatment or assault before and after psychosis onset. The number of people living with the patient was assessed and constituted living with family members, with other patient in mental care institute, with housemates or alone. For the assessment urbanicity at birth and current urbanicity, participants were asked to report the postal codes were they had lived/live. These were then coupled to the national database of Statistics Netherlands to determine the level of urbanicity (i.e. population density in number of inhabitants/km^2).

S2. DATA SELECTION AND RESCALING

Within each modality, we excluded predictor variables with ≥20% missing values and subjects if ≥20% of the data for that subject was missing. Remaining missing data were imputed, using an expectation maximization algorithm (Little and Rubin, 1987) in the statistical software package IBM SPSS version 22.0. In total, 539 (.5%) missing values out of 113,049 values were imputed. Since the data was missing at very low percentages and completely at random in each block, (mean, sd=1.0%, 1.1%) this is unlikely to be a problem (Schafer, 1999).

The range of features with a continuous level of measurement was rescaled to normalize the range by subtracting the mean and dividing by two times the standard deviation, except when a feature had established minimum and maximum scores. In that case the following equation was used: $x = \frac{x\text{-scale minimum}}{\text{scale range}}$. Age was scaled by dividing the age in years by 50.

TABLE S1. Features per modality.

Socio–demographic features T_0 (baseline measurement)
1. Age
2. Gender
3. Educational degree
4. Special education
5. Number of staying backs
6. Educational years
7. Socioeconomic status; educational level father
8. Socioeconomic status; educational degree father
9. Socioeconomic status; educational level mother
10. Socioeconomic status; educational degree mother
11. Number of moves
12. Subject has lost parent
13. Ethnicity
14. Household independent living
15. Subject has children
16. Employment
17. Student
18. Illness duration
Illness related features T_0
19. Frequency depression lifetime
20. Chronic course of illness
21. Episodic course of illness
22. One psychotic episode lifetime
23. Recent illness onset, in past year
24. Recent illness onset, in past two years
25. Quality of Life, health
26. Quality of Life
27. Duration untreated psychosis; first contact mental care institute
28. Duration untreated psychosis; start antipsychotic medication
29. Antipsychotic medication; current use
30. Antipsychotic medication; polytherapy
31. Clozapine current use
32. Suicide attempt lifetime
33. Diagnosis schizophrenia/psychosis related disorders
34. Global Assessment of Functioning; global functioning
35. Global Assessment of Functioning; degree of disabilities
36. Early age of onset, <19 years old
37. Normal age of onset, 20–30 years old
38. Late age of onset, >30 years old

Positive and Negative Symptom Scale T_0

39. Delusions
40. Conceptual disorganization
41. Hallucinatory behaviour
42. Excitement
43. Grandiosity
44. Suspiciousness/persecution
45. Hostility
46. Flat affect
47. Emotional withdrawal
48. Poor rapport
49. Passive/Apathetic Social withdrawal
50. Difficulty in abstract thinking
51. Lack of spontaneity
52. Stereotyped thinking
53. Somatic concern
54. Anxiety
55. Guilt feelings
56. Tension
57. Mannerism and posturing
58. Depression
59. Motor retardation
60. Lack of cooperation
61. Unusual thought content
62. Disorientation
63. Poor Attention
64. Poor Judgement and Insight
65. Avolition
66. Poor Impulse control
67. Preoccupation
68. Active social avoidance

Substance use T_0

69. Cannabis abuse/dependence & positive urinalysis
70. Cannabis abuse/dependence lifetime
71. Other illicit drug use present state
72. Other illicit drug use lifetime
73. Amount daily cigarettes (range 0–70)
74. Amount of weekly alcoholic units (range 0–70)

Neurocognition T_0

75. Wechsler Adult Intelligence Scale; digit symbol substitution (scaled score)
76. Wechsler Adult Intelligence Scale; block design (scaled score)
77. Wechsler Adult Intelligence Scale; calculation (scaled score)
78. Wechsler Adult Intelligence Scale; information (scaled score)
79. Continuous Performance Task; reaction time hits

80. Continuous Performance Task; number of false positives
81. Continuous Performance Task; number of false negative
82. Continuous Performance Task; number of correct positives
83. Response Shifting Task; accuracy cost score
84. Word Learning Task, 15 words; immediate recall
85. Word Learning Task, 15 words; delayed recall

Social cognition T_0

86. Hints total score
87. Benton Facial Recognition
88. Degraded Facial Affect Recognition; Neutral faces, amount correct
89. Degraded Facial Affect Recognition; Happy faces, amount correct
90. Degraded Facial Affect Recognition; Fearful faces, amount correct
91. Degraded Facial Affect Recognition; Angry faces, amount correct

Premorbid Adjustment Scale (retrospective assessment, measured at T_0)

92. Social Behaviour <12 years old
93. Social Behaviour 12–16 years old
94. Social Behaviour 16–19 years old
95. Friendship <12 years old
96. Friendship 12–16 years old
97. Friendship 16–19 years old
98. School performance <12 years old
99. School performance 12–16 years old
100. School performance 16–19 years old
101. School adaptation <12 years old
102. School adaptation 12–16 years old
103. School adaptation 16–19 years old
104. Social sexual aspects 12–16 years old
105. Social sexual aspects 16–19 years old
106. Independence 16–19 years old
107. Highest level of functioning 16–19 years old
108. Social personal adaptation 16–19 years old
109. Interest in life 16–19 years old
110. Energy level 16–19 years old

Camberwell Assessment of Needs Short Appraisal (CANSAS) T_0

111. Number of no need
112. Number of unmet needs
113. Number of met needs
114. Housing need
115. Housing unmet need
116. Food need
117. Food need unmet need
118. Household need
119. Household unmet need

120. Self–care need
121. Self–care unmet need
122. Day time activities need
123. Day time activities unmet need
124. Physical health need
125. Physical health unmet need
126. Psychotic disorder need
127. Psychotic disorder unmet need
128. Information need
129. Information unmet need
130. Psychological distress need
131. Psychological distress unmet need
132. Safety to self need
133. Safety to self unmet need
134. Safety to others need
135. Safety to others unmet need
136. Alcohol need
137. Alcohol unmet need
138. Drugs need
139. Drugs unmet need
140. Company need
141. Company unmet need
142. Intimate relationships need
143. Intimate relationships unmet need
144. Sexual expression need
145. Sexual expression unmet need
146. Childcare need
147. Childcare unmet need
148. Education need
149. Education unmet need
150. Telephone need
151. Telephone unmet need
152. Transport need
153. Transport unmet need
154. Money need
155. Money unmet need
156. Welfare benefits need
157. Welfare benefits unmet need
158. Work need
159. Work unmet need
160. Side effects medication need
161. Side effects medication unmet need

Community Assessment of Psychic Experiences T_0

162. Feeling Sad
163. Feeling Sad– Distress
164. Other people say things with double meaning
165. Other people say things with double meaning– Distress
166. Lack of enthusiasm
167. Lack of enthusiasm– Distress
168. Not talkative when with other people
169. Not talkative when with other people– Distress
170. Messages on TV have special meaning
171. Messages on TV have special meaning– Distress
172. People are not what they seem (false appearance)
173. People are not what they seem (false appearance)– Distress
174. Persecution
175. Persecution– Distress
176. Lack of emotions
177. Lack of emotions– Distress
178. Feeling pessimistic
179. Feeling pessimistic– Distress
180. Conspiracy
181. Conspiracy– Distress
182. Important person
183. Important person– Distress
184. No future
185. No future– Distress
186. Special person
187. Special person– Distress
188. Suicidal
189. Suicidal– Distress
190. Telepathy
191. Telepathy– Distress
192. No interest in others
193. No interest in others– Distress
194. Influenced by devices
195. Influenced by devices– Distress
196. Lack of motivation
197. Lack of motivation– Distress
198. Crying
199. Crying– Distress
200. Voodoo
201. Voodoo– Distress
202. Lack of energy
203. Lack of energy– Distress
204. Odd look

205. Odd look– Distress
206. Empty mind
207. Empty mind– Distress
208. Thought withdrawal
209. Thought withdrawal– Distress
210. Lack of activity
211. Lack of activity– Distress
212. Thought insertion
213. Thought insertion– distress
214. Blunted affect
215. Blunted affect– Distress
216. Blunted emotions
217. Blunted emotions– Distress
218. Thought broadcasting
219. Thought broadcasting– Distress
220. Lack of spontaneity
221. Lack of spontaneity– Distress
222. Thought echo
223. Thought echo– Distress
224. External control
225. External control– Distress
226. Hallucinations
227. Hallucinations– Distress
228. Voices conversing
229. Voices conversing– Distress
230. Lack of personal hygiene
231. Lack of personal hygiene– Distress
232. Unable to terminate
233. Unable to terminate– Distress
234. Lack of hobbies
235. Lack of hobbies– Distress
236. Guilty
237. Guilty– Distress
238. Failure
239. Failure– Distress
240. Feeling tense
241. Feeling tense– Distress
242. Capgras
243. Capgras– Distress
244. Visual hallucinations
245. Visual hallucinations– Distress

Extrapyramidal symptoms T_0

246. Akathisia
247. Dystonia
248. Abnormal Involuntary Movement rating Scale
249. Unified Parkinson Disease Rating Scale

Genetic characteristics T_0

250. Polygenic risk score (PRS threshold p=0.1)
251. Familial loading; psychotic disorder
252. Familial loading; bipolar disorder
253. Familial loading; drug abuse

Environmental T_0

254. Number of people living with the patient
255. Maltreatment/assault before psychosis
256. Maltreatment/assault after psychosis
257. Urbanicity at birth
258. Ubanicity current

Set of predictors of 4–week Global Assessment of Functioning–based outcome European First Episode Schizophrenia Trial (EUFEST)

1. Employment
2. Student
3. Daytime activities need (CANSAS)
4. Daytime activities unmet need (CANSAS)
5. Psychological distress need (CANSAS)
6. Psychological distress unmet need (CANSAS)
7. Company need (CANSAS)
8. Company unmet need (CANSAS)
9. Money need (CANSAS)
10. Money unmet need (CANSAS)
11. Global Assessment of Functioning, global functioning
12. Global Assessment of Functioning, degree of disabilities
13. Total Positive and Negative Symptom Scale symptom severity score
14. Sum of no–need items (CANSAS)
15. Education of mother, highest level
16. Educational years patient (excluding staying backs)
17. Sum of unmet–need items (CANSAS)
18. Information need (CANSAS)
19. Information unmet need (CANSAS)
20. Present diagnosis of schizophrenia
21. Accommodation need (CANSAS)
22. Accommodation unmet need (CANSAS)
23. Sexual expression need (CANSAS)
24. Sexual expression unmet need (CANSAS)

Set of predictors of 52-week Global Assessment of Functioning–based outcome EUFEST

1. Employment
2. Student
3. Company need (CANSAS)
4. Company unmet need (CANSAS)
5. PANSS P04: hyperactivity
6. Daytime activities need (CANSAS)
7. Daytime activities unmet need (CANSAS)
8. Psychological distress need (CANSAS)
9. Psychological distress unmet need (CANSAS)
10. Gender
11. PANSS positive score
12. PANSS P02: conceptual disorganization
13. Suicide attempt lifetime
14. Global Assessment of Functioning, global functioning
15. Global Assessment of Functioning, degree of disabilities
16. Safety to others need (CANSAS)
17. Safety to others unmet need (CANSAS)
18. Present diagnosis of schizophrenia
19. Number of needs (CANSAS)
20. Special education
21. Number of staying backs
22. Sum of unmet–need items(CANSAS)

SUPPLEMENTARY TABLE S2. Summary of the amount of features in each unimodal predictor modality, sample sizes per modality and per outcome, and distributions of good versus poor symptomatic and functional outcome.

Modalities (T_{0})	No of features	N Rem T_3	% good/poor symptomatic outcome T_3	N Rem T_6	% good/poor symptomatic outcome T_6	N GAF T_3	% good/ poor global outcome T_3	N GAF T_6	% good/ poor global outcome T_6
Demographic	18	523	37/63	523	41/59	442	44/56	484	36/64
Illness related	20	523	37/63	523	41/59	442	44/56	484	36/64
PANSS	30	523	37/63	523	41/59	442	44/56	484	36/64
Substance use	6	523	37/63	523	41/59	442	44/56	484	36/64
Neurocognition	11	437	37/63	437	39/61	368	44/56	404	35/65
Social cognition	6	437	37/63	437	39/61	368	44/56	404	35/65
PAS	19	422	38/62	422	42/58	389	45/55	427	37/63
CANSAS	51	332	38/62	332	40/60	274	46/54	313	38/62
CAPE	84	445	37/63	445	42/58	377	44/56	414	35/65
EPS	4	506	38/62	506	41/59	426	44/56	468	37/63
Genetic	4	291	38/62	291	42/58	240	46/54	268	37/63
Environmental	5	280	33/67	280	40/60	237	41/59	270	34/66

SUPPLEMENTARY TABLE S3. Results of linear nested cross–validated models, of T_0 GROUP features as predictors, classifying schizophrenia patients in good versus poor symptomatic outcome (remission); good versus poor global outcome (GAF).

Feature blocks	Sens Rem T_3	Spec Rem T_3	BAC Rem T_3	PPV/NPV Rem T_3	Sens Rem T_6	Spec Rem T_6	BAC Rem T_6	PPV/NPV Rem T_6
Demographics	55.2	61.1	58.2	70.1/44.7	55.9	59.2	57.6	64.8/46.5
Illness related	62.3	65.8	64.1	77.0/52.4	65.8	53.6	59.7	65.5/49.8
PANSS	54.4	71.9	63.1	77.8/49.1	69.3	58.0	63.7	72.7/51.4
Substance use	48.1	58.6	53.3	64.7/38.9	54.9	43.1	49.0	52.2/31.7
Neurocognition	53.6	54.5	54.1	66.1/39.7	56.6	54.4	55.5	63.0/40.6
Social cognition	44.1	48.3	46.2	53.9/28.8	38.8	64.4	51.6	57.7/36.5
PAS	53.4	56.8	55.1	65.8/41.8	49.6	64.0	56.8	58.8/43.2
CANSAS	53.2	59.1	56.1	69.2/44.3	57.8	60.5	59.1	67.4/47.5
CAPE	55.4	55.0	55.2	67.5/41.6	52.2	55.5	53.9	63.1/46.5
EPS	34.9	73.9	54.4	69.5/40.6	38.0	72.8	55.4	67.6/45.8
Genetics	43.2	64.2	53.7	56.9/35.1	36.3	61.2	48.8	47.7/36.1
Environmental	47.2	61.4	54.3	74.4/38.1	30.0	70.7	50.4	52.3/36.1
	Sens GAF T_3	Spec GAF T_3	BAC GAF T_3	PPV/NPV GAF T_3	Sens GAF T_6	Spec GAF T_6	BAC GAF T_6	PPV/NPV GAF T_6
Demographics	60.6	61.6	61.1	65.3/53.9	60.1	62.1	61.1	74.8/52.0
Illness related	66.3	58.8	62.6	68.3/59.3	69.8	57.2	63.5	74.8/52.0
PANSS	61.2	67.5	64.3	72.0/59.2	55.7	68.4	62.0	77.5/48.2
Substance use	45.1	67.1	56.1	64.0/49.3	53.8	53.4	53.6	65.2/37.6
Neurocognition	59.3	50.5	54.9	58.3/47.3	59.1	54.6	56.9	70.0/41.7
Social cognition	54.8	41.1	47.9	51.5/39.0	46.7	62.8	54.8	68.0/38.0
PAS	48.8	62.9	55.9	61.3/50.0	53.3	62.1	57.7	69.6/42.6
CANSAS	61.5	58.6	60.1	3.3//56.3	59.2	62.3	60.8	69.9/46.7
CAPE	59.7	58.2	59.0	64.8/52.5	52.8	58.8	55.8	70.4/40.3
EPS	30.6	81.0	55.8	68.3/48.1	33.7	78.7	56.2	70.7/40.3
Genetics	41.9	68.5	55.2	68.3/48.1	51.8	65.8	58.8	68.3/40.8
Environmental	42.4	42.2	42.3	44.9/27.7	42.3	53.7	48.0	63.9/31.8

TABLE S4. Prediction of symptomatic outcome at T_3 with predictors of PANSS, demographic, illness related and need of care.

Feature	psel	beta	beta sd
PANSS Poor Judgement and Insight	1.00	0.47	0.35
CANSAS housing need	1.00	0.35	0.11
PANSS Hallucinatory behaviour	0.99	0.18	0.18
DEMO Age	0.99	0.50	0.46
ILL GAF disabilities	0.99	−0.22	0.20
ILL Diagnosis schizophrenia/psychosis related disorders	0.98	0.28	0.11
CANSAS number of no need	0.96	0.03	0.16
ILL Quality of Life health	0.94	−0.46	0.37
PANSS Suspiciousness/persecution	0.92	0.37	0.31
CANSAS number of met needs	0.90	−0.04	0.13
DEMO duration of illness	0.80	0.05	0.09
DEMO Educational degree	0.76	0.04	0.11

TABLE S5. Prediction of symptomatic outcome at T3 with predictors of PANSS, demographic, illness related and lifetime psychotic experiences.

Feature	psel	beta	beta sd
PANSS Hallucinatory behaviour	1.00	0.29	0.17
ILL Diagnosis schizophrenia/psychosis related disorders	1.00	0.45	0.12
ILL GAF disabilities	1.00	−0.43	0.26
CAPE Guilty	1.00	−0.15	0.16
PANSS Poor Judgement and Insight	1.00	0.51	0.27
ILL GAF symptoms	0.98	−0.12	0.12
DEMO age	0.96	0.45	0.45
CAPE Suicidal	0.92	0.35	0.27
ILL Quality of Life health	0.91	−0.38	0.25
CAPE Guilty– Distress	0.89	−0.35	0.20
PANSS Suspiciousness/persecution	0.88	0.19	0.15
PANSS Lack of spontaneity	0.84	0.19	0.18
PANSS Excitement	0.79	0.28	0.27
ILL Quality of Life	0.79	−0.09	0.12
PANSS Depression	0.75	0.25	0.23

TABLE S6. Prediction of symptomatic outcome at T_6, with predictors of PANSS, demographic, illness related and need of care features.

Feature	psel	beta	beta sd
ILL Status Antipsychotics	1.00	0.48	0.15
ILL GAF symptoms	1.00	−0.29	0.21
PANSS Delusions	0.99	0.29	0.19
PANSS Poor Judgement and Insight	0.99	0.54	0.38
DEMO Socioeconomic status; educational degree father	0.98	−0.32	0.19
ILL Diagnosis schizophrenia/psychosis related disorders	0.98	0.20	0.08
DEMO Subject has children	0.96	−0.36	0.14
ILL GAF disabilities	0.93	0.10	0.20
CANSAS food need	0.92	−0.35	0.16
CANSAS psychotic disorder unmet need	0.92	0.25	0.11
DEMO Socioeconomic status; educational degree mother	0.91	−0.27	0.22
PANSS Flat affect	0.90	0.25	0.24

TABLE S7. Prediction of symptomatic outcome at T_6 with predictors of PANSS, demographic, illness related and lifetime psychotic experiences.

Feature	psel	beta	beta sd
ILL GAF symptoms	1.00	−0.53	0.34
ILL GAF disabilities	1.00	−0.27	0.19
PANSS Unusual thought content	0.99	0.22	0.14
PANSS Hallucinatory behaviour	0.99	0.26	0.17
PANSS Emotional withdrawal	0.97	0.25	0.20
PANSS Delusions	0.95	0.31	0.16
CAPE Lack of activity– Distress	0.93	0.13	0.13
PANSS Flat affect	0.93	0.23	0.16
ILL Status Antipsychotics	0.92	0.29	0.12
CAPE Hallucinations	0.91	0.19	0.13
PANSS Lack of spontaneity	0.91	0.15	0.14
PANSS Poor Judgement and Insight	0.90	0.24	0.18
PANSS Motor retardation	0.88	0.17	0.14
CAPE Lack of activity	0.87	0.25	0.19
PANSS Difficulty in abstract thinking	0.87	0.23	0.22

TABLE S8. Prediction of global outcome at T_3 with predictors of PANSS, demographic, illness related and need of care features.

Feature	psel	beta	beta sd
ILL GAF symptoms	1.00	−0.23	0.19
PANSS Stereotyped thinking	1.00	0.73	0.46
ILL GAF disabilities	1.00	−0.28	0.26
CANSAS number of no need	1.00	−0.15	0.27
PANSS Hallucinatory behaviour	0.99	0.67	0.37
CANSAS number of met needs	0.93	−0.21	0.23
PANSS Motor retardation	0.88	0.36	0.29
PANSS Unusual thought content	0.86	0.27	0.22
PANSS Flat affect	0.84	0.38	0.31
PANSS Passive/Apathetic Social withdrawal	0.81	0.45	0.38
CANSAS housing need	0.81	0.18	0.13
CANSAS food need	0.74	0.13	0.12

TABLE S9. Prediction of global outcome at T_3 with predictors of PANSS, demographic, illness related and lifetime psychotic experiences.

Feature	psel	beta	beta sd
ILL GAF symptoms	1.00	−0.58	0.22
ILL GAF disabilities	1.00	−0.68	0.27
PANSS Stereotyped thinking	1.00	0.47	0.21
PANSS Motor retardation	1.00	0.63	0.25
PANSS Passive/Apathetic Social withdrawal	0.99	0.74	0.30
PANSS Unusual thought content	0.98	0.34	0.18
PANSS Flat affect	0.95	0.42	0.18
PANSS Difficulty in abstract thinking	0.92	0.45	0.26
PANSS Poor Judgement and Insight	0.92	0.35	0.17
PANSS Conceptual disorganisation	0.91	0.27	0.16
ILL Quality of Life	0.90	−0.41	0.23
PANSS Grandiosity	0.84	0.38	0.26
CAPE Feeling tense– Distress	0.81	0.40	0.25
PANSS Emotional withdrawal	0.79	0.22	0.16
DEMO Educational degree	0.76	0.01	0.16

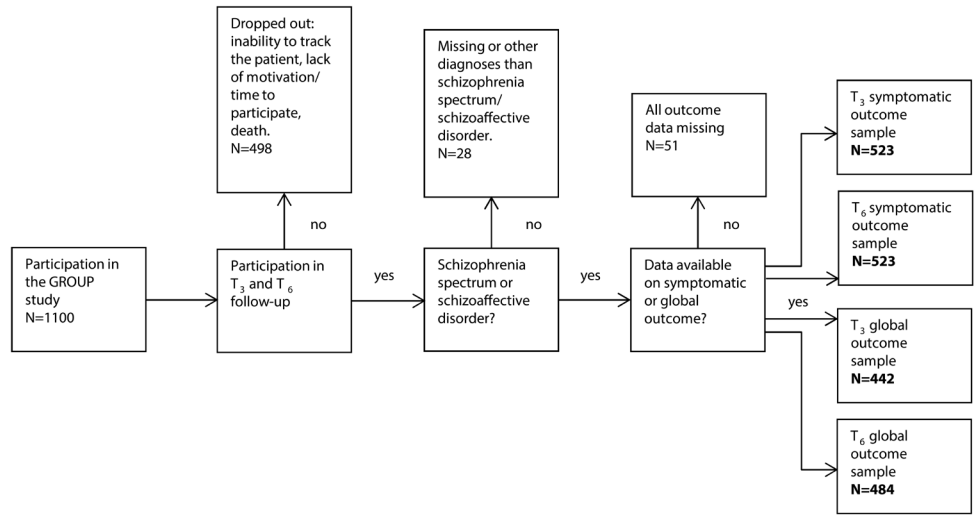
TABLE S10. Prediction of global outcome at T_6 with predictors of PANSS, demographic, illness related and need of care features.

Feature	psel	beta	beta sd
ILL GAF symptoms	1.00	−0.14	0.21
ILL GAF disabilities	1.00	−0.46	0.37
CANSAS number of no need	1.00	−0.05	0.20
CANSAS number of met needs	1.00	−0.11	0.25
CAN housing need	0.96	0.24	0.09
PANSS Hallucinatory behaviour	0.95	0.41	0.29
ILL Quality of Life	0.95	−0.45	0.37
PANSS Poor Judgement and Insight	0.94	0.22	0.18
PANSS Tension	0.92	0.23	0.24
ILL Status Antipsychotics	0.89	0.32	0.16
CANSAS number of unmet needs	0.83	−0.08	0.22
CANSAS day time activities need	0.83	0.06	0.07

TABLE S11. Prediction of global outcome at T_6 with predictors of PANSS, demographic, illness related and lifetime psychotic experiences.

Feature	psel	beta	beta sd
ILL GAF symptoms	1.00	−0.32	0.18
ILL GAF disabilities	1.00	−0.89	0.44
DEMO Employment	0.99	−0.28	0.07
PANSS Unusual thought content	0.98	0.19	0.18
ILL Quality of Life	0.98	−0.42	0.21
PANSS Grandiosity	0.97	0.81	0.38
PANSS Tension	0.92	0.57	0.34
PANSS Motor retardation	0.89	0.16	0.19
ILL Quality of Life health	0.89	−0.41	0.23
PANSS Flat affect	0.88	0.26	0.18
PANSS Depression	0.88	0.33	0.21
PANSS Poor Judgement and Insight	0.84	0.09	0.17
PANSS Passive/Apathetic Social withdrawal	0.81	0.19	0.18
PANSS Hallucinatory behaviour	0.81	0.26	0.20
CAPE Telepathy	0.78	0.30	0.21

Abbreviations for table S2–S11: T_3 is follow–up at 3 years interval after the baseline; T_6 is follow–up at 6 years interval after the baseline; sens is sensitivity; spec is specificity; BAC is balanced accuracy; PPV is positive predictive value; NPV is negative predictive value; GAF is global assessment of functioning; PANSS is positive and negative syndrome scale; CANSAS is Camberwell Assessment of Needs Short Appraisal; ILL is illness related feature; DEMO is demographic feature; CAPE is community assessment of psychic experiences. PAS is premorbid adjustment scale; EPS is extrapyramidal symptom.



SUPPLEMENTAL FIGURE S1. Selection process of the sample used in this study.

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CHAPTER 4

CONNECTOME ORGANIZATION IS RELATED TO LONGITUDINAL CHANGES IN GENERAL FUNCTIONING, SYMPTOMS AND IQ IN CHRONIC SCHIZOPHRENIA

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ABSTRACT

Emerging evidence suggests schizophrenia to involve widespread alterations in the macro–scale wiring architecture of the human connectome. Recent findings of attenuated connectome alterations in unaffected siblings of schizophrenia patients suggest that altered connectome organization may relate to the vulnerability to develop the disorder, but whether it relates to the progression of illness after disease onset is currently unknown. Here, we examined the interaction between connectome structure and longitudinal changes in general functioning, clinical symptoms and IQ in the 3 years following MRI assessment in a group of chronically ill schizophrenia patients. Effects in patients were compared to associations between connectome organization and changes in subclinical symptoms and IQ in healthy controls and unaffected siblings of schizophrenia patients. Analyzing the patient sample revealed a relationship between structural connectivity–particularly among central 'brain hubs'– and progressive changes in general functioning ($p = 0.007$), suggesting that more prominent impairments of hub connectivity may herald future functional decline. Our findings further indicate that affected local connectome organization relates to longitudinal increases in overall PANSS symptoms ($p = 0.013$) and decreases in total IQ ($p = 0.003$), independent of baseline symptoms and IQ. No significant associations were observed in controls and siblings, suggesting that the findings in patients represent effects of ongoing illness, as opposed to normal time–related changes. In all, our findings suggest connectome structure to have predictive value for the course of illness in schizophrenia.

Keywords: connectome, diffusion–weighted imaging, brain hubs, rich club, schizophrenia, outcome

1. INTRODUCTION

Schizophrenia's etiology has long since been related to alterations in the wiring architecture of the brain's network (Fornito et al., 2012; Rubinov and Bassett, 2011; Stephan et al., 2009; van den Heuvel and Fornito, 2014; van den Heuvel and Kahn, 2011; Wheeler and Voineskos, 2014). A comprehensive map of the white matter pathways connecting disparate areas of the human brain is referred to as the macroscale connectome (Hagmann, 2005; Sporns et al., 2005). Emerging evidence on connectome structure in schizophrenia suggests disease–related changes to include affected neural communication, aberrant local organization and modular structure and a less central position of brain hubs (Bassett et al., 2008; Lynall et al., 2010; Skudlarski et al., 2010; van den Heuvel et al., 2010). These putative brain hubs have been suggested to reside in multimodal association areas of the cortex, to participate in complex and diverse neuronal communication (de Reus and van den Heuvel, 2014; Rubinov and Bullmore, 2013; Senden et al., 2014; van den Heuvel and Sporns, 2013) and to be mutually connected into a core collective referred to as a 'rich club' (van den Heuvel and Sporns, 2011; van den Heuvel et al., 2012). Network studies suggest that white matter pathways comprising this central communication system are disproportionally affected in schizophrenia (van den Heuvel et al., 2013). Moreover, unaffected siblings of patients show similar, though attenuated, effects (Collin et al., 2014). Findings of connectome alterations in first–degree relatives (Collin et al., 2014; Fornito et al., 2013; Repovs et al., 2011), who are at increased genetic risk for schizophrenia but lack the potential impact of (untreated) psychosis (Cahn et al., 2009) and psychotropic medication (Nejad et al., 2012; Vita et al., 2012), have led to the hypothesis that affected connectome organization might be reflective of an inherited neurodevelopmental vulnerability to the disorder (Collin and van den Heuvel, 2013; Skudlarski et al., 2013; van den Heuvel and Fornito, 2014).

Cross–sectional investigations of brain network organization in relation to illness severity in schizophrenia have suggested global and local connectome efficiency to be related to severity of both positive (Wang et al., 2012) and negative (Wang et al., 2012; Yu et al., 2011) symptoms. In addition, reduced levels of functional network cost–efficiency have been associated with poorer working memory performance (Bassett et al. 2009). An open question regarding connectome abnormalities in schizophrenia (Dauvermann et al., 2014)–altered hub connectivity in particular (van den Heuvel and Kahn, 2011)–is whether, and if so how, alterations in macro–scale connectome wiring relate to illness progression and outcome. Persistent symptoms (Lieberman, 1999) and real–world deficits in areas such as employment (Harvey and Velligan, 2011) and everyday living (Harvey et al., 2009; Leifker et al., 2009) are common in patients, but prognosis at the

individual level is heterogeneous (Schultz and Andreasen, 1999). Relating connectome architecture to progression of illness and functional deficits might inform prognostic estimations. In this longitudinal study, a group of schizophrenia patients investigated previously in cross–sectional connectome studies (Collin et al., 2014; van den Heuvel et al., 2013) was re–assessed after three years follow–up. Changes over time in general and intellectual functioning and clinical symptoms were evaluated and related to prior connectome structure. Particular emphasis was placed on examining the predictive value of measures of connectome topology (e.g. clustering, global efficiency and rich club organization) on illness progression in the three years following MRI assessment.

2. MATERIALS AND METHODS

2.1. PARTICIPANTS

A sample of 30 schizophrenia patients, from a total sample of 40 patients of whom diffusion–weighted imaging data was examined previously as part of two studies on connectome architecture in patients (Van den Heuvel et al., 2013) and their unaffected siblings (Collin et al., 2014), was included in the current study. Longitudinal data on functional outcome, IQ and symptomatology at 3–year follow–up was examined in relation to connectome structure. In addition, from the baseline sample containing 51 healthy controls and 54 unaffected siblings of patients (Collin et al., 2014), 45 controls and 48 siblings were reassessed after three years and included in the current study. In these subjects, longitudinal changes in IQ and subclinical psychotic symptoms were investigated for a link with connectome structure, to disentangle disease–related effects from 'normal' changes with time in unaffected subjects, in absence / presence of increased familial risk for schizophrenia. All participants were recruited at the University Medical Center Utrecht, as part of a longitudinal study on schizophrenia in the Netherlands (Genetic Risk and Outcome of Psychosis, or 'GROUP', study) (Korver et al., 2012). The affiliated medical ethics committee approved the study and all subjects provided written informed consent prior to participation.

2.2. CLINICAL MEASURES

2.2.1. CLINICAL MEASUREMENTS AT TIME OF SCAN ACQUISITION AND FOLLOW–UP

All subjects were assessed at two time points: 1) at the time of MRI acquisition (T–MRI) and 2) at 3–years follow–up (T–FU). At both assessments, current and lifetime psychopathology was established using the Comprehensive Assessment of Symptoms and History (Andreasen, 1992). Patients met Diagnostic and Statistical Manual of Mental Disorders (DSM) fourth edition (American Psychiatric Association, 2000) criteria for schizophrenia or related spectrum disorders at T–MRI. Siblings had no diagnosis of a current or lifetime psychotic disorder, including bipolar disorder. Healthy controls had no current or lifetime psychotic disorder and no first– or second–degree family member with a lifetime psychotic disorder. The baseline characteristics of the total sample of patients, siblings and controls from our previous cross–sectional study were described in detail in Collin et al. (2014). The baseline characteristics of those subjects that were re–evaluated at T–FU (N=30 patients, N=48 siblings, N=45 controls) are provided in the Supplementary material.

For all study participants, total IQ was estimated using four subtests of the Dutch version of the Wechsler Adult Intelligence Scale (WAIS): Vocabulary, Comprehension, Block Design and Picture Arrangement (Stinissen et al., 1970). For patients, the type and chlorpromazine equivalent daily dose of antipsychotic medication was recorded, symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and symptom remission (Andreasen et al., 2005), employment and living arrangements were recorded as indices of overall functioning. In controls and siblings, the Community Assessment of Psychic Experiences (CAPE) was used to assess subclinical symptoms (Stefanis et al., 2002). All clinical characteristics were assessed at both time points, and differences between the T–MRI and T–FU were tested for statistical significance using paired samples t–tests for continuous and McNemar's chi–square tests for (bi–) nominal variables (McCrum–Gardner, 2008) (table 1).

2.2.2. LONGITUDINAL CHANGES IN GENERAL FUNCTIONING, SYMPTOMS AND IQ

General functioning (GF) of patients was determined at T–MRI and T–FU by combining data on three intuitive measures of functioning: employment, independent living and symptom remission (figure 1a, see Supplementary material for details). GF was computed at both time points as a composite score between 0 (meeting none of the requirements) and 3 (employed, living independently and in symptomatic remission) and longitudinal change in GF was computed as the difference between assessments. Four major trajectories of change in GF during follow–up were discerned: increased GF at T–FU as compared to T–MRI (N=5), stable GF (N=12), minor decrease in GF (N=11) and major decrease (i.e. dropping two levels between T–MRI and T–FU) in GF (N=2) (figure 1b). Patients were grouped according to the trajectory of change in GF during follow–up. Differences between groups in demographic and clinical characteristics were tested for statistical significance using Kruskal–Wallis ANOVA for continuous and Chi–Square tests for categorical variables.

In addition, longitudinal changes in IQ and symptoms, computed as the difference in total IQ and total PANSS symptoms between T–MRI and T–FU, were examined. IQ changes in patients were compared to 'normal' differences between IQ measurements in unaffected subjects. Longitudinal changes in subclinical symptoms, as assessed by the difference in total CAPE symptoms between T–MRI and T–FU, were investigated in controls and siblings.

TABLE 1. Demographic and clinical characteristics at the time of MRI assessment (T–MRI) and 3–year follow–up (T–FU) of patients evaluated at both time points (N=30).

	Time of scan	3 year follow–up	p–value
Age in years, mean (sd) [range]	30.6 (6.3) [22–45]	33.7 (6.3) [25–48]	<0.01
Gender, M / F	27 / 3	27 / 3	n/a
DSM–diagnosis			
Schizophrenia, N (%)	24 (80.0%)	24 (80.0%)	1.0
Schizoaffective disorder, N (%)	5 (16.7%)	3 (10.0%)	0.50
Other schizophrenia spectrum, N (%)	1 (3.3%)	2 (6.7%)	1.0
Bipolar disorder, N (%)	0 (0%)	1 (3.3%)	n/a
Duration of illness, mean (sd) [range]	8.1 (4.2) [2.5–18.3]	11.2 (4.2) [5.9–21.0]	< 0.01
IQ, mean (sd) [range]	99.5 (15.0) [71–132]	96.7 (16.4) [63–128]	0.09
PANSS total symptoms	46.2 (11.6) [30–83]	56.3 (14.9) [31–80]	< 0.01
Remission			
Symptomatic remission, yes / no	19 / 11	12 / 18	0.07
Formal remission[a], yes / no	7 / 21[e]	7 / 23	1.0
Employment (paid), yes / no	19 / 11	16 / 14	0.13
Household, independent / dependent	16 / 14	18 / 12	0.50
Living single / with partner	14 / 2	17 / 1	1.0
Living with parents / sheltered / other[b]	8 / 4 / 2	5 / 6 / 1	0.39
Antipsychotic medication			
Clozapine / other atypical[c] / typical / none	7 / 20 / 1 / 1[f,g]	7 / 20 / 1 / 0[e]	0.56
CPZ[d] equivalent dose, mean (sd) [range]	256.7 (141.4) [50–625][g]	266.3 (213.4) [50–1067]	0.80

[a] Formal remission is defined as symptomatic remission during at least 6 months
[b] Other household includes hospitalization, homelessness, living with sister
[c] Other atypical medication includes risperidone, olanzapine, quetiapine and aripiprazole
[d] CPZ = chlorpromazine.
Data missing for [e] N=2, [f] N=1 [g] Data complemented at follow–up for two subjects

2.3. NEUROIMAGING

Neuroimaging involved acquisition of 1.5 Tesla Magnetic Resonance Imaging (MRI) scans, including an anatomical T1 scan (TE/TR 4.6/30 ms, flip angle 30º, 160–180 contiguous slices, 1× 1× 1.2mm voxels, FOV=256 mm, SENSE 1.5/1.5) and a diffusion–weighted imaging (DWI) scan with each two sets of 8 unweighted scans (b–factor=0 s/mm2, TE/TR 88/9822 ms, parallel imaging factor: 2.5; flip angle 90, 60 slices, 2.5 mm isotropic voxels, no slice gap, FOV 240 mm, 128 × 128 reconstruction matrix) and 32 diffusion weighted images (non–collinear, b–factor=1000 s/mm^2) (Mandl et al., 2013; van den Heuvel et al., 2010). Preprocessing of the T1 and DWI data (described in detail in the Supplementary material) included parcellation of the cerebral cortex into 68 cortical regions (i.e., 34 per hemisphere) using Freesurfer software (Fischl, 2012) and deterministic fiber tracking (Mori and van Zijl, 2002) to reconstruct white matter pathways. Fiber tracking, in short, involved starting seeds in each voxel, subsequently following the preferred diffusion direction from one voxel to the next, to generate a total collection of streamlines reflective of the underlying white matter anatomy (Collin et al., 2014; van den Heuvel et al., 2013).

2.4. CONNECTOME EVALUATION

2.4.1. CONNECTOME RECONSTRUCTION

Connectome reconstructions were taken from Collin et al. (2014); van den Heuvel et al. (2013). In short, for each individual dataset, a connectome map was reconstructed from the collection of parcellated cortical regions and reconstructed white matter streamlines, resulting in a matrix describing the level of structural connectivity between each pair of brain regions (figure 2a). Each connectome map was represented as a graph G = (V, E) consisting of a set of nodes V (representing 68 cortical regions) and connections E between nodes (reflecting cortico–cortical connections between regions) weighted according to the number of reconstructed streamlines (NOS) (figure 2b). Connections consisting of 5 or more streamlines were included as cortico–cortical pathways, effectively reducing the inclusion of potentially false positive registrations (de Reus and van den Heuvel, 2013a).

2.4.2. CONNECTOME EXAMINATION

Connectome reconstructions were examined in terms of a number of graph attributes, together providing a description of the networks' overall architecture (figure 2c). Common descriptive graph metrics were investigated in relation to longitudinal changes in GF, symptoms and IQ: Overall connectivity S, describing the total level

of connectivity strength of the reconstructed network; clustering C, providing an estimate of local information segregation, computed as the average likelihood that two neighbors of a node are mutually connected; global efficiency GE, an estimate of overall communication efficiency throughout the network, computed as the average inverse shortest path between each possible pair of nodes in the graph. Graph metrics were computed from NOS weighted networks (Rubinov and Sporns, 2010). Previous cross–sectional analysis of the metrics describing global connectome architecture in these subjects indicated significant reductions in S, GE and C in patients, and intermediate levels of connectome clustering in unaffected siblings of patients (see Collin et al. 2014).

2.4.3. RICH CLUB ORGANIZATION

Rich club organization implies that hubs (i.e., highly connected and central nodes) are more densely mutually interconnected than is to be expected based on their high degree alone (Colizza et al., 2006; van den Heuvel and Sporns, 2011). Studies have shown the neural networks of several species to possess such an organization (Zamora–Lopez et al., 2009; Harriger et al., 2012; de Reus and van den Heuvel, 2013b;

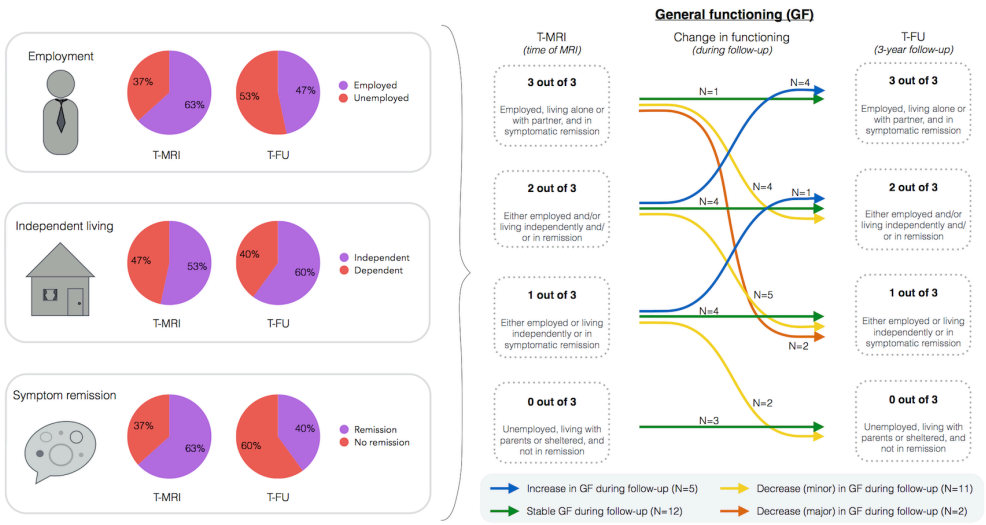

FIGURE 1. Three intuitive measures of real–world functioning in schizophrenia (employment, independent living and symptom remission) were combined in one composite measure of general functioning (GF). GF was assessed at the time of MRI acquisition (T–MRI) and three–year follow–up (T–FU). Four major trajectories of change in GF during follow–up were discerned (increase in GF, stable GF, minor decrease in GF, major decrease in GF) and patients were grouped accordingly.

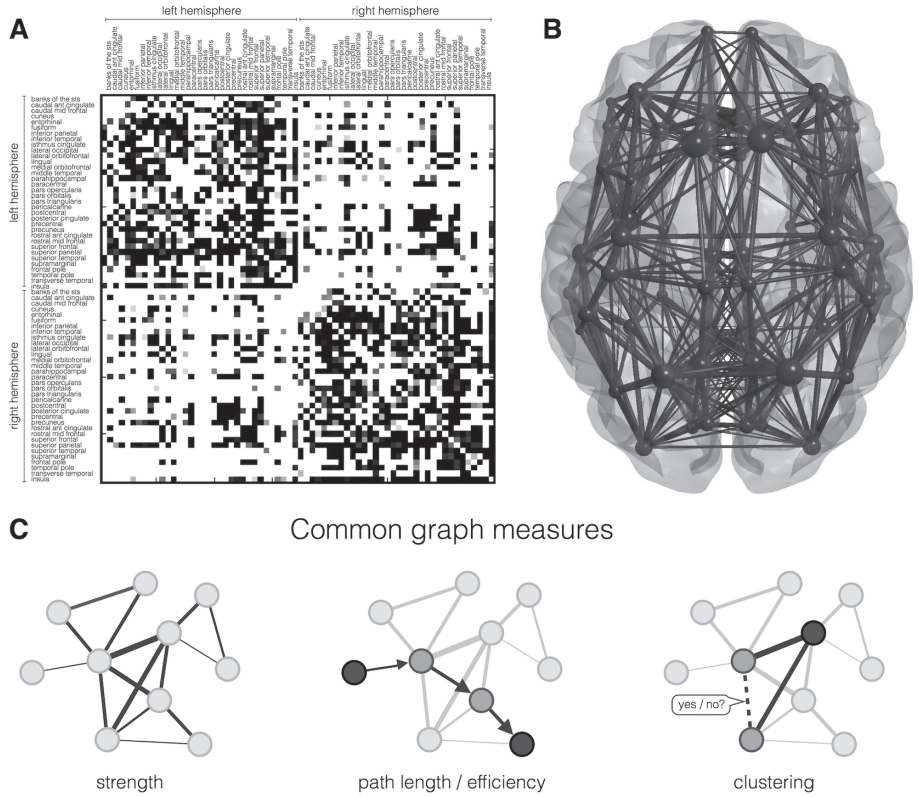

FIGURE 2. Connectome map, depicted as a matrix a) and neural graph b), with rows/columns a) and nodes b) representing parcellated cortical brain regions (N=68), and edges b) and matrix–entries a) representing cortico–cortical connections, were examined using common graph metrics c): strength, reflecting the total level of connectivity; global efficiency, describing overall communication efficiency in the network, computed as the average inverse shortest path length; clustering, providing an estimate of local information segregation.

Shanahan et al.,2013; Towlson et al., 2013; Scholtens et al., 2014; van den Heuvel and de Reus, 2014) and the level of connectivity within this system is reduced in schizophrenia patients (van den Heuvel et al., 2013) and their siblings (Collin et al., 2014). In this study, hubs were a priori defined as the superior frontal and parietal gyrus, precuneus and insula bilaterally (as taken from Collin et al., 2014; van den Heuvel et al., 2013), regions well validated as key brain hubs in previous research (van den Heuvel and Sporns, 2013) (see Supplementary material for details). Based on the classification of networks nodes into 'hubs' and 'non–hubs', network edges were sub–divided into connection classes based on their participation in rich club formation, as 'rich club' connections

(connecting hubs), 'feeder' connections (linking hubs to non–hubs) and 'local' connections (connecting non–hubs) (van den Heuvel et al., 2012). The computation of rich club organization was taken from Collin et al. (2014) and examined here in relation to longitudinal changes in clinical measures.

2.5. STATISTICAL ANALYSIS

Measures of connectome organization were examined in terms of their relationship with longitudinal changes in GF, clinical symptoms and IQ. Specifically, it was examined whether the most intact connectome at T–MRI belonged to subjects who show increased GF at T–FU, the most affected networks to those showing progressive decrease in GF over time, with intermediate network metrics in subjects showing stable GF. Non–parametric Jonckheere Terpstra permutation analysis (Bewick et al., 2004)– for details see Collin et al. (2014)– was performed to test ordered differences in connectome impairments across groups signifying the extent of longitudinal change in GF. In addition, Pearson's correlations were computed to examine linear associations between connectome organization and subsequent changes in IQ and (sub)clinical symptoms. As connectome measures are related to overall connectivity, partial correlations with C and GE, with overall connectivity included as a covariate, were also computed. Results were subjected to a false–discovery rate (FDR) threshold of $q<0.05$, indicating statistical significance. Findings with a $p<0.05$ not reaching the FDR–threshold were interpreted as trend–level findings.

3. RESULTS

3.1. CLINICAL MEASUREMENTS AT TIME OF SCAN ACQUISITION AND FOLLOW–UP

Out of the original forty patients in our previous investigations (Collin et al., 2014; van den Heuvel et al., 2013), thirty were reassessed after 3 years (T–FU) and ten were lost to follow–up (see Supplementary material for details). There were no significant differences in clinical or MRI measures between subjects that were lost to follow–up, relative to those re–evaluated at T–FU (Supplementary material).

On average, patients showed more clinical symptoms as measured by PANSS total symptoms at T–FU as compared to T–MRI ($p = 0.005$). Specifically, twenty patients showed no clinically relevant (Hermes et al., 2012) difference in total PANSS symptoms (± 15 points), one patient showed a decrease of 24 points; and nine patients showed a clinically significant increase (range 16–37 points) in total symptoms. On average, mean (sd) IQ was lower at T–FU–96.7 (16.4)–than at T–MRI–99.5 (15.0)–but this effect

did not reach significance ($p = 0.09$). The effects were similar when all subjects at T–MRI (N = 40) were included.

Table 2 summarizes the characteristics of the subjects per GF trajectory group. The only significant difference in clinical measures was IQ at follow–up, which was higher in the group showing increased GF at T–FU as compared to T–MRI than in the other groups.

3.2. LONGITUDINAL CHANGES IN FUNCTIONING, SYMPTOMS AND IQ

3.2.1. GENERAL FUNCTIONING

Examining connectome organization revealed a trend–level positive effect on longitudinal changes in GF of overall connectivity S ($p = 0.030$, not surviving FDR–correction; figure 3a, c) and GE ($p = 0.034$, non–FDR significant). No clear effect of overall clustering was observed ($p = 0.08$). Strength of rich club and local connections was positively ($p = 0.007$ and $p = 0.003$ respectively, FDR–significant) related to change in GF during follow–up, with a trend–level effect for feeder connections ($p = 0.037$, non–FDR significant), consistent with the overall effect of S (figure 3b, d). To examine the impact of S on these findings (Lynall et al., 2010; Scholtens et al., 2014), the proportion of connectivity per connection class (i.e. rich club, feeder, local) relative to overall S was examined in a post–hoc analysis, revealing only rich club connectivity to be independently associated with longitudinal change in GF ($p = 0.030$; figure 3e), such that, independent of overall connectivity (S), greater rich club connectivity was associated with positive changes in general functioning during follow–up and vice–versa.

3.2.2. ROBUSTNESS OF GENERAL FUNCTIONING FINDINGS

Post–hoc analyses were performed to assess the robustness of the findings on general functioning (see Supplementary material for details). First, distinguishing three trajectories of GF change (increase, stable, decrease)–i.e., including two patients with a major decrease in functional outcome in one larger group of all patients with decreased GF–confirmed the main finding ($p = 0.018$). Second, excluding patients with other than formal schizophrenia diagnosis (DSM 295.10; 295.30; 295.60; 295.90) did not change the association between rich club connectivity and general functioning change ($p = 0.024$). Third, excluding patients with GF level 0 at baseline (N=3), to eliminate a possible floor effect, did not alter the main effect ($p = 0.011$). Fourth, correcting for dosage of antipsychotic medication and cannabis abuse/dependency through linear regression analysis did not change the main finding ($p=0.019$).

TABLE 2. Characteristics of subjects grouped by trajectory of change in general functioning (GF) during follow–up.

	Stable outcome (N=12)		Increased outcome (N=5)		Decreased outcome (minor) (N=11)		Decreased outcome (major) (N=2)		p–value	
	Scan	FU	Scan	FU	Scan	FU	Scan	FU	S	FU
Age at scan, mean (sd)	29.4 (4.9)		33.3 (7.6)		29.0 (5.2)		26.5 (2.1)		0.36	
Gender, M/F	5/0		10/2		10/1		2/0		0.71	
Duration of illness T–MRI, mean (sd)	7.5 (5.4)		8.1 (2.9)		9.1 (5.1)		4.1 (1.1)		0.44	
DSM–diagnosis									0.77	0.13
Schizophrenia, N (%)	4 (80)	4 (80)	8 (66.7)	7 (58.3)	10 (90.9)	11 (100)	2 (100)	2 (100)	0.45	0.08
Schizoaffective disorder, N (%)	1 (20)	0 (0)	3 (25)	3 (25)	1 (9.1)	0 (0)	0 (0)	0 (0)	0.68	0.17
Other schizophrenia spectrum, N (%)	0 (0)	0 (0)	1 (8.5)	2 (16.6)	0 (0)	0 (0)	0 (0)	0 (0)	0.67	0.36
Bipolar disorder, N (%)	0 (0)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)		0.16
IQ, mean (sd)	111.8 (14.8)	115.8[#] (10.3)	97.8 (12.3)	91.7 (12.7)	96.6 (17.1)	94.7 (17.6)	95.0 (11.3)	87.0 (11.3)	0.30	.04
PANSS symptoms										
Total, mean (sd)	40.0 (8.0)	43.0 (7.5)	47.2 (10.2)	60.9* (16.1)	47.8 (14.9)	55.9 (14.2)	47.5 (6.4)	64.5 (7.8)	0.50	0.15
Positive scale, mean (sd)	9.6 (3.6)	10.0 (1.9)	10.2 (2.5)	14.0* (4.5)	10.8 (5.7)	13.7 (5.2)	10.0 (1.4)	17.0* (1.4)	0.84	0.26
Negative scale, mean (sd)	10.4 (3.4)	11.0 (2.9)	12.5 (3.6)	16.8 (6.7)	12.4 (3.2)	14.8 (3.9)	13.5 (2.1)	15.5 (2.1)	0.60	0.24
General scale, mean (sd)	20.0 (4.1)	22.0 (5.4)	24.5 (5.2)	30.2 (8.6)	24.6 (7.5)	27.4 (8.1)	24.0 (2.8)	32.0 (4.2)	0.45	0.22
Antipsychotic medication										
Clozapine/other atypical[a]/typical/none	0/4/0/1	0/4/0/1	5/5/1/0[c]	5/5/1/0[c]	1/10/0/0[c]	2/9/0/0[c]	0/2/0/0	0/2/0/0	0.23	0.42
CP2[b] dose, mean (sd)	200.0 (0.0)	138.3 (73.7)	296.2 (191.2)	243.3 (159.0)	247.3 (113.9)	369.3 (279.2)	200.0 (0.0)	133.3 (0.0)	0.93	0.06

[a]atypical antipsychotics other than clozapine include risperidone, olanzapine, quetiapine and aripiprazole [b]CPZ = chlorpromazine. Data missing for N=1 [#]Group with increased GF at follow–up differs from other groups. *Significant change between assessments.

3.2.3. CLINICAL SYMPTOMS AND IQ

Longitudinal changes in total PANSS symptoms and IQ were significantly associated with C, such that a less clustered connectome at T–MRI predicted subsequent increases in symptoms (r=–0.46, p=0.013, FDR–significant) and decreases in IQ (r=0.54, p=0.003, FDR–significant) and vice–versa (figure 4). These effects remained highly significant when total IQ and symptoms at T–MRI were included as predictors (p=0.001 and p=0.001 respectively). Moreover, the effect with IQ change remained significant when controlling for overall connectivity (p=0.016). In addition, trend–level effects (all not surviving FDR–correction) were observed between symptom change and S (p=0.030), and IQ change and S (p=0.031) and GE (p=0.026). There were no significant cross–sectional associations between network measures and baseline symptoms and IQ (all p>0.25, see Supplementary material). A post–hoc analysis revealed the correlation between C and symptom change to be driven mainly by disorganization symptoms (Supplementary material). Notably, controls and siblings showed no significant correlations between longitudinal changes in subclinical psychotic symptoms and IQ, and measures of connectome organization (Supplementary material).

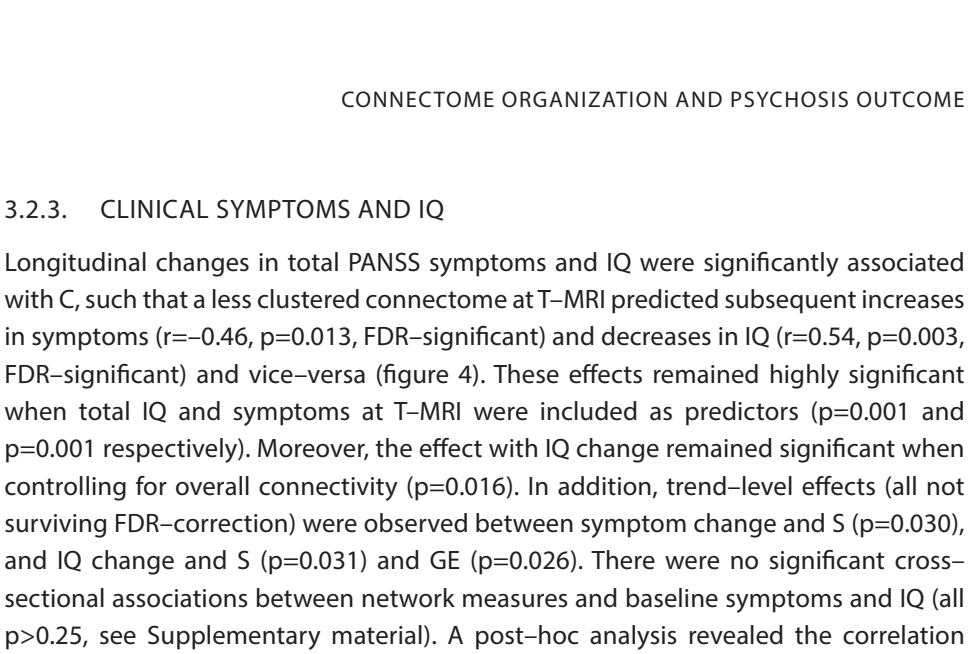

FIGURE 3. Overall connectivity S (a) and connection classes (rich club, feeder, and local connections) (b) were examined for a link with change in general functioning (GF) during follow–up. Total connectivity showed a trend–level effect with subsequent change in GF (c); rich club and local connectivity both showed significant associations (d), but only rich club connections remained significantly associated with GF change when examined as a proportion of S (e).

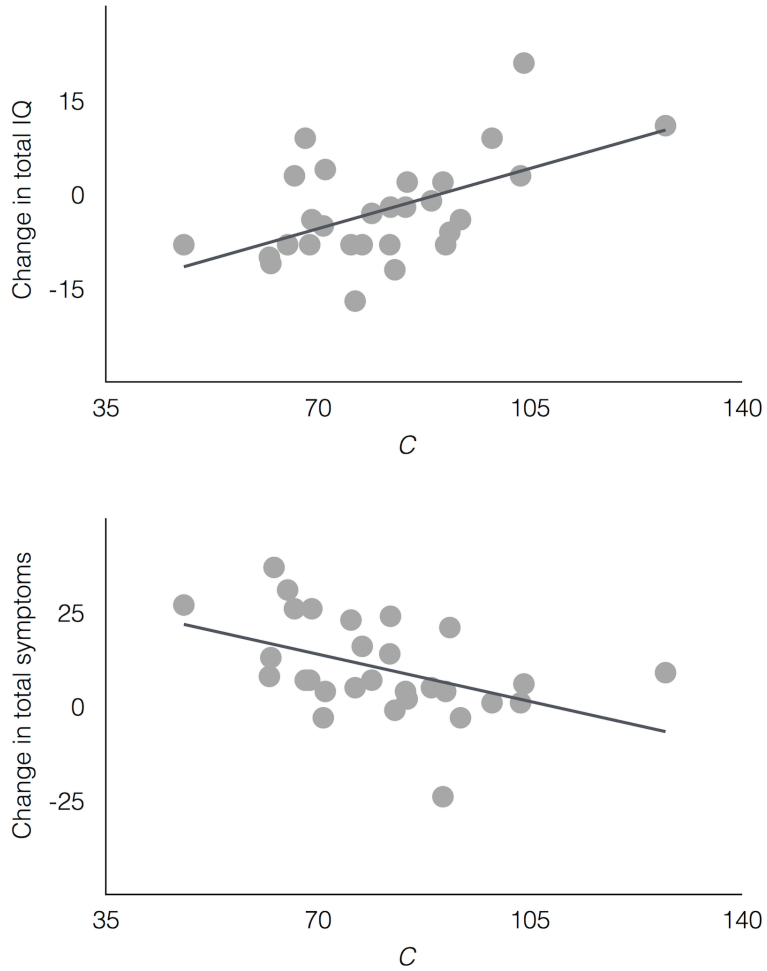

FIGURE 4. Associations between connectome clustering C at T–MRI and subsequent changes in IQ (top) and total PANSS symptoms (bottom) during follow–up.

4. DISCUSSION

Structural connectome wiring was examined in relation to longitudinal changes in general and intellectual functioning and clinical symptoms in 3 years following MRI assessment in a cohort of chronically ill schizophrenia patients. Examining patients' functioning over time revealed more severely affected wiring of the connectome, especially regarding rich club connections, to precede a progressive decrease in functional performance over time, while relative sparing of these connections preceded stable or improved general functioning. Moreover, stronger alterations in global connectome topology–network clustering in particular–were shown to herald subsequent increases in total symptoms and decline in intellectual function, independent of baseline measures. Finding no such associations with change in IQ and subclinical symptoms in controls and unaffected siblings suggests that the findings in patients represent effects of ongoing illness, as opposed to normal age–related changes. Our findings are thus indicative of potential predictive value of connectome structure on illness progression in schizophrenia.

Abnormalities in connectome and rich club organization were previously shown to be present at intermediate levels in unaffected siblings of schizophrenia patients (Collin et al., 2014). This suggests that connectome alterations may reflect a neurodevelopmental insult or aberration of brain maturation (Collin and van den Heuvel, 2013; Fornito et al., 2012; van den Heuvel and Fornito, 2014) related to familial, possibly reflecting genetic (Terwisscha van Scheltinga et al., 2013), factors. If connectome abnormalities are neurodevelopmental in nature, an explanation for the current findings might be that more affected connectome structure reflects a more severe phenotype that is associated with a higher probability of functional deterioration over time. In addition, a less efficiently wired connectome might be more susceptible for progressive white matter deterioration, which could in turn give rise to more severe functional decline. Indeed, theories of schizophrenia have characterized the illness as a progressive neurodevelopmental disorder, implying a pathogenic process that begins in early neurodevelopment, evolves until it reaches a critical threshold and subsequently causes progressive brain decline (Rapoport and Gogtay, 2011; Swapnil and Kulhara, 2010; Woods, 1998). Brain hubs may be pertinent in this respect as their topological centrality may make them vulnerable to pathogenic factors, rendering hubs a 'hot spot' for (progressive) neural changes (van den Heuvel and Sporns, 2013; Crossley et al., 2014). Our current finding that the level of connectivity among brain hubs best predicted progressive changes in real–world functioning adds that this central infrastructure may be pertinent to illness progression. Longitudinal studies examining possible progressive changes in connectome and hub wiring over time are needed to provide more insight in this matter.

The current study examined connectome organization in relation to longitudinal changes in functional and clinical outcome in chronic schizophrenia. While the greatest changes in brain measures and functioning are presumed to occur in earlier stages of illness, brain tissue continues to decline in the chronic phase (Hulshoff Pol and Kahn 2008), and so do social (Martin et al. 2015) and certain neurocognitive functions (Zanelli 2012; Barder et al. 2013; Thompson et al. 2013). Moreover, cognitive trajectories

appear to be heterogeneous across individual patients (Thompson et al., 2013) and cognitive domains (Jahshan et al., 2010), with some improving with stabilization in the early stages while others decline with progressing illness. In addition, ongoing brain changes until 12 years after first diagnosis have been shown to correlate with functional outcome (Ho et al., 2003). In all, changes in functioning occur in advanced illness, in diverging trajectories, and related to ongoing brain changes. Our current study extends these findings by suggesting that brain network organization may be predictive of subsequent changes in outcome some years after first diagnosis, at which time patients may question their future perspective in terms of symptoms and functioning, for example in relation to study or work.

With regard to predicting outcome, previous investigations of first–episode (van Veelen et al., 2011) and chronic (Khodayari–Rostamabad et al., 2010) schizophrenia patients, have shown that functional MRI and EEG measurements may be useful in predicting treatment response. In addition, reduced volume of dorsolateral prefrontal and superior frontal cortices–highly connected cortical regions and putative brain hubs (van den Heuvel and Sporns, 2013)–was demonstrated to predict worse socio–occupational functioning (Prasad et al. 2005; Behere et al. 2013) and greater negative symptoms (Behere et al. 2013), and to differentiate between poor and good functioning patients at follow–up (Kasparek et al. 2009). In addition, fronto–parietal components of functional brain networks were reported to contain most predictive information regarding later improvement in negative symptoms (Nejad et al. 2013). In all, brain (network) measures relating to frontal brain hubs and their connections to other hub regions of the brain, may include useful new metrics to inform prognostic estimations in schizophrenia (van den Heuvel and Kahn, 2011).

Studies examining individuals at clinical or genetic high risk for psychosis have shown that neurophysiological, neurochemical and neurostructural markers can be used to predict subsequent symptom progression (Tognin et al., 2013), transition to psychosis (Allen et al., 2012; Howes et al., 2011; Andrea Mechelli et al., 2011) and functional outcome (Allen et al., 2014) in these individuals. In this context, a worthwhile avenue for future research may be to examine whether measures of brain network organization are also predictive of future functioning in the first–episode, or in high–risk individuals.

Our findings are limited by the inherent nature of the applied methodology. Limitations associated with diffusion–weighted imaging, a technique that relies on water diffusion as an indirect marker for axon geometry, include difficulties in resolving complex fiber architecture, such as crossing, diverging or converging fibers (for a review, see Jbabdi and Johansen–Berg, 2011). In addition, the majority of patients in this study used antipsychotic medication which may influence structural brain connectivity

(Szeszko et al., 2014). However, in this context it should be noted that altered white matter connectivity has also been shown in medication–naïve patients (Cheung et al., 2008; Mandl et al., 2013) and in our current study population, no clear influence of the chlorpromazine equivalent dosage of antipsychotic treatment on connectome measures was observed (Collin et al., 2014), nor on the relationship with longitudinal changes in general functioning, as examined here.

This study provides evidence that connectome and rich club organization may be predictive of illness progression, including longitudinal changes in general functioning, clinical symptoms and IQ, in chronically ill schizophrenia patients. These findings highlight the potential of connectome measures in informing prognosis in schizophrenia.

SUPPLEMENT

SUPPLEMENTARY METHODS

DETERMINING GENERAL FUNCTIONING (GF)

To determine real–world functional performance, a composite measure was computed based on three robust and intuitive features of overall functioning: 1) Employment was defined as having a paid job. Volunteer work, as a consequence, did not constitute employment in this study. 2) Independent living included subjects with a single–person household, or those living with their partner and/or own family. Dependent living was defined as either sheltered living, living with parents, or 'other' (hospital admission, homelessness, living with sibling). Living with parents was considered as deviant from the norm as subjects were on average around 31 years (range 22–45) at T–MRI and 34 years of age (range 25–48) at T–FU. 3) Symptom remission was defined according to the severity component of the operational criteria for remission developed by the Remission in Schizophrenia Working Group (Andreasen et al., 2005). Consensus definition of remission in schizophrenia was defined as a level of core schizophrenia symptoms that does not interfere with an individual's behaviour and is below that required for a diagnosis of schizophrenia according to the DSM–IV (Lambert et al., 2010). The definition involves a symptom criterion such that five criteria for schizophrenia specified in the DSM–IV, reflected by eight PANSS items (supplemental table 1), are all scored ≤ 3 points ('mild' or better). The time component, requiring that severity criteria are met for a duration of at least 6 months, was not considered for the GF measure (see next).

SUPPLEMENTAL TABLE 1. Remission criteria items

DSM–IV criteria	PANSS items (item number)
Delusions	Delusions (P1)
	Unusual Though Content (G9)
Hallucinations	Hallucinations (P3)
Disorganized speech	Conceptual Disorganization (P2)
Grossly disorganized or catatonic behaviour	Mannerisms/posturing (G5)
Negative symptoms	Blunted affect (N1)
	Social withdrawal (N4)
	Lack of spontaneity (N6)

DSM–IV criteria and corresponding Positive and Negative Syndrome Scale (PANSS) items comprising the symptom criterion for remission (Andreasen, 2005). Each of the PANSS items has to be scored 3 points or less ('mild' or better). Alternatively, the Scale for the Assessment of Negative Symptoms and Positive Symptoms (SANS / SAPS), or the Brief Psychiatric Rating Scale (BPRS) can be applied, for details see (Lambert et al., 2010).

TIME COMPONENT OF OPERATIONAL CRITERIA FOR REMISSION

In the current study, symptomatic remission was based exclusively on the symptom–based criterion, similar to many previous studies (Bodén et al., 2009; Buckley et al., 2007; Ciudad et al., 2009; Dunayevich et al., 2006; Helldin et al., 2006). The time criterion was not considered for the GF measure as the number of patients meeting formal remission criteria was low (22% and 23% respectively at T–MRI and T–FU), resulting in poor contrast to distinguish between patients. The low proportion of formal remission was due to missing data on the duration of symptom remission (N=3) or duration shorter than six months. The latter may be particularly relevant as the applied six–month criterion of remission is still debated (Lambert et al., 2010), and 3–month (Cassidy et al., 2010) or shorter (Lambert et al., 2009, 2007) time periods have shown comparable predictive validity for the stability of remission over time. Moreover, remission was not examined exclusively, but combined with information on employment and living situation to derive an aggregate estimate of general functioning.

IMAGE PREPROCESSING

Preprocessing of anatomical T1–weighted and diffusion–weighted scans was performed previously as reported in Collin et al. (2014); van den Heuvel et al. (2013). ANATOMICAL T1 SCAN: Freesurfer software, version 5.0 (http://surfer.nmr.mhg.harvard.edu) was used for tissue classification and reconstruction of the cortical surface of each subject in its native space. Reconstructed surfaces were registered and compared to Freesurfer's Desikan Killiany atlas for parcellation of the cortical surface into 68 distinct regions (i.e. 34 regions per hemisphere), ensuring compatibility of cortical regions across subjects. DIFFUSION WEIGHTED SCAN: The two sets of b=0 images were averaged and the 2x32 diffusion directions were realigned and corrected for small–head movements and common gradient–induced distortions (Andersson and Skare, 2002). Second, a diffusion tensor model was used to examine the preferred diffusion direction, fitting a tensor to the diffusion profile within each voxel using a robust tensor fitting method (Chang et al., 2005). Third, the main diffusion direction was determined by eigenvalue decomposition of the tensor, with the principal eigenvector of each tensor signifying the main diffusion direction per voxel. Fourth, streamline tractography was used to reconstructed white matter pathways, based on the fiber assignment by continuous tracking (FACT) algorithm (Mori and Van Zijl, 2002). Within each voxel, eight streamline seeds were started. Fiber tracking was stopped when the streamline reached a voxel of low preferred diffusion direction (FA<0.1), exceeded the grey/white matter mask or made a sharp turn (>45 degrees). Fifth, the T1 image was realigned with the b=0 images, enabling anatomical overlap between the cortical parcellation maps and the collection of reconstructed streamlines.

HUB DEFINITION

Hub definition was based on previous investigations in low– and high–resolution networks, in human as well as non–human subjects (Collin et al., 2014; Harriger et al., 2012; Scholtens et al., 2014; van den Heuvel and Sporns, 2011; van den Heuvel et al., 2013, 2012). In these and other studies, precuneus, superior frontal and parietal, and insular cortices have consistently been identified as key brain hubs, across individual subjects and even species, and verified against individual definitions. The a priori definition applied currently ensured unbiased hub selection across subjects.

LONGITUDINAL CHANGE IN IQ AND SUBCLINICAL SYMPTOMS IN CONTROLS and SIBLINGS

The main aim of this study was to examine connectome structure in relation to illness progression in schizophrenia patients, as examined in terms of longitudinal changes in general functioning, clinical symptoms and IQ. To examine whether effects in patients were related to the effects of progressing illness, rather than 'normal' evolution with time, in the absence or presence of increased familial risk for the disorder, a group of controls (N=51) and unaffected siblings (N=54) was also investigated (Collin et al., 2014). Specifically, measures of brain network organization were examined for associations with change between assessments in estimated total IQ and in CAPE subclinical symptoms using Pearson's correlations.

SUPPLEMENTARY RESULTS

BASELINE CHARACTERISTICS OF INCLUDED SUBJECTS

From a total of 40 schizophrenia patients examined previously in a cross–sectional study of connectome architecture (Collin et al., 2014), 30 patients were re–evaluated after 3 years follow–up. These subjects formed the focal point of the current study. In addition, from a total of 54 siblings and 51 controls, 48 siblings and 45 controls reassessed at T–FU were added in order to differentiate between disease–related effects and 'normal' change with time. A brief description of the demographic and clinical characteristics at T–MRI of each subject group is provided in supplemental table 2. There were significantly more males in the patient group, IQ was higher in controls as compared to patients and siblings (with a trend–level difference between patients and siblings, p=0.08) and CAPE total symptoms were higher in patients, with no significant difference between siblings and controls (p=0.57). Notably, the characteristics of the entire baseline sample were described previously (Collin et al., 2014).

CHARACTERISTICS OF PATIENTS THAT WERE LOST TO FOLLOW–UP

Ten patients were lost to follow–up. Of these subjects, one had died, one had emigrated, four refused to participate and we were unable to contact the remaining four at T–FU. Examining demographic and clinical characteristics of patients that were lost to follow–up, as compared to those that were reassessed at T–FU (summarized in supplemental table 3.), showed no significant differences between these subject groups (all p>0.1).

SUPPLEMENTAL TABLE 2. Baseline characteristics of re–evaluated patients, siblings and controls.

	Patients (N=30)	Siblings (N=48)	Controls (N=45)	p–value
Age in years, mean (sd)	30.6 (6.3)	28.6 (6.9)	29.2 (8.8)	0.52
Gender, M / F	27 / 3*	19 / 29	21 / 24	<0.01
IQ, mean (sd)	99.5 (15.0)	105.6 (14.6)	114.9 (17.6)*	<0.01
CAPE[a] total (subclinical) symptoms, mean (sd)	29.2 (16.2)*	11.2 (8.5)	10.2 (7.9)	<0.01

Baseline characteristics of schizophrenia patients, unaffected siblings and healthy controls that were re–evaluated at three years follow–up. [a] Community Assessment of Psychic Experiences (CAPE). * indicates the subject group that is statistically different from the other subject groups.

SUPPLEMENTAL TABLE 3. Characteristics at T–MRI of patients re–evaluated vs. lost to follow–up

	Re–evaluated at follow–up (N=30)	Lost to follow–up (N=10)	p
Demographic and clinical measures			
Age in years, mean (sd) [range]	30.6 (6.3) [22–45]	30.5 (5.5) [22–40]	0.94
Gender, M/F	27 / 3	9 / 1	0.99
Duration of illness	8.1 (4.2)	6.0 (3.1)	0.17
IQ, mean (sd) [range]	99.5 (15.0) [71–132]	89.3 (18.3) [65–124]	0.11
PANSS total symptoms	46.2 (11.6) [30–83]	49.8 (15.6) [30–77]	0.48
CPZ[a] equivalent dose of AP[b], mean (sd)	256.7 (141.4)	285.0 (158.2)	0.69
MRI measures			
S, mean (sd) x 10^3	140.9 (39.2)	144.1 (27.9)	0.81
C, mean (sd)	81.5 (17.5)	86.7 (11.2)	0.38
GE, mean (sd) x 10^{-3}	133.6 (35.8)	135.8 (24.3)	0.86
Rich club connectivity, mean (sd) x 10^3	11.1 (5.4)	9.7 (3.8)	0.47
Feeder connectivity, mean (sd) x 10^3	23.1 (7.1)	23.8 (5.0)	0.78
Local connectivity, mean (sd) x 10^3	83.8 (21.6)	86.8 (16.8)	0.68

Demographic and clinical characteristics at T–MRI of patients that were re–evaluated at T–FU and thus included in the current study, versus those that were lost to follow–up. [a] CPZ = chlorpromazine. [b] AP = antipsychotic medication.

DISTINGUISHING THREE GF CHANGE TRAJECTORIES (INCREASE, STABLE, DECREASE)

Only two subjects showed a major decrease in functional outcome at T–FU relative to T–MRI. Therefore, in an additional analysis, these subjects were included in one larger group of all patients showing decreased GF (major and minor). Regarding clinical characteristics, these groups confirmed the observed differences in IQ at follow–up, with significantly higher IQ in the group showing increased GF (mean=115.8), as compared to stable (mean=91.7) and decreased (mean=93.5) GF (p=0.02). There was a trend–level difference of type of antipsychotic medication at T–MRI such that the prevalence of clozapine treatment was higher in the group going on to show stable (41.7%), as opposed to decreased (7.7%) functioning (p=0.05). In accordance with our main findings, significant effects for rich club and local connectivity (p=0.018 and p=0.006 respectively) were observed, and the proportion of rich club connectivity (relative to S) was also associated with change in GF (p=0.041).

EXCLUDING DIAGNOSES OTHER THAN FORMAL SCHIZOPHRENIA

To explore the influence of (changes in) diagnosis on the main findings, two additional analyses were performed. First, the patient who was diagnosed with bipolar disorder at T–FU (schizoaffective disorder at T–MRI) was excluded. Re–analysis resulted in highly comparable findings including significant effects of rich club and local connectivity (p=0.017; p=0.007 respectively) and a trend–level effect for the proportion of rich club connectivity (p=0.056). Second, all patients with a diagnosis other than formal schizophrenia (295.10, 295.30, 295.60, 295.90) at either T–MRI or T–FU were excluded. This analysis also confirmed main effects (rich club: p=0.024; local: p=0.021; rich club proportion of S: p=0.059), although findings were slightly attenuated, likely due to reduced power (N=24).

EXCLUDING SUBJECTS IN GENERAL FUNCTIONING LEVEL 0 AT BASELINE

From our measurement of general functioning (GF), we cannot conclude that the patients with GF level 0 at baseline (N=3) remained stable during follow–up, due to a possible floor effect. Moreover, none of the patients in this group showed an increase in their level of functioning, suggesting that they might be different from those with other than 0 baseline GF. Re–analysis after excluding these subjects yielded results highly comparable to the main findings (rich club: p=0.011; local: p=0.003; rich club proportion of S: p=0.058).

ASSESSING POSSIBLE CONFOUNDERS: ANTIPSYCHOTIC MEDICATION AND CANNABIS

To assess the effect of antipsychotic treatment, rich club connectivity was corrected for the CPZ equivalent dosage of antipsychotic medication at T–MRI through linear regression analysis, and the association with longitudinal change in general functioning was re–examined. This analysis revealed that rich club connectivity remained significantly associated with change in GF (p=0.019).

There were no significant differences in the number of subjects with cannabis abuse/dependence between GF change groups (two subjects in the group with minor decrease in GF, one in the stable group and one in the group with increased GF at T–FU; p=0.51, chi–squared test) and direct comparison of subjects with versus without (a history of) cannabis abuse/dependency through independent t–tests revealed no significant differences in connectome metrics (all p>0.6).

PEARSON'S CORRELATIONS BETWEEN C AND SYMPTOM DIMENSIONS

To further explore the association between brain network clustering C at T–MRI and change in total PANSS symptoms during follow–up, a post–hoc analysis was performed in which correlations with three main factor–analysis derived symptom dimensions (positive, negative, disorganization) were examined. This analysis indicated that C correlated with subsequent change in disorganization (r=–.47, p=0.013, FDR–significant), which has previously been associated with progressive brain changes (Collin, 2012) and, to a lesser extent, positive (r=–0 .39, p=0.039, trend–level) symptoms.

CROSS–SECTIONAL CORRELATIONS BETWEEN NETWORK MEASURES AND BASELINE SYMPTOMS AND IQ

To assess whether the observed associations between network measures and longitudinal changes in symptoms and IQ were driven by possible cross–sectional correlations with baseline symptoms and IQ, these associations were also examined. In accordance with our previous studies on (baseline) connectome architecture of these subjects, we found no significant correlations between network measures and baseline total PANSS symptoms (range r=–0.07 to r=–0.15, all p>0.37) or IQ (range r=0.13 to r=0.16, all p>0.25).

LONGITUDINAL CHANGE IN IQ AND SUBCLINICAL SYMPTOMS IN CONTROLS and SIBLINGS

Examining measures of connectome organization in relation to change in estimated total IQ and total subclinical symptoms, as measured by the CAPE, between T–MRI and T–FU in healthy controls and unaffected siblings of schizophrenia patients, there were no significant correlations (Supplemental table 4). This suggests that the observed correlations between brain network structure and longitudinal changes in markers of illness progression and functional performance in patients are related to the effects of ongoing illness, as opposed to e.g. normal changes with time.

SUPPLEMENTAL TABLE 4. Correlations between connectome structure and change in IQ and subclinical symptoms in absence of psychotic illness

	Controls		Siblings	
	IQ (Δ) (N=40)	Symptoms (Δ) (N=45)	IQ (Δ) (N=42)	Symptoms (Δ) (N=46)
S	0.13	0.07	0.07	–0.18
C	0.13	0.13	0.09	–0.17
GE	0.16	0.06	0.09	–0.14
Rich club connectivity	0.04	–0.16	0.05	–0.06
Feeder connectivity	0.28	0.11	0.07	–0.08
Local connectivity	0.06	0.08	0.07	–0.25

Correlation coefficients describing the association between change in IQ and CAPE subclinical symptoms between T–MRI and T–FU in healthy controls and unaffected siblings of schizophrenia patients. None of the correlations reached statistical significance (all p>0.09), also when subjects were combined in one group (all p>0.13).

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PART II

PHYSICAL OUTCOMES

CHAPTER 5

ASSOCIATIONS BETWEEN OLFACTORY IDENTIFICATION AND (SOCIAL) COGNITIVE FUNCTIONING: A CROSS-SECTIONAL STUDY IN SCHIZOPHRENIA PATIENTS AND HEALTHY CONTROLS

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ABSTRACT

Schizophrenia patients have difficulties identifying odours, possibly a marker of cognitive and social impairment. This study investigated olfactory identification (OI) differences between patients and controls, related to cognitive and social functioning in childhood and adolescence, to present state cognition and to present state social cognition. 132 schizophrenia patients and 128 healthy controls were assessed on OI performance with the Sniffin' Sticks task. Multiple regression analyses were conducted investigating OI in association with cognitive and social functioning measures in childhood/adolescence and in association with IQ, memory, processing speed, attention, executive functioning, face recognition, emotion recognition and theory of mind. Patients had reduced OI performance compared to controls. Also, patients scored worse on childhood/adolescence cognitive and social functioning, on present state cognitive functioning and present state social cognition compared to controls. OI in patients and controls was significantly related to cognitive and social functioning in childhood/adolescence, to present state cognition and to present state social cognition, with worse functioning being associated with worse OI. In this study, findings of worse OI in patients relative to controls were replicated. We also showed associations between OI and cognitive and social functioning which are not specific to schizophrenia.

Keywords: olfactory identification deficit, cognition, social cognition, childhood/adolescent functioning

1. INTRODUCTION

Schizophrenia patients have difficulties identifying odours (Moberg et al., 2014). The degree of this reduced odour identification (OI) compared to healthy controls has been examined extensively. A meta–analysis by Cohen et al. (2012) showed that OI in schizophrenia is nearly a standard deviation below the mean of controls. Schizophrenia is also characterized by cognitive and social cognitive deficits, particularly in IQ, memory, processing speed, attention, executive functioning, emotion recognition and theory of mind (Mesholam–Gately et al., 2009). These deficits appear to be present before illness onset, as previous birth cohort studies showed that on average, subjects who later develop schizophrenia report poorer cognitive and social functioning in childhood and adolescence (Welham et al., 2009). Interestingly, impairments in social behaviour and social cognition (i.e. emotion recognition) in schizophrenia have been related to OI deficit (Malaspina and Coleman, 2003; Kohler et al., 2007 resp.). Furthermore, previous studies have shown that OI and cognition are positively associated in schizophrenia (Brewer et al., 1996; Compton et al., 2006; Good et al., 2002; Goudsmit et al., 2004; Malaspina and Coleman, 2003; Moberg et al., 2006; Purdon, 1998; Saoud et al., 1998; Seckinger et al., 2004; Seidman et al., 1997, 1991; Stedman and Clair, 1998) and in controls (Brewer et al., 1996; Compton et al., 2006; Seidman et al., 1991), with moderate strength in both groups. However, in the majority of these studies only one or two cognitive domains were examined in relation to OI and often a range of possible confounders such as age, gender, smoking and the use of antipsychotics associated with OI (Moberg et al., 2014) was not taken into account. Moreover, most studies lacked a control group.

Olfactory development is dependent on the development of frontal and temporal lobe areas (Nguyen et al., 2010; Turetsky et al., 2009) and its cognitive (i.e. IQ, memory, processing speed, attention, executive functioning) and social cognitive related functioning (Aleman, 2014). Since cognitive and social functioning in childhood and adolescence is already dependent on the brain maturation of these areas early in life we expect a relationship between OI and cognitive and social functioning in childhood and adolescence. To date, no studies have been performed linking OI to cognitive and social functioning in childhood and adolescence and to present state functioning on multiple social cognitive domains. In this study we therefore comprehensively examine whether OI is related to cognitive and social functioning in childhood and adolescent, as well as to a range of present state social cognitive domains in a large sample of schizophrenia patients and healthy controls. Furthermore, we aim to replicate whether olfactory functioning is associated with present state cognition.

2. METHODS

2.1. STUDY DESIGN AND POPULATION

Data from this cross–sectional study pertain to the multicentre 'Genetic Risk and Outcome in Psychosis'– project (GROUP). This trial was part of an add–on study during the second measurement of this Dutch longitudinal GROUP–project. Participants were assessed extensively and were invited to participate in diagnostic interviews, questionnaires and neuropsychological tasks. The study protocol was approved by the accredited Medical Ethics Review Committee. All participants signed informed consent. More detail on the GROUP study is described by Korver et al. (2012). A subsample of 132 patients with a diagnosis of schizophrenia (DSM–IV: 295.1/295.3/295.6/295.9; mean ± sd age: 30.68 ± 7.03) and 128 healthy controls (mean ± sd age: 32.41 ± 9.50), assessed on present state OI, present state cognitive functioning and present state social cognitive functioning, as well as a retrospective questionnaire on childhood social and cognitive functioning were included in the current study. Nine participants missed cognitive data and three missed social cognitive data. Controls had no diagnosis according to DSM–IV and no first degree family member with a lifetime psychotic disorder.

2.2. OI, COGNITIVE AND SOCIAL MEASURES

OI was assessed with the Sniffin' Sticks, based on pen–like odour dispensing sticks (Hummel et al., 2001). Participants identified 16 odours by multiple choice from four descriptions. Odour sticks were presented birhinally in a fixed order by a trained researcher. The time interval between odour presentations was 30 s. OI was defined as number of correct responses. Although tests of odour threshold and discrimination are also available, only OI was assessed due to time constraints, and since this olfactory domain is most commonly affected in schizophrenia patients (Cohen et al., 2012). The Sniffin' Sticks have been employed previously to assess OI in patients with psychosis (Meijer et al., 2016; Kamath et al., 2014; Rupp et al., 2005; Ugur et al., 2005).

Cognitive and social functioning in childhood/adolescence was measured retrospectively with the Premorbid Adjustment Scale (PAS; Cannon–Spoor et al., 1982; Quee et al., 2014). Scores of cognitive functioning and social functioning were calculated separately by summing scores of corresponding cognitive (school performance and school adaptation) and social (social behavior, peer relations and social–sexual aspect) subscales across age epochs and subsequently divided by the number of scores. Informants were either a parent, another family member of the patient, or the patients themselves. Healthy controls provided the information themselves. With an ANOVA we compared whether PAS informants differed in their assigned scores.

A cognition composite score was calculated as a mean of seven transformed z–scores for each tested cognitive domain, accordant with Quee et al. (2011; i.e. these domains were an assessment of present state cognitive functioning), which were 1) IQ measured with the Wechsler adult intelligence scale–third edition, using the subtasks: Arithmetic, Information, Digit–Symbol Coding and Block Design, 2) immediate recall, 3) delayed recall and 4) recognition measured with the 15–word learning task, 5) attention and 6) processing speed measured with the continuous performance task–HQ, and 7) executive functioning measured with the response set–shifting task. A social cognition composite score was calculated, which is an average of four following domains (i.e. assessment of these domains was of present state social cognition), converted to z–scores: 1) face recognition measured with the Benton facial recognition task, 2) emotion recognition measured with the degraded affect recognition task and 3) theory of mind of emotions and 4) theory of mind of beliefs measured with the emotional mentalizing task. For references of the tasks, see Korver et al. (2012); emotional mentalizing task reference is Shaw et al. (2004). We found predictive validity of childhood/adolescence functioning for present state functioning in patients and controls: Pearson's correlation between mean scores of childhood/adolescence measures and mean scores of both present state measures indicated significant correlations in patients ($r=-0.213$; $p<0.001$), and in controls ($r=-0.325$; $p=0.015$).

2.3. STATISTICAL ANALYSES

Separate multiple linear regression models were built for cognitive functioning and social functioning in childhood/adolescence, for present state cognition composite score and present state social cognition composite score. First, we investigated whether group (patient versus controls) had a main effect on OI. Patients were set as the reference group in the regressions. Second, we investigated whether cognitive and social functioning in childhood/adolescence, present state cognition composite score and present state social cognition composite score (predictors) were associated with OI (dependent variable). Interaction terms were added to test whether associations between OI and each predictor differed between patients and controls. If the interaction term was not significant it was removed from the model, containing only main effects and covariates. Regressions were repeated, adjusting for gender ratio, age, APD use and smoking. For multiple comparisons correction, False Discovery Rate (FDR) was applied at alpha=0.05. Post–hoc analyses were performed to look at the associations between individual domains comprising our four composite score and OI. These latter results are interpreted at $p=0.05$.

3. RESULTS

3.1. SAMPLE CHARACTERISTICS

Table 1 summarizes socio–demographic differences between patients and controls. Clinical characteristics of patients are also summarized in table 1. OI, cognitive and social functioning in childhood/adolescence, present state cognition and present state social cognition were significantly lower in patients compared to controls (see table 2). Lower OI performance in patients compared to controls remained significant after correcting for gender, age, APD use and smoking. The R^2 did not change when adding each of our covariates. Informant group (parent, other family member, participant) used for the PAS did not have a significant effect on PAS cognitive score ($F(2,101)=1.23$; $p=0.297$) nor on PAS social score ($F(2,101)=0.05$; $p=0.954$).

TABLE 1. Differences between patients and controls on demographic characteristics; clinical characteristics of patients.

	Controls (N=128)	Patients (N=132)	p–value
Socio–demographic characteristics			
Gender, % (n): male[a]	55.47 (71)	81.06 (107)	<0.001*
Age (year; mean ± sd)[b]	32.41±9.50	30.68±7.03	0.097
Smoking, % (n): yes/no/missing[c]	23.4(30)/75.0 (96)/1.6(2)	62.1(82)/ 39.9 (50)/0	<0.001*
Hay fever, % (n): yes/no/missing[c]	2.3(3)/95.3 (122)/2.3(3)	1.5(2)/97.7(129)/.8(1)	0.522
Clinical characteristics			
DSM–IV diagnosis			–
% (n): 295.10 (schizophrenia, disorganized type)	–	6.8 (9)	–
% (n): 295.20 (schizophrenia, catatonic type)	–	0 (–)	–
% (n): 295.30 (schizophrenia, paranoid type)	–	81.1 (107)	–
% (n): 295.60 (schizophrenia, residual type)	–	6.8 (9)	–
% (n): 295.90 (schizophrenia, undifferentiated type)	–	5.3 (7)	–

TABLE 1. Continued

	Controls (N=128)	Patients (N=132)	p–value
PANSS positive symptoms (mean ± sd)	–	11.55 ± 4.62	–
PANSS negative symptoms (mean ± sd)	–	12.53 ± 4.96	–
PANSS general symptoms (mean ± sd)	–	24.91 ± 6.99	–
Age at psychosis onset (mean ± sd)	–	21.90 ± 5.95	–
Illness duration (mean ± sd)	–	8.04 ± 4.34	–
APD, % (n): currently using/not using/missing	–	87.1(115)/10.6(14)/2.3(3)	–
Generation APD, % (n): typical/atypical/mixed/missing [d]	–	7.8(9)/87.8(101)/1.7(2)/2.6(3)	–
Haloperidol equivalent (mean ± sd) [e]	–	7.71 ± 4.70	–

Abbreviations: DSM–IV is Statistical Manual of Mental Disorders, Fourth Edition; PANSS is Positive and Negative Syndrome Scale; APD is antipsychotic drugs.
[a] Chi–square test was used.
[b] T–test (independent samples) was used.
[c] Fisher's exact test was used.
[d] Atypical APD include olanzapine, clozapine, aripiprazole, quetiapine and risperdone; typical APD include haloperidol, pimozide, zuclopenthixol, perphenazine, flupenthixol and bromperidol in this sample.
[e] Two patients had missing data on cumulative APD daily dose. Significant results are presented as: *p < 0.05.

TABLE 2. Differences between patients and controls in odour identification (OI) and (social) cognitive measures.

	N	Controls	Patients	p–value
OI (mean ± sd)[a]	260	13.41±1.33	13.01±1.48	0.021*
Childhood/adolescence cognitive functioning (mean ± sd)[a]	260	1.25±0.74	1.86±0.86	<0.001*
Childhood/adolescence social functioning (mean ± sd)[ab]	260	0.94± 0.29	1.18±0.32	<0.001*
Cognition composite score (mean ± sd)[a]	251	0.18±0.39	–0.16±0.55	<0.001*
Social cognition composite score (mean ± sd)[a]	257	0.25±0.51	–0.24±0.69	<0.001*

[a] T–test (independent samples) was used.
[b] Logarithmic transformation was applied to correct for positive distribution skew.
Note that for childhood/adolescence cognitive and social functioning higher scores indicate worse functioning.
Significant results are presented as: *p < 0.05.

3.2. OI AND CHILDHOOD/ADOLESCENCE COGNITIVE AND SOCIAL FUNCTIONING ASSOCIATIONS

Results from the regression models showed that there was a significant main effect of status on OI (β=0.143, p=0.021). Cognitive functioning in childhood/adolescence (β=–0.193, p=0.003) and social functioning in childhood/adolescence (β=–0.228, p=0.001) were significantly associated with OI, FDR corrected; worse functioning being associated with worse OI (see table 3). Adding gender, age, APD use and smoking as covariates did not change these results. The R^2 did not significantly change when adding each of these covariates. There was no significant interaction effect between group and childhood/adolescence cognitive functioning (β=–0.070, p=0.574); group and childhood/adolescence social functioning (β=–0.077, p=0.707).

Post–hoc analyses on separate domains of childhood/adolescence cognitive and social functioning comprising the composite scores revealed that all the domains were significantly associated with OI: school performance: β=–0.169, p=0.008; school adaptation: β=–0.134, p=0.042; friendship: β=–0.149, p=0.025; social functioning: β=–0.191, p=0.004 (see Supplemental table 1).

3.3. OI AND PRESENT STATE COGNITION AND SOCIAL COGNITION ASSOCIATIONS

Results from the regression models showed that there was a significant main effect of status on OI (β=0.127, p=0.044, and β=0.132, p=0.034 for respective models of present state cognition and social cognition). Lower cognitive score and lower social cognitive score were significantly associated with reduced OI after FDR correction (β=0.200, p=0.003 ; β=0.277, p<0.001 respectively; see table 3). Adding gender, age, APD use and smoking as covariates did not change these results. The R^2 did not significantly change when adding each of these covariates. There was no significant interaction between group and cognitive score (β=0.040, p=0.616). There was a trend level effect for group × social cognitive score (β=0.141, p=0.072).

Post–hoc analyses on separate domains comprising the composite scores of cognition and social cognition showed that most domains were significantly associated with OI: IQ: β=0.213, p=0.001; memory: β=0.162, p=0.014; attention: β=0.161, p=0.011; executive functioning: β=–0.151, p=0.019; face recognition: β=0.217, p<0.001; emotion recognition: β=0.168, p=0.008; theory of mind: β=0.137, p=0.036, except for processing speed/ reaction time: β=–0.087, p=0.165 (see Supplemental table 1).

TABLE 3. The association between odour identification (OI) and childhood/adolescence and present state functioning measures.

Predictor	N	b	β	t	R^2	p–value
Group (patients, control)	260[a]	0.406	0.143	2.33	0.021	0.021*
Childhood and adolescence cognitive functioning[b]	260	–0.318	–0.193	–2.96	0.053	0.003**
Childhood and adolescence social cognitive functioning[c]	260	–0.992	–0.228	–3.51	0.065	0.001**
Present state cognitive functioning[d]	251	0.560	0.200	3.03	0.051	0.003**
Present state social cognitive functioning[e]	257	0.597	0.277	4.28	0.083	<0.001**

[a] Significance did not change in the models with smaller sample size.
[b,c,d,e] Each row represents a separate regression model; adding covariates age, gender, smoking and antipsychotic use did not change the results.
Note that for childhood/adolescence cognitive and social functioning higher scores indicate worse functioning.
*Significant at an alpha level of 0.05.
**Significant after FDR– correction.

4. DISCUSSION

In the largest group of schizophrenia patients (N=132) and healthy controls (N=128) up to date, we examined OI in relation to childhood and adolescent cognitive and social functioning as well as present state cognition and social cognition. The most original and novel finding of our study is that social and cognitive functioning in childhood/ adolescence and present state social cognition domains of theory of mind and face recognition are related to OI.

We found that reduced OI was related to worse cognition in patients and controls, consistent with previous studies (Brewer et al., 1996; Compton et al., 2006; Good et al., 2002; Goudsmit et al., 2004; Kohler et al., 2007; Malaspina and Coleman, 2003; Moberg et al., 2006; Purdon, 1998; Saoud et al., 1998; Seckinger et al., 2004; Seidman et al., 1997, 1991; Stedman and Clair, 1998). Most of these previous studies focused on only one or two (social) cognitive domains in association to OI.

We were the first to find that OI was positively associated with a large range of cognitive measures (IQ, immediate recall, delayed recall, recognition, attention and executive functioning), except for processing speed, as well as to social cognition measures (i.e. face recognition, emotion recognition and theory of mind) and to cognitive and social functioning in childhood and adolescence. These results indicate that the underlying mechanism causing OI deficits and cognitive/social impairment may share similar

neural substrates, in particular of the frontotemporal structures (Aleman, 2014; Nguyen et al., 2010; Turetsky et al., 2009), but this seems to be unspecific to schizophrenia.

Patients had reduced OI performance compared to controls, which was corroborated by other studies (Cohen et al., 2012). Previous studies except one (Warner et al., 1990) demonstrated that patients with schizophrenia perform worse on OI compared to healthy controls. In our study we found a small, but reliable group effect on OI. Other studies tend to find moderate to large effects (Moberg et al., 2014; Cohen et al., 2012). This is possibly due to the fact that our patient group scored better on OI than schizophrenia patients in other studies (mean ± sd Sniffin' Sticks scores for patients have ranged from 11.4 ± 1.1 (Kamath et al., 2014) to 11.7 ± 2.8 (Ugur et al., 2005) and 12.1 ± 2.4 (Rupp et al., 2005); while in our study the mean ± sd OI score was 13.41 ± 1.33). Since we assessed OI at three–year follow–up after the baseline measurement, a higher OI score in patients is likely due to drop–out from the first to the follow–up assessment of the GROUP project, which may have resulted in a healthier patient group. A longitudinal GROUP study indeed reported completers of the trial to have higher IQ, lower symptom scores and were less likely to use atypical antipsychotics compared to those who only completed the baseline measurement (Maat et al., 2015).

Also, in line with previous studies, patients performed worse on a broad set of present state cognitive (IQ, memory, processing speed, attention and executive functioning) and social cognitive measures (face recognition, emotion recognition and theory of mind) compared to controls, consistent with the notion that cognitive impairment in schizophrenia is a trait dependent characteristic of the illness (Kahn and Keefe, 2013). That patients with schizophrenia had lower cognitive and social performance in childhood and adolescence compared to controls also fits with the current literature (for an overview see Schmael et al., 2007).

There are some limitations to this study. First, a methodological limitation of this study is the retrospective design of the PAS, which may have caused a recollection bias, although Brill et al. (2008) confirm predictive and concurrent validity of this retrospective method in schizophrenia patients. Second, as the informant of PAS was not consequently the parent, this may have caused inconsequent PAS scoring. However, PAS scores were similar between informant groups. Third, we cannot exclude the possibility that worse OI in patients with schizophrenia is caused by medication use as compared to controls. However, the majority of studies report OI in both medicated and neuroleptic–naïve patients (Moberg et al., 2014). Also, we corrected for current APD use, which did not affect the results. Lastly, a limitation of the study is that there are considerably more males in the patient group compared to the control group (81% vs. 55% respectively). It was found that gender distribution influenced the magnitude of OI group differences across studies (Moberg 2014), thus a difference in gender distribution between our groups may have influenced our results. However our results did not change when adding gender as a covariate in our analyses.

In conclusion, we replicated associations between worse OI and a broad range of cognitive deficits. Moreover, we were the first to find that reduced OI is associated with worse cognitive and social functioning in childhood and adolescence and to worse present state social cognition. This association was found not only in patients with schizophrenia but also in healthy controls, however, with the notion that patients scored worse in all the assessed domains. This suggests that although reduced OI ability is related to poorer (social) cognitive functioning, it is not specific to schizophrenia.

SUPPLEMENT

SUPPLEMENTAL TABLE 1. Associations between odour identification (OI) and domains of childhood/adolescence and present state functioning measures.

Predictor	b	β	t	R^2	p–value
Childhood and adolescence school performance	–0.207	–0.169	–2.685	0.038	0.008*
Childhood and adolescence school adaptation	–0.212	–0.134	–2.048	0.028	0.042*
Childhood and adolescence friendship	–0.179	–0.149	–2.255	0.033	0.025*
Childhood and adolescence social functioning	–0.209	–0.191	–2.939	0.048	0.004*
IQ	0.302	0.213	3.221	0.054	0.001*
Memory	0.266	0.162	2.468	0.037	0.014*
Processing speed	–0.124	–0.087	–1.391	0.011	0.165
Attention	0.229	0.161	2.578	0.032	0.011*
Executive functioning	–0.237	–1.151	–2.375	0.024	0.019*
Face recognition	0.115	0.217	3.535	0.053	<0.001*
Emotion recognition	0.237	0.168	2.676	0.036	0.008*
Theory of mind	0.221	0.137	2.111	0.028	0.036*

*Significant at an alpha level of 0.05.

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CHAPTER 6

METABOLIC SYNDROME IN SCHIZOPHRENIA PATIENTS ASSOCIATED WITH POOR PREMORBID SCHOOL PERFORMANCE IN EARLY ADOLESCENCE

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ABSTRACT

Objective: More than 40% of schizophrenia patients have an additional diagnosis of the metabolic syndrome (MetS), possibly related to poor cognition. This study investigated premorbid and current cognitive functioning in schizophrenia and co–occurrence of MetS.

Method: 104 participants with schizophrenia with MetS and 142 without MetS were included. Neuropsychological assessment was done using the Wechsler Adult Intelligence Scale–III, Word Learning Task and Continuous Performance Test–HQ. Premorbid functioning was assessed retrospectively with the Premorbid Adjustment Scale. ANOVAs were used to examine differences between participants with and without MetS.

Results: Subjects with and without MetS did not differ concerning current, lifetime and amount substance use, duration/severity of illness, parental socioeconomic status and type/amount of antipsychotic medication. We found that poor school performance between the ages 12–16 is associated with MetS in schizophrenia. Educational level and current cognitive functioning in participants with MetS deviate as compared to those without MetS.

Conclusion: Subjects with MetS had impaired premorbid cognition in adolescence and lower educational achievement, irrespective of parental socioeconomic status. This suggests poor premorbid cognitive functioning is a risk factor for metabolic complications later in life. Future studies are needed to examine whether cognitive interventions have beneficial effects on general health in schizophrenia.

Keywords: schizophrenia, metabolic syndrome, cognition, premorbid functioning

1. INTRODUCTION

Metabolic complications and related cardiovascular risk are widespread in schizophrenia and contribute to the reduced life expectancy of about 15–20 years in patients (Nordentoft et al., 2013). It has been estimated that more than 40% of schizophrenia patients suffer from MetS (Ko et al., 2013; Mcevoy et al., 2005) as compared to 20–30% in the European non–psychiatric population (Grundy, 2008). Prevention and treatment of MetS in schizophrenia is needed to improve the life expectancy as MetS leads to a two– to threefold increase in cardiovascular mortality (Malik et al., 2004) and a threefold risk of diabetes mellitus type 2 (Ford, 2005).

In non–psychiatric samples MetS has been found related to cognitive impairments in terms of intelligence, memory, executive functioning, processing speed and attention (Hassenstab et al., 2010; Mcevoy et al., 2012; Yau et al., 2012; Segura et al., 2009). It has been proposed that impaired cognition and MetS are part of a circular, reinforcing mechanism and disturbances in intelligence, memory, executive functioning, processing speed and attention might contribute to unhealthy lifestyles and metabolic complications (Smith et al., 2011). Interestingly, findings of worse executive functioning serving as a predictor for unhealthy lifestyle (less fruit/vegetables intake and physical activity) confirm this notion (Riggs et al., 2010). Given the high prevalence of MetS and the broad range of cognitive impairment which is an intrinsic characteristic of schizophrenia (Kahn and Keefe, 2013), it is of particular interest to examine the relation between MetS and cognitive functioning in this population.

Only few studies examined MetS and cognition in schizophrenia. Lindenmayer and colleagues (Lindenmayer et al., 2012) reported associations between MetS diagnosis and cognitive impairment (i.e. worse processing speed, working memory and problem solving). Boyer and colleagues (Boyer et al., 2013, 2014) confirmed this and reported that worse memory, attention and flexibility was associated with MetS. Li and colleagues (Li et al., 2014) also found an association between MetS and impaired cognition in terms of lower attention, immediate and delayed memory scores. However, Meyer and colleagues (Meyer et al., 2005) failed to show an association between MetS and neurocognitive composite score, consisting of (working) memory, processing speed, vigilance and reasoning. As children and adolescents who later develop schizophrenia already exhibit subtle cognitive deficits relative to their healthy peers (Seidman et al., 2006; Fuller et al., 2002), one could argue that worse cognitive functioning in childhood and adolescence is associated with the co–occurrence of MetS in schizophrenia. Although population based epidemiological studies found that lower intelligence in child– and early adulthood predicts the presence of MetS or cardiovascular risk in

mid–adulthood (Batty et al., 2008; Power et al., 2010), no studies have examined early cognitive development of schizophrenia and its relation to MetS.

The aim of this study was to examine the association of metabolic syndrome and cognitive functioning in schizophrenia. We hypothesized that premorbid cognitive performance in childhood and adolescence, lower level of education and poor cognition is associated with metabolic syndrome in schizophrenia.

2. MATERIAL AND METHODS

2.1. STUDY POPULATION

This trial was part of the Dutch longitudinal Genetic Risk and Outcome of Psychosis study (GROUP–project). Participants were assessed extensively and were invited to diagnostic interviews, neuropsychological tasks, physical examination, blood and urine sampling.

Inclusion criteria were the following: 1) age range between 16 and 50 years, 2) diagnosis of non–affective psychotic disorder and 3) good command of the Dutch language. The study protocol was approved by the accredited Medical Ethics Review Committee. Participants signed informed consent (Korver et al., 2012).

Data pertain to a subsample of the GROUP–project full–sample, who consented to physical examination and venipuncture and had available information on premorbid adjustment (N=246 participants with schizophrenia diagnosis). This sample is compared to demographic and clinical characteristics of the participants with schizophrenia who were not included in this study (N=265), because of missing data. Researchers involved in data collection at time of subject inclusions were blinded to the study design.

The sample of 246 participants was subdivided into two groups, those with MetS (MetS+) and without (MetS–). Subjects were diagnosed with MetS if they displayed central obesity (males: ≥ 94 cm or 37 in.; females: ≥ 80 cm or 31 in.) plus two of the following criteria defined by the International Diabetes Federation (IDF): Hyperglycemia (Haemoglobin A_{1c} ≥ 39 mmol/mol or 117 mg/dL); elevated diastolic or systolic blood pressure (≥ 130/85 mm Hg); hypertriglyceridemia (triglycerides ≥ 1.70 mmol/L or 150.58 mg/dL); and/or low HDL–cholesterol (males: < 1.03 mmol/L or 39.83 mg/dL; females: < 1.29 mmol/L or 49.88 mg/dL) (Alberti et al., 2006). Venipuncture in participants was done either in fasting or non–fasting status. A total of 104 subjects (42.3%) met the criteria for MetS.

2.2. CLINICAL AND COGNITIVE MEASURES

Subjects met the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM–IV) (APA, 2000) for schizophrenia. Diagnosis was assessed with the Comprehensive Assessment of Symptoms and History interview (CASH) (Andreasen et al., 1992) or the Schedules for Clinical Assessments in Neuropsychiatry (SCAN) (Wing et al., 1990). Positive and negative symptoms, as well as general psychopathology of schizophrenia during the past week were obtained with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Urinalysis by an external laboratory revealed recent cannabis, amphetamine and cocaine use. Cutoff levels were 50 ng/ml, 1000 ng/ml and 300 ng/ml respectively. Furthermore, current/lifetime use and amount of tobacco (section B), alcohol (section J) and illicit drug (section L) were assessed using the Composite International Diagnostic Interview (CIDI) (WHO 1990). Current dosage of antipsychotic medication was converted into haloperidol equivalents (Andreasen et al., 2010; Farmacotherapeutisch Kompas, 2015).

Subjects completed a cognitive test battery, which consisted of assessment of Intelligence Quotient (IQ), short– and long–term verbal memory, vigilance and processing speed. Wechsler Adult Intelligence Scale– Third Edition short form (WAIS–III SF) (Christensen et al., 2007; Velthorst et al., 2013) was used to measure the IQ, using the subtasks: Arithmetic, Information (verbal intelligence), Digit–Symbol Coding and Block Design (performance intelligence). Short– and long–term verbal memory were assessed using the Word Learning Task (WLT) (Brand and Jolles, 1985) with immediate memory, delayed memory, and recognition as outcome measures. Vigilance and processing speed were assessed using accuracy and reaction time of the Continuous Performance Task–HQ respectively (CPT–HQ) (Nuechterlein and Dawson, 1984). In this task the participant is asked to respond to target letter Q, only when it is preceded by letter H. CPT–HQ accuracy and WLT recognition were not normally distributed. As data transformation was not successful in achieving normal distribution, scores were dichotomized in affected (score < mean) / unaffected (score > mean). Academic achievement was self–reported.

Parental socioeconomic status (SES) was operationalized by 1) mean educational level of both parents of the participants and 2) net annual household income based on the average income of the Dutch postal code area of subjects, at time of birth (source: Statistics Netherlands institute; CBS) (CBS, 2011). For 18 subjects information on parental education was missing for either one or both parents. For 12 subjects no information was available on postal code at time of birth; another 33 subjects were not born in the Netherlands, and for both groups data on household income was missing. A SES composite score was calculated, which is an average of the two SES variables after conversion to z–scores.

2.3. THE PREMORBID ADJUSTMENT SCALE

The Premorbid Adjustment Scale (PAS) (Cannon–Spoor et al., 1982) was designed to retrospectively evaluate the degree of achievement of academic and social goals in three distinct age epochs: in childhood (0 to 12 years), early adolescence (12 to 16 years) and late adolescence (16 to 19 years). Two distinctive factors have been found in PAS: 1) school adjustment, consisting of school performance and school adaptation subscales and 2) social adjustment, consisting of social behavior, peer relations and social–sexual aspect subscales (Allen et al., 2005). Premorbid cognitive functioning was assessed with the school performance subscale. Information on participants' premorbid functioning was gathered from their parents. Scoring range of the PAS is 0–6, where 0 indicates highest and 6 indicates lowest functioning. The social–sexual aspect subscale was not included in the analyses since it does not cover childhood. Small and colleagues reported that interrater reliability and internal consistency of the PAS were high (Small et al., 1984).

2.4. STATISTICAL ANALYSIS

Statistics were performed using SPSS version 20.0. Analyses were interpreted with alpha of 0.05 at two–tailed significance level, unless otherwise specified. After correction for multiple testing 0.05 was the cut–off p–value for trend–level significance. Differences between MetS+ and MetS– on demographic and clinical variables were examined using independent sample t–tests and χ^2 tests, and Mann–Whitney U test for nonparametric variables. Fisher's exact test instead of χ^2 test was used if categories of variables within the MetS groups had small sample sizes.

We also compared the metabolic subcomponents between fasting conditions (i.e. fasting, non–fasting and unknown) and interaction of MetS groups and fasting conditions on MetS subcomponents with ANOVAs.

Extreme values, more than 3 sd from the corresponding means were excluded. Continuous variables were examined for normality and homogeneity of variance with the W–statistic of Shapiro–Wilk and Levene's test respectively.

Differences between MetS groups on cognitive variables and academic level of achievement were analysed using separate analyses of variance (ANOVA) for continues variables and χ^2 for categorical variables. For Bonferroni correction, alpha level of 0.05 was divided by the number of tasks (IQ, WLT, CPT–HQ). Interactions and main effects of MetS groups and age epochs of PAS subscales were analysed with ANOVAs. Alpha level of 0.05 in PAS tests was divided by the four subscales as Bonferroni correction. A Wilcoxon signed–rank test as non–parametric paired samples test was implemented

to analyse whether the difference between PAS age epochs (0–12 minus 12–16 and 12–16 minus 16–19) differed within both MetS groups.

The analyses were repeated with potential moderators which could be associated with MetS. P–value <0.2 was used as a cutoff and those variables with a p–value beneath the cutoff were implemented as covariates if applicable. Effect sizes (Cohen's d for F–test and in case of two dichotomous variables Pearson's r (or the phi coefficient)) were calculated.

3. RESULTS

3.1. SAMPLE CHARACTERISTICS

Subjects included in this study were significantly more likely to be male (p=0.001), were older (p=0.002) and had longer duration of illness (p=0.001). No statistical group difference was found on IQ (p=0.051), PANSS total score (p=0.543) and on generation of antipsychotic medication (p=0.206) as compared to subjects who were not included in the sample.

Table 1 summarizes socio–demographic and clinical characteristics of both MetS groups. MetS groups did not differ on socio–demographic variables (parental SES, age, gender, ethnicity and illicit drug use) and clinical variables (duration of illness, number of psychotic episodes, severity of symptoms, pharmacological treatment and diagnosis).

Fasting condition did not differ between the MetS groups. Moreover, fasting condition had no main effect on either waist circumference (F(2,240)=0.630; p=0.534), Haemoglobin A1c (F(2,240)=0.934; p=0.395), diastolic blood pressure (F(2,240)=0.861; p=0.424), systolic blood pressure (F(2,240)=0.462; p=0.631), triglycerides (F(2,240)=1.888; p=0.154) or HDL–cholesterol (F(2,240)=0.938; p=0.393). Also, there was no significant interaction effect of MetS group and fasting condition on waist circumference (F(2,240)=0.951; p=0.388), Haemoglobin A1c (F(2,240)=0.602; p=0.549), diastolic blood pressure (F(2,240)=1.948; p=0.145), systolic blood pressure (F(2,240)=1.998; p=0.138), triglycerides (F(2,240)=0.136; p=0.873) or HDL–cholesterol (F(2,240)=0.481; p=0.619).

3.2. NEUROCOGNITIVE FUNCTIONING AND EDUCATION IN METS

Cognitive differences between MetS groups are illustrated in table 2. MetS+ participants performed significantly worse on IQ, immediate memory, delayed

memory, recognition, processing speed and vigilance than MetS– participants, although differences in recognition did not survive Bonferroni correction. Results showed a post–hoc significant worse performance on verbal IQ as well as performance IQ on trend level in the MetS+ group compared with the MetS– (table 2). Educational level was significantly lower in MetS+, as compared to MetS– (t(236)=2.645; p=0.009).

3.3. PREMORBID DEVELOPMENT AND METS

A main effect of age epoch was found on PAS school performance score: older age epoch was associated with worse scores on PAS school performance (F(2,243)=49.115; p<0.001). There was no main effect of MetS group (F(1,244)=2.044; p=0.154), indicating that there was no overall difference in PAS school performance between groups. The effect of age epoch differed significantly between MetS groups (i.e. MetS group by age epoch interaction). School performance scores in age epoch 12–16 in MetS+ were significantly worse than in MetS– participants (effect size: d=–0.35). No differences were found in age epochs 0–12 and 16–19 between MetS+ and MetS– (table 3; figure 1). A Wilcoxon signed–rank test showed that for MetS– participants lowering of school performance between 12–16 to 16–19 was significantly higher than lowering between 0–12 to 12–16 (Z=–4.106; p<0.0001). In the MetS+ group lowering of school performance was stable between age epochs (Z=–.99; p=0.322).

For the school adaptation and social adjustment subscales (social behavior and friendship), a main effect of age epoch was found (F(2,243)=73.227; p<0.001, F(2,243)=18.003; p<0.001, F(2,243)=20.346; p<0.001; respectively), with subjects scoring worse as age epoch gets higher.

This effect of age epoch did not differ between MetS groups (i.e. no interaction effect between MetS group and age epochs) for school adaptation, social behavior and friendship (table 3), indicating similar scores between MetS groups on the premorbid adjustment PAS subscales in all age epochs. No main effects for MetS groups were found (F(1,244)=0.134; p=0.836; F(1,244)=0.026; p=0.952; F(1,244)=0.070; p=0.791 respectively). Repeating the analyses with adjusting for gender ratio did not change any of the significance results displayed in table 2 and 3.

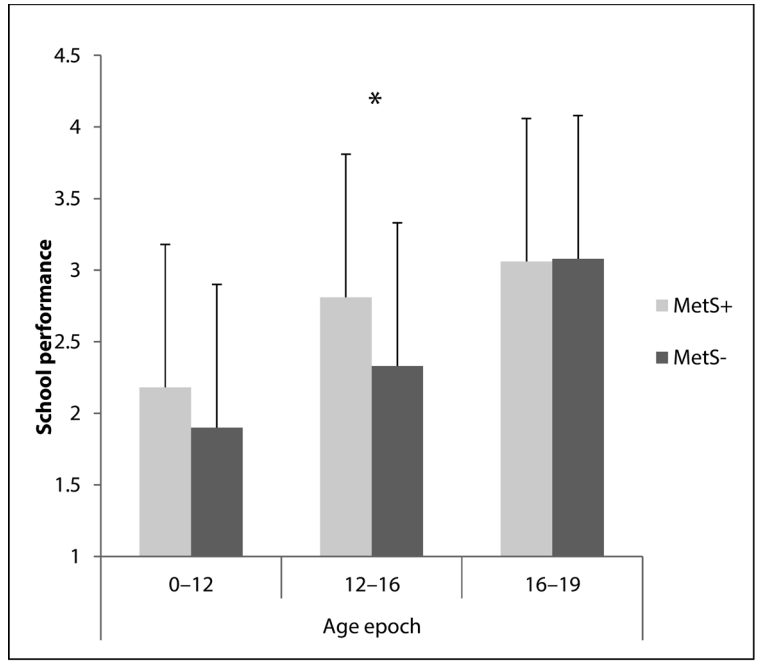

FIGURE 1. PAS school performance scores per age epoch for both MetS groups. Displayed are the mean and sd. Higher scores indicate worse functioning.
* significant at an alpha level of 0.012 (0.05/4)

TABLE 1. Socio–demographic and clinical characteristics of MetS+ and MetS– subjects.

	MetS+ (N=104)	MetS– (N=142)	p–value
Gender (ratio male/female) [a]	86/18	126/16	0.175
Age (yr.; mean±sd) [b]	31.32±6.78	30.77±5.60	0.506
Duration of illness (yr.; mean±sd) [b]	8.13±4.07	7.93±3.83	0.939
Number of psychotic episodes (mean±sd) [b]	2.09±1.24	2.05±1.10	0.769
Schizophrenia diagnosis DSM–IV [c]			0.180
Disorganized Type, % (n)	3.8 (4)	8.5 (12)	–
Catatonic Type, % (n)	0.0	0.7 (1)	–
Paranoid Type, % (n)	80.8 (84)	81.7 (116)	–
Residual Type, % (n)	6.7 (7)	2.1 (3)	–
Undifferentiated Type, % (n)	8.7 (9)	7.0 (10)	–
Ethnicity [c]			0.287
White, % (n)	91.3 (95)	88.0 (125)	–
Supra–Saharan, % (n)	2.9 (3)	3.5 (5)	–
Middle eastern, % (n)	1.9 (2)	0.0	–
Mixed, % (n)	3.8 (4)	8.5 (12)	–
SES composite score (mean±sd) [d]	–0.05±0.72	–0.05±0.78	0.718
PANSS symptoms (mean±sd)			
Positive [d]	12.61±5.28	11.79±4.85	0.754
Negative [d]	12.63±5.17	11.87±5.11	0.211
General [d]	25.32±8.63	24.42±6.92	0.752
Illicit drug use			
Present state,% yes/no/unknown (n) [c e]	32.7(34)/66.3(69)/1.0(1)	36.6(52)/62.7(89)/0.7(1)	0.798
Lifetime,% yes/no/unknown (n) [c]	62.5(65)/35.6(37)/1.9(2)	69.0(98)/28.9(41)/2.1(3)	0.475
Currently drinking alcohol, % yes/no/unknown (n) [c]	55.8(58)/44.2(46)/0	64.1(91)/35.2(50)/0.7(1)	0.230
Glasses alcohol/week (mean±sd) [d]	9.88±11.03	8.53±8.93	0.606
Currently smoking, % yes/no (n) [a]	62.5(65)/37.5(39)	62.0(88)/38.0(54)	0.993
Cigarettes/day (mean±sd) [b]	20.69± 9.47	20.94± 10.11	0.875
Status antipsychotic medication, % currently using 0/1/2/unknown (n) [c f]	6.7(7)/75.0(78)/14.4(15)/3.8(4)	9.9(14)/73.2(104)/8.5(12)/8.5(12)	0.209
Antipsychotic medication type [c]			0.381
None, % (n)	6.7(7)	9.9 (14)	–
Typical, % (n)	9.6(10)	4.9(7)	–
Olanzapine, % (n)	17.3(18)	22.5(32)	–
Clozapine, % (n)	20.2(21)	17.6(25)	–
Quetiapine, % (n)	2.9(3)	4.9(7)	–
Aripiprazole, % (n)	19.2(20)	15.5(22)	–
Risperdone, % (n)	19.2(20)	13.4(19)	–
Paliperidone, % (n)	–	2.1(3)	–
Sulpiride, % (n)	–	0.7(1)	–
Unknown, % (n)	4.8(5)	8.5(12)	–
Haloperidol equivalent (mg; mean±sd) [b]	7.78±5.11	8.30±6.81	0.547
Generation antipsychotic medication, % 1st/2nd (n) [c g]	10.9(10)/89.1(82)	6.0(7)/94.0(109)	0.216
Other psychopharmaca, % currently using/not using/unknown (n) [c]	38.5(40)/59.6(62)/1.9(2)	40.1(57)/54.2(77)/5.6(8)	0.325
Fasting condition, % fasting/non–fasting/unknown (n) [a]	17.3(18)/59.6(62)/23.1(24)	21.8(31)/58.5(83)/19.7(28)	0.622

[a] Chi–square test was used.
[b] T–test (independent samples) was used.
[c] Fisher's exact test was used.
[d] Mann–Whitney U test was used.
[e] Based on self–reported use and urine analysis.
[f] One subject was excluded for non–compliance with drug therapy and 16 subjects had missing data on antipsychotic medication use; six subjects missed data on antipsychotic medication dose. One subject had missing data on antipsychotic medication type.
[g] Atypical antipsychotic medication include olanzapine, clozapine, risperdone, aripiprazole, quetiapine, sulpiride, paliperidone; typical antipsychotic medication include flupentixole, pimozide, perphenazine, haloperidol, zuclopenthixol, bromperidol in this sample.

TABLE 2. Cognitive characteristics of MetS+ and MetS– subjects. Illustrated are the mean and sd or ratios for cognitive functioning in MetS+ and MetS– subjects. [a]

	MetS+	MetS–	Statistic	p value	Cohen's d/ r
WAIS–III IQ	95.46±17.19	101.30±16.01	F=7.26	0.008**	0.35
VIQ (scaled score) [b]	9.90±2.88	11.06±2.77	F=10.11	0.002**	0.42
PIQ (scaled score) [c]	8.60±2.75	9.37±2.47	F=5.24	0.023*	0.29
WLT Immediate memory [d]	23.56±6.08	25.91±6.42	F=8.30	0.004**	0.38
WLT Delayed memory [d]	7.71±3.07	8.66±2.99	F=5.88	0.016**	0.31
WLT Recognition (% affected) [d]	48.15	32.08	χ^2=4.98	0.026*	0.16
CPT–HQ Reaction time (ms) [e]	466.72±92.79	432.47±71.61	F=9.86	0.002**	–0.41
CPT–HQ Accuracy (% affected) [e]	42.42	25.78	χ^2=6.99	0.008**	0.18

[a] Higher scores indicate better cognitive functioning for the continuous variables, except for CPT–HQ; higher reaction time indicates worse functioning.
[b, c] VIQ: Verbal IQ; PIQ: Performance IQ.
[d] WLT (Word Learning Task) Immediate memory: number of retained words out of 45 (in 3 trials); WLT Delayed memory: number of retained words after 20 minutes; WLT Recognition: (true positives – false positives)+(true negatives – false negatives).
[e] CPT–HQ (Continues Performance Task–HQ) Reaction time: reaction time for correct detections; CPT–HQ Accuracy: proportion of correct detections.
* significant at trend level given our Bonferroni correction ** significant at an alpha level of 0.017 (0.05/3).

TABLE 3. Interaction effect between PAS subscale age epoch and MetS group and tests of between subject effects. Differences between MetS groups are displayed as δ (MetS+ minus MetS–).

ANOVAs				Tests of between subject effects								
MetS group × age epoch			0–12		12–16			16–19				
PAS subscales	F	p value	δ	F	p–value	δ	p–value	F	p–value	δ	F	p–value
School performance	5.154	0.006*	0.23	1.436	0.232	0.47	7.111	0.008*	0.04	0.040	0.842
School adaptation	0.634	0.532	0.10	0.798	0.373	0.08	0.221	0.639	–0.10	0.228	0.633
Social behavior	0.309	0.734	0.10	0.228	0.634	0.01	0.003	0.957	–0.07	0.096	0.756
Friendship	0.938	0.393	0.10	0.282	0.596	0.08	0.188	0.665	–0.15	0.486	0.487

* significant at an alpha level of 0.013 (0.05/4).

4. DISCUSSION

To our knowledge, this is the first study to investigate premorbid cognitive functioning in childhood and adolescence and the co–occurrence of MetS in schizophrenia. We found that poor school performance between the ages 12 and 16, irrespective of parental SES, is associated with MetS in schizophrenia. This suggests that cognitive (dys)functioning in early adolescence is associated with prevalence of MetS later in life. Moreover, it also suggests that in addition to antipsychotic medication and low SES, cognitive factors may be responsible for the increased MetS rates in schizophrenia. Our finding is in line with prospective population–based studies reporting that poor cognition in childhood is a risk factor for metabolic complications later in life (Batty et al., 2008; Power et al., 2010; Mcgurn et al., 2008). Furthermore, our finding of cognitive deterioration before the onset of schizophrenia is consistent with previous studies in schizophrenia using the PAS (Larsen et al., 2004; Walshe et al., 2007). That worse premorbid cognitive functioning in early adolescence and not social functioning is associated with the co–occurrence of MetS in schizophrenia has not been reported previously. Like others (Lindenmayer et al., 2012; Boyer et al., 2013, 2014; et al., Li 2014), we found a relationship between MetS and current cognitive functioning. Participants with comorbid MetS performed worse in terms of IQ, immediate and delayed memory, speed of processing and vigilance as compared to those without MetS. Only one study failed to detect a relationship between MetS and cognition (Meyer et al., 2005), which can be explained by discrepancies in demographics and the use of different MetS criteria.

Our findings of worse cognition in those participants with schizophrenia and comorbid MetS, together with the fact that the cognitive deficits precede MetS and already occur in adolescence, could indicate that impaired cognition and MetS are part of a circular, reinforcing mechanism, in which a decrease in cognitive functioning may lead to unhealthy behavior and associated metabolic complications. MetS in turn can negatively impact brain areas involved in cognitive functioning. It could be that deleterious neurophysiological consequences of MetS include an exaggerated inflammatory response, altered lipid metabolism, endocrine abnormalities through insulin resistance and hypertension, causing atherosclerosis, hypoxia, oxidative stress, cerebral lesions and micro–bleeds (Yaffe et al., 2004).

The findings of this study have clinical implications. Prevention of MetS should focus on those patients with psychosis, who have lower school performance and lower educational achievement in their personal history and exhibit major cognitive deficits. In particular, MetS should be carefully monitored during treatment with antipsychotic

medication in those with severe cognitive deficits, as antipsychotic medication is known to cause weight gain and facilitate either the onset or worsening of MetS (Bak et al., 2014). Interventions aiming to break the vicious circle between MetS and cognitive impairment, as earlier proposed by Nasrallah (Nasrallah, 2010), could include lifestyle interventions, switching antipsychotic medication or somatic drug interventions (to lower blood pressure, glucose and lipids), and cognitive remediation, which might be beneficial to improve physical health in schizophrenia. Especially at a young age health education programs should aim at populations with low cognition. Future studies should be performed examining such interventions. Furthermore, searching for specific biomarkers of mortality in schizophrenia may help predict and prevent adversary health outcomes. For example, Koola and colleagues (Koola et al., 2012) found a reduced arterial elasticity in schizophrenia patients, irrespective of antipsychotic treatment. Future research could more specifically focus on interaction between MetS, and MetS associated risk factors, such as arterial integrity, cognition, and life expectancy in schizophrenia.

Several limitations should be acknowledged. First, although various cognitive domains have been tested, no information was obtained on executive functioning; a cognitive domain of which we know is affected in schizophrenia (Orellana and Slachevsky 2013). Second, we did not collect information on caloric intake and energy expenditure. Third, not all participants included in GROUP consented to physical examination and venipuncture. This could have resulted in a sampling bias. However, no statistical differences were found in symptom severity, IQ and generation antipsychotic treatment between GROUP participants who were and were not included in this study. Another major limitation of this study was due to its cross–sectional design, so that a causal relationship between MetS and cognition could not be determined. Beside these limitations, our study has several strengths. We found similar prevalence rates of MetS as in other studies (Ko et al., 2013; Mcevoy et al., 2005; Lindenmayer et al., 2012). Furthermore, the two groups of participants (MetS– and MetS+) with schizophrenia are statistically similar enabling us to investigate the association between MetS and cognition, without confounding effects of parental SES, age, gender, ethnicity, illness severity, substance and medication use.

In summary, poor premorbid cognitive functioning in early adolescence in schizophrenia is related to MetS prevalence later in life. This suggests that the cognitive trajectory is an essential factor in relation to (general) health and life expectancy in schizophrenia. It further underlines that new treatments are needed to improve cognition in schizophrenia.

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CHAPTER 7

REWARD RELATED BRAIN STRUCTURES ARE SMALLER IN PATIENTS WITH SCHIZOPHRENIA AND COMORBID METABOLIC SYNDROME

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ABSTRACT

Objective: Metabolic syndrome (MetS) is highly prevalent in schizophrenia and often a consequence of unhealthy behavior. Reward related brain areas might be associated with MetS, since they play a major role in regulating health behavior. This study examined the relationship between MetS and brain volumes related to the reward system in schizophrenia.

Method: We included patients with schizophrenia, with MetS (MetS+; N=23), patients with schizophrenia, without MetS (MetS–; N=48) and healthy controls (N=54). Global brain volumes and volumes of (sub)cortical areas, part of the reward circuit were compared between patients and controls. In case of a significant brain volume difference between patients and controls, the impact of MetS in schizophrenia was examined.

Results: Patients had smaller total brain (TB; p=0.001), GM (p=0.010), larger ventricles (p=0.026) and smaller reward circuit volume (p<0.001) than controls. MetS+ had smaller TB (p=0.017), GM (p=0.008), larger ventricles (p=0.015) and smaller reward circuit volume (p=0.002) than MetS–. MetS+ had smaller orbitofrontal cortex (OFC; p=0.002) and insula volumes (p=0.005) and smaller OFC (p=0.008) and insula cortical surface area (p=0.025) compared to MetS–.

Conclusion: In schizophrenia structural brain volume reductions in areas of the reward circuitry appear to be related to co–morbid MetS.

Keywords: schizophrenia, metabolic syndrome, neuroimaging

1. INTRODUCTION

In schizophrenia it is well established that total brain (TB), gray matter (GM) and white matter (WM) are smaller in patients as compared with controls (Haijma et al., 2013). It has been suggested that these smaller brain volumes play a crucial role in the development of schizophrenia (Kahn and Sommer, 2015). Brain volume in patients has been found related to disease–related factors, such as the use of antipsychotic drugs (Haijma et al., 2013; Veijola et al., 2014; van Haren et al., 2011), cannabis use (Rais et al., 2008) and physical inactivity (Scheewe et al., 2013). Here we focus on metabolic syndrome (MetS; a cluster of metabolic risk factors, i.e. abdominal adiposity, hypertension, dyslipidemia and hyperglycemia), which might also be associated with brain volume abnormalities in schizophrenia.

MetS is highly prevalent in schizophrenia and patients have approximately a two–fold risk of developing MetS as compared to the general population (Papanastasiou, 2013). MetS is a major risk factor for cardiovascular disease and diabetes mellitus type two (Mitchell et al., 2013). In schizophrenia, high MetS prevalence appears the result of interactions between antipsychotic drug (APD) use, an unhealthy lifestyle, genetic vulnerability, cognitive impairment and other environmental factors (De Hert et al., 2009). Interestingly, MetS in healthy individuals has been shown to negatively impact TB volume (Tiehuis et al., 2014; Yau et al., 2012) and it has been found associated with a loss of GM and WM integrity (Sala 2014) and a ventricular volume increase (Tiehuis et al., 2014). These are brain abnormalities that are consistently reported in patients with schizophrenia (Haijma et al., 2013; van Erp et al., 2016).

Despite these previous findings, no structural MRI (sMRI) studies have been performed to examine the effect of MetS on brain volumes in schizophrenia. In addition to the question whether MetS can explain some of volume reduction in global brain structure in patients with schizophrenia, the involvement of the reward circuitry is highly relevant. That is, reward related brain areas play a major role in the regulation of health behavior (Elman et al., 2006). Indeed, obesity, which is a major risk factor for MetS, was related to smaller GM volumes in the reward circuitry (i.e. orbitofrontal cortex (OFC), insula, anterior cingulate cortex (ACC), amygdala and striatum) (Shott et al., 2015). Also, functional MRI showed hypoperfusion in left OFC and increased functional connectivity from left frontal cluster in left insula and middle/superior frontal gyrus in patients with schizophrenia and MetS compared to those without MetS (Boyer et al., 2014). Interestingly, there is consistent and convincing evidence for cognitive vulnerability in the reward system in schizophrenia as well, irrespective of having MetS (Strauss et al., 2014).

In the present study, we investigate volume differences in global and reward circuit related brain structures between patients with a schizophrenia spectrum disorder and healthy controls. In case of a significant finding, we will examine the impact of MetS in patients. In addition to a region of interest (ROI) approach, we also apply a whole–brain approach to investigate the specificity of the reward circuit difference between patients with schizophrenia, with and without MetS. We expect structural brain reductions to be more pronounced in patients with schizophrenia and comorbid MetS as compared to those without MetS.

2. MATERIAL AND METHODS

2.1. POPULATION SELECTION

MRI scans were conducted as an add–on study during the second measurement of the multicentre 'Genetic Risk and Outcome in Psychosis'– project (GROUP) at the University Medical Centre Utrecht in the Netherlands. Procedure of recruitment, informed consent, approval by the accredited Medical Ethics Review Committee and inclusion and exclusion criteria for participants have previously been described in a report on the GROUP study (Korver et al., 2012).

The sample of this add–on study included 122 patients with available sMRI data. 23 patients were excluded because of bipolar or schizoaffective disorder diagnosis. 21 patients with schizophrenia could not be included because of missing data on obesity. Seven patients were excluded because of missing blood samples. The remaining sample was composed of 71 subjects (32% MetS+) with a non–affective schizophrenia spectrum disorder according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM–IV) (APA, 2000), assessed by the Schedules for Clinical Assessment for Neuropsychiatry (SCAN 2.1) (Wing et al., 1990). A group of 54 healthy controls was included for whom MRI data was available. Controls had no DSM–IV diagnosis and no first degree family member with a lifetime psychotic disorder. We have previously reported on brain measures in part of this sample (Boos et al., 2012; Kubota et al., 2015).

Patients with schizophrenia were subdivided into two groups, those with (MetS+) and without MetS (MetS–). Subjects were diagnosed with MetS if they displayed central obesity (males: ≥94 cm; females: ≥80 cm), plus two of the following criteria defined by the International Diabetes Federation (IDF) (Alberti et al., 2006): Hyperglycemia (Hemoglobin A1c ≥ 39 mmol/mol; elevated diastolic or systolic blood pressure (≥130/85 mm Hg); hypertriglyceridemia (triglycerides ≥1.70 mmol/L); and/or low HDL–

cholesterol (males: <1.03 mmol/L; females: <1.29 mmol/L). It was unknown whether controls had MetS.

2.2. CLINICAL, DEMOGRAPHIC AND IQ MEASURES

Symptom severity during the past week was obtained with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Urine analysis by an external laboratory (Jellinek institute Amsterdam, The Netherlands) was performed to reveal recent cannabis, amphetamine and cocaine use. Cutoff levels were 50 ng/ml, 1000 ng/ml and 300 ng/ml respectively. Current and lifetime use and amount of tobacco (section B), alcohol (section J) and illicit drug (i.e. cannabis, cocaine and amphetamines; section L) was assessed with the Composite International Diagnostic Interview (CIDI) (WHO, 1990). APD dosage was converted into haloperidol equivalents according to the standardized method for comparing exposure to different drugs, developed by Andreasen and colleagues (Andreasen et al., 2010). Two APDs prescribed in our sample (penfluridol, pipamperone; N=2), were not described in this method. A Dutch pharmaco–therapeutic reference guide (Farmacotherapeutisch Kompas; zorginstituut Nederland http://www.fk.cvz.nl/ College van Zorgverzekeraars) was used to calculate these haloperidol equivalents. In case patients used more than one APD at time of inclusion, cumulative haloperidol equivalent daily dose was calculated. Socioeconomic status (SES) is conceptualized as a combination of parental educational and occupational influences (Erola et al., 2016). We therefore operationalized parental SES in our sample by calculating a composite score, which is an average of two SES variables after conversion to z–scores: 1) average educational level of both parents of the patient and 2) annual net household income based on the average income of the Dutch postal code area of subjects at birth (source: statistics institute Netherlands; Centraal Bureau voor de Statistiek; /informatie/beleid/ publicaties/ maatwerk/ archief, 2011. http://www.csb.nl.). IQ assessment was based on a Dutch translation of the Wechsler adult intelligence scale–third edition (using the subtasks: Arithmetic, Information, Digit–Symbol Coding and Block Design; see Korver and colleagues (Korver et al., 2012) for a more elaborate description and references).

2.3. ANATOMICAL T1 SCAN /MRI CORTICAL AND SUBCORTICAL ACQUISITION

Scans were obtained on a 1.5 Tesla MRI–scanner (Philips Medical Systems, Eindhoven, The Netherlands). Three–dimensional T1–weighted scans (FFE pulse sequence, TR/TE=30 ms/4.6 ms, 30° flip–angle, FOV 256×256 mm2, voxel size 1×1×1.2 mm3, 160–180 contiguous slices) were acquired of the whole brain. Processing was done on the

computer network of the Department of Psychiatry at the University Medical Center Utrecht. Images were coded to ensure blindness to subject identification and diagnosis.

An in–house developed and validated automatic processing pipeline was used to calculate TB, cerebral GM, WM and ventricular volume (Brouwer et al., 2010; Schnack et al., 2001). Data were realigned into Talairach–orientation (Talairach and Tournoux, 1988) and images were corrected for intensity non–uniformity (Sled et al., 1998). Assessment of TB, GM and WM cerebrum volumes were performed based on histogram analysis followed by mathematical morphology operators in the T1–weighted image, using the intracranial volume (ICV) as mask. If available, intracranial masks from the previous GROUP study measurement were non–linearly warped to the scan of the present measurement and were visually checked and edited. If unavailable, model brain ICV masks were used (Brouwer et al., 2010). Lateral and third ventricular volume automatic segmentation was done with an in–house developed algorithm (Schnack et al., 2001). Manual corrections on the intracranial mask (mostly at dura–cortex borders), ventricles and cerebellum, were performed in Display (Montreal Neurological Institute, Montreal, Canada). After checking the quality of corrected intracranial masks, TB, GM and WM and ventricular volumes were extracted. Ventricular volume was logarithmically transformed to correct for positive distributional skew.

T1–weighted images were further processed with FreeSurfer software (version 5.1.0, http://surfer.nmr.mgh.harvard.edu). According to automated parcellation (Fischl et al., 2002, 2004; Desikan et al., 2006) each hemisphere was parcellated into 34 cortical and seven subcortical brain structures. Reward related ROIs were selected, i.e. 1) OFC consisting of lateral/medial OFC and pars orbitalis, 2) insula, 3) ACC consisting of rostral/caudal anterior cingulate cortex, 4) striatum consisting of nucleus accumbens, caudate nucleus and putamen, 5) amygdala and 6) thalamus. Volumes of the left and right hemisphere were summed.

To ensure accurate automated segmentation in FreeSurfer, each segmented brain was visually checked and cortical topological errors were manually corrected. Subcortical structures were quality checked in accordance with the ENIGMA protocol (http://enigma.ini.usc.edu). In our study, subjects were excluded when one or more ROI within the reward circuit was an outlier (mean±2.698 sd). As a result of this procedure a group of five patients failed processing for regional parcellation (due to poor quality and one outlier), and were excluded for regional analyses.

2.4. STATISTICAL ANALYSIS

Statistics were carried out using SPSS version 22. Differences between MetS+, MetS– groups and controls on demographic, lifestyle and clinical variables were examined using ANOVA, t–test or Mann Whitney–U test as non–parametric statistic, and chi square test. Continuous variables were visually checked for normal distribution and by using the W–statistic of the Shapiro Wilk's test. Levene's test was used to check equality of variances.

First, ANCOVAs were performed to investigate differences between patients with schizophrenia and controls on TB, GM, WM, ventricular volume and total volume the reward circuit (i.e. 1) ROIs summed and 2) ROIs converted to z–scores and summed). In case of a significant group effect, patients with schizophrenia and MetS were compared to those without MetS. Furthermore, ANCOVAs were applied, adding brain volume of each structure in the reward circuit separately (i.e. OFC, insula, ACC, striatum, amygdala and thalamus volumes) as dependent variable and MetS group as fixed factor. In case of a significant difference in cortical volume between groups, additional ANCOVAs were performed to determine whether this volume difference was explained by differences in cortical surface area, cortical thickness, or both. For global measures, a p–value cutoff of 0.05 was taken for significance threshold. For regional ROIs analyses False Discovery Rate (FDR) – correction was applied at 0.05, correcting for multiple testing.

Finally, to investigate the specificity of the reward circuitry in case of significant group differences, similar analyses were done at the level of the whole brain, with $p<0.01$ as significance alpha level cutoff. All analyses were adjusted for age, gender and ICV (except when cortical thickness was the dependent variable).

3. RESULTS

3.1. SAMPLE CHARACTERISTICS

Table 1 summarizes socio–demographic differences between controls, MetS+ and MetS– patients with schizophrenia and clinical characteristics differences between both schizophrenia MetS groups. IQ was lowest in MetS+ compared to MetS– ($p=0.016$) and controls ($p<0.001$), and MetS– had significantly lower IQ than controls ($p<0.001$). MetS+ and MetS– had significantly higher percentage of daily cigarette users ($p<0.001$ and $p<0.001$ respectively) and percentage of current cannabis users ($p=0.025$ and $p=0.020$ respectively) compared to controls. MetS groups did not differ significantly on percentage of daily cigarette users and percentage of current cannabis users ($p=0.472$ and $p=0.747$). The use of other illicit drugs was significantly higher in MetS+ compared

to controls (p=0.010) but not compared to MetS– (p=0.126), and did not differ between MetS– and controls (p=0.241).

3.2. GROUP COMPARISONS BETWEEN PATIENTS AND CONTROLS

Volumes of TB (F(1,120)=10.771, p=0.001) and GM (F(1,120)=6.882, p=0.010) were significantly smaller and ventricles were significantly larger (F(1,120)=5.055, p=0.026) in patients compared with controls. In addition, WM volume was smaller in patients at trend level (F(1,120)=3.417, p=0.067). Regional analysis showed a significantly smaller volume of the total reward circuit in patients compared to controls (F(1,115)=14.675, p=<0.001; table 2). Standardizing the separate reward regions to z–scores before summing them did not change this.

3.3. GROUP COMPARISONS BETWEEN PATIENTS WITH AND WITHOUT METS

MetS+ had significantly smaller TB (F(1,66)=6.014, p=0.017) and GM (F(1,66)=7.569, p=0.008) and larger ventricular volumes (F(1,66)=6.271, p=0.015) than MetS–, but groups did not differ significantly on WM (F(1,66)=0.567, p=0.454). The latter comparison was performed since we found a trend level significant difference between patients and controls. MetS+ had a significantly smaller total reward circuit volume compared to the MetS– (F(1,61)=10.407, p=0.002). First standardizing to z–scores before summing the separate reward regions did not change this.

Furthermore, the ROI analysis indicated that there was an FDR–corrected significantly smaller OFC and insula volume in MetS+ as compared with MetS– (F(1,61)=10.838, p=0.002, F(1,61)=8.515, p=0.005 respectively). No significant group differences were found for ACC and subcortical volumes between patients with and without MetS (table 3; figure 1). OFC and insula cortical surface areas were significantly smaller in MetS+ compared to MetS– (OFC: F(1,61)=7.458, p=0.008; insula: F(1,61)=5.274, p=0.025). Cortical thickness of OFC and insula did not differ significantly between the MetS groups (OFC: F(1,61)= 3.605, p=0.062; insula: F(1,61)= 3.759, p=0.057; table 3; figure 1).

TABLE 1. Demographic information of MetS+ and MetS– patients with schizophrenia and controls and clinical information of patients.

	Patients MetS+ (N=23)	Patients MetS– (N=48)	Controls (N=54)	Test–statistics	p–value	Comparison
Age (mean±sd)	31.87±7.24	29.23±4.97	29.94±8.57	F(2,122)=1.071	0.346	–
Gender (% male)	82.6	87.5	68.5	χ2(2)=5.701	0.058	–
WAIS IQ (mean±sd) [a]	88.70±11.20	98.34±16.80	113.0±14.99	F(2,122)=24.722	<0.001*	MetS+ < MetS– < Controls
Ethnicity (% white)	90.9	89.6	87.0	χ2(2)=0.294	0.863	–
SES composite score (mean±sd)	–0.13±.19	0.08±0.13	0.01±0.12	F(2,118)=0.408	0.666	–
Daily use cigarettes past 12 months (% yes)	65.2	56.3	22.2	χ2(2)=17.560	<0.001	Controls < MetS+, MetS–
Heavy alcohol use present state (% yes) [b]	8.70	12.50	14.81	χ2(2)=0.547	0.761	–
Cannabis use present state (% yes) [c]	47.8	43.8	22.2	χ2(2)=7.133	0.028*	Controls < MetS+, MetS–
Other illicit drug past 3 years (% yes) [d]	26.1	14.6	5.6	χ2(2)=6.314	0.043*	Controls, MetS– < MetS+
DSM–IV schizophrenia diagnosis (% 295.1,2,3)	78.3	79.2	–	χ2(1)=0.008	0.930	–
Illness duration (years; mean±sd)	7.86±3.13	7.51±3.87	–	t(68)=–0.367	0.715	–
APD use (% 0/1/2) [e]	8.7/69.6/21.7	20.8/62.5/16.7	–	χ2(1)=1.694	0.429	–
Haloperidol equivalent (mg; mean±sd)	8.30±6.18	8.64±5.26	–	t(55)=0.218	0.828	–
PANSS positive symptoms (mean±sd)	11.14±3.69	11.34±4.07	–	U(69)=516.0	0.990	–
PANSS negative symptoms (mean±sd)	12.95±5.14	12.41±5.23	–	U(68)=464.0	0.580	–
PANSS general symptoms (mean±sd)	24.64± 5.98	24.21±6.01	–	t(67)=–0.273	0.786	–

Abbreviations: MetS is metabolic syndrome; WAIS is Wechsler Adult Intelligence Scale; SES is socioeconomic status; DSM–IV is Diagnostic and Statistical Manual of Mental Disorders Fourth Edition; APD is antipsychotic drug; PANSS is Positive and Negative Syndrome Scale; U is Mann–Whitney U test. [a] IQ estimation based on a short version of the Wechsler Adult Intelligence Scale– Third Edition short form (WAIS–III SF) (Christensen et al., 2007; Velthorst et al., 2013). [b] Heavy alcohol use is defined as consuming 15 drinks or more per week for men. For women, heavy alcohol use is defined as consuming eight drinks or more per week. [c] Based on self–reported use and urine analysis. For cannabis urine analysis a detection window of one month was used. [d] Other illicit drug use: cocaine and amphetamines. [e] One patient was non–compliant with drug therapy. For one patient data was missing on the type of APD and for another one on daily dose; atypical APD include olanzapine, clozapine, risperdone, aripiprazole and quetiapine; typical APD include flupentixole, perphenazine, haloperidol, pipamperon and penfluridole in this sample. In case of treatment with two APDs clozapine was combined with either a typical of atypical APD; and in one case perfenazine was combined with pipamperon.
Significant results are presented as: *p < 0.05.

TABLE 2. Differences in global brain volume and regional brain volume between patients with schizophrenia and controls. Values are shown in mean±sd ml.

Global brain volume	Patients (N=71)	Controls (N=54)	F	p–value
Total brain	1294.79±130.14	1323.72±134.16	10.771	0.001*
Gray matter	612.26±61.28	626.58±63.88	6.882	0.010*
White matter	518.75±67.76	533.74±70.17	3.417	0.067
Ventricular volume [a]	19.79±10.79	15.90±7.73	5.055	0.026*
ROI volume	(N=66)	(N=54)		
Reward circuit volume	91.81±8.89	94.86±8.51	14.675	<0.001*

[a] Statistics were performed on log–transformed volumes. However, mean ventricular volume is shown before log transformation.
* Significant at an alpha level of 0.05, adjusted for age, gender and intracranial volume.

TABLE 3. a. Differences in global brain volume and **b.** regional brain volume between patients with schizophrenia, with and without MetS. Values are shown in mean±sd ml. **c.** results on regions of interest cortical surface area (shown in mean±sd mm2) and cortical thickness (shown in mean±sd mm) of significant volume differences between patients with schizophrenia, with and without MetS.

a. Global brain volume	MetS+ (N=23)	MetS– (N=48)	F	p–value
Total brain	1259.73±117.75	1311.59±133.59	6.014	0.017*
Gray matter	591.99±52.58	621.98±63.26	7.569	0.008*
White matter [a]	506.56±61.49	524.59±70.44	0.567	0.454
Ventricular volume [b]	23.66±13.71	17.94±8.64	6.271	0.015*
b. ROIs volume	**(N=18)**	**(N=48)**		
Reward circuit	87.16±8.23	93.55±8.58	10.407	0.002*
OFC volume	28.06±2.92	30.77±3.29	10.838	0.002**
ACC volume	8.35±1.47	8.98±1.53	1.357	0.249
Insula volume	13.58±1.45	14.87±1.58	8.515	0.005**
Striatum volume	18.24±2.36	19.41±2.28	0.697	0.407
Amygdala volume	3.12±0.38	3.29±0.37	0.982	0.326
Thalamus volume	15.82±1.67	16.23±1.52	0.030	0.864
c. Surface area and thickness	**(N=18)**	**(N=48)**		
OFC cortical surface area	9779.56±818.44	10382.31±1051.92	7.458	0.008**
Insula cortical surface area	4399.33±457.36	4688.23±482.42	5.274	0.025**
OFC cortical thickness	2.58±0.15	2.65±0.13	3.605	0.062
Insula cortical thickness	3.11±0.11	3.17±0.12	3.759	0.057

Abbreviations: MetS+ is group of patients with schizophrenia and metabolic syndrome; MetS– is group of patients with schizophrenia and without metabolic syndrome; ROI is region of interest; OFC is orbitofrontal cortex; ACC is anterior cingulate cortex.
[a] White matter comparison is performed since a trend level difference occurred between patients and controls.
[b] Statistics were performed on log–transformed volumes. However, mean ventricular volume is shown before log transformation.
* Significant at an alpha level of 0.05, adjusted for age, gender and intracranial volume.
** Significant after FDR–correction, adjusted for age, gender and intracranial volume (except when cortical thickness was the dependent variable).

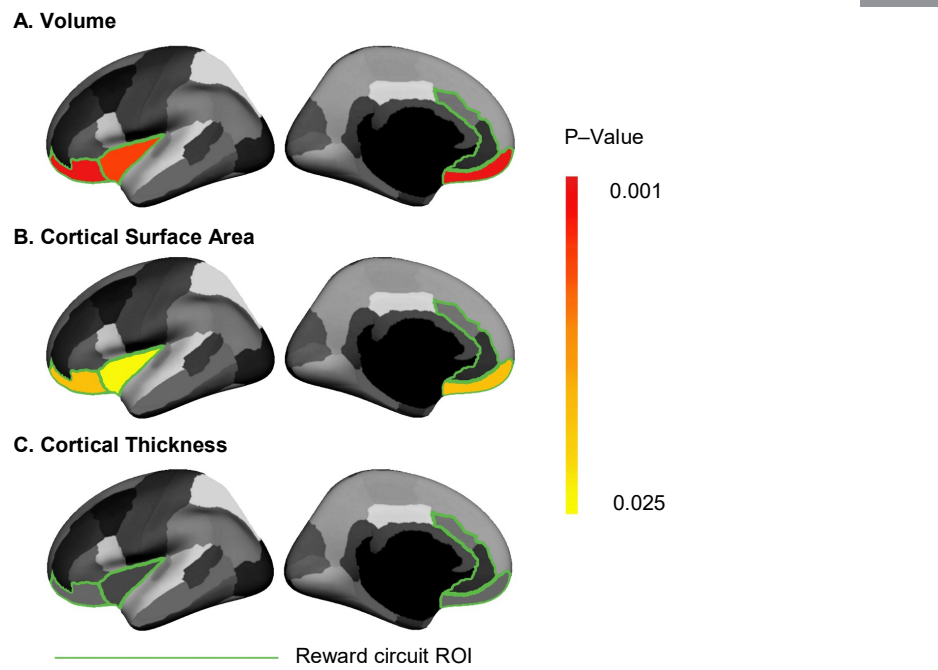

FIGURE 1. Statistical comparison brain maps of cortical gray matter regions of interest (ROIs) **A.** volume, **B.** cortical surface area and **C.** cortical thickness between patients with schizophrenia and MetS (MetS+) and those without MetS (MetS–) in lateral and medial view. Red–yellow indicates an FDR–corrected significant volume decrease in MetS+ compared to MetS–, adjusted for age, gender and intracranial volume (except when cortical thickness was the dependent variable). Cortical gray matter ROIs are indicated with a green line.

Table 4 shows the significantly different structures between MetS+ and MetS– of the whole–brain analyses, showing that only OFC and insula volumes were significantly smaller in MetS+ compared to MetS–.

TABLE 4. Differences between MetS+ and MetS– patients with schizophrenia on regional structures at a whole–brain level.

Brain region	MetS+	MetS–	F	p–value
Frontal lobe				
Superior Frontal Gyrus	43.90±5.40	46.64±6.41	0.300	0.586
Rostral Middle Frontal Gyrus	32.39±4.69	33.88±5.19	0.035	0.852
Caudal Middle Frontal Gyrus	12.08±2.37	12.63±2.32	0.067	0.797
Inferior Frontal Gyrus, Pars Opercularis	8.49±1.22	8.93±1.11	0.563	0.456
Inferior Frontal Gyrus, Pars Triangularis	7.13±0.95	8.33±1.42	6.714	0.012
Orbitofrontal Cortex	28.06±2.92	30.77±3.29	10.838	0.002*
Precentral Gyrus	23.68±3.20	25.95±3.47	3.248	0.076
Paracentral Gyrus	6.73±1.23	7.02±0.99	0.011	0.916
Frontal Pole	1.96±0.21	1.98±0.31	0.028	0.867
Anterior Cingulate Cortex	8.35±1.47	8.98±1.53	1.357	0.249
Insular lobe				
Insula	13.58±1.45	14.87±1.58	8.515	0.005*
Parietal lobe				
Superior Parietal Gyrus	24.27±3.68	26.81±3.68	4.475	0.038
Inferior Parietal Gyrus	27.33±4.17	29.24±4.0	1.040	0.312
Supramarginal Gyrus	20.84±3.30	22.63±3.06	2.463	0.122
Postcentral Gyrus	17.63±3.08	18.82±2.64	0.798	0.375
Precuneus Gyrus	18.18±2.78	19.82±2.74	3.117	0.082
Posterior Cingulate Gyrus	6.25±0.74	6.72±0.91	2.364	0.129
Isthmus Cingulate Gyrus	4.78±0.73	5.32±0.84	1.925	0.170
Temporal lobe				
Superior Temporal Gyrus	22.87±3.22	25.06±3.08	4.381	0.041
Middle Temporal Gyrus	22.80±3.02	24.51±3.41	1.173	0.283
Inferior Temporal Gyrus	19.67±2.89	20.94±2.95	0.694	0.408

TABLE 4. Continued

Brain region	MetS+	MetS–	F	p–value
Banks of Superior Temporal Sulcus	5.05±0.89	5.23±0.86	0.158	0.692
Fusiform Gyrus	18.66±2.58	20.24±2.60	1.544	0.219
Transverse Temporal Gyrus	2.04±0.43	2.15±0.36	0.421	0.519
Entorhinal Gyrus	4.05±0.61	4.17±0.63	0.072	0.789
Temporal Pole	5.18±0.59	5.16±0.68	1.364	0.247
Parahippocampal Gyrus	4.07±0.44	4.42±0.65	3.266	0.076
Occipital lobe				
Lateral Occipital Gyrus	20.62±2.96	21.95±2.66	1.651	0.204
Lingual Gyrus	11.58±1.70	12.35±1.63	1.348	0.250
Cuneus	5.43±0.99	5.64±0.84	0.010	0.921
Pericalcarine Gyrus	3.86±0.64	3.82±0.66	0.402	0.529
Subcortical structures				
Amygdala	3.12±0.38	3.29±0.37	0.982	0.326
Hippocampus	8.82±0.85	9.18±0.90	1.137	0.291
Pallidum	3.44±0.42	3.67±0.40	1.406	0.240
Striatum	18.24±2.36	19.41±2.28	0.697	0.407
Thalamus	15.82±1.67	16.23±1.52	0.030	0.864

* Significant at an alpha level of 0.01, adjusted for age, gender and intracranial volume.

4. DISCUSSION

To our knowledge, we are the first to show that in schizophrenia comorbid MetS is related to global structural brain reductions and regional abnormalities of reward circuit structures. Our main finding is that the reward circuit, and specifically volumes and cortical surface area of OFC and insula, are smaller in patients with schizophrenia and MetS compared to those without. The reward circuit is implicated in the evaluation of reward and risk (Haber and Knutson, 2010), and structural alterations in the reward circuit might lead to poor health choices, such as poor dietary decision making in patients with schizophrenia (Elman et al., 2006) and in non–psychiatric subjects (Shott et al., 2015; Maayan et al., 2011) and to substance use (Franklin et al., 2002; Makris et al., 2008). These are health risk factors that increase the chance of MetS (Brown et al., 1999; Papanastasiou et al., 2012). Since the reward brain circuit is also found to be functionally impaired in schizophrenia (Strauss et al., 2014) and in those at high risk of developing psychosis (De Leeuw et al., 2015), the cognitive regulation of adaptive health behavior may be affected, increasing the chance of MetS in schizophrenia.

Volume reduction in OFC and insula showed to be most pronounced in patients with schizophrenia and MetS compared to those without MetS. Since OFC is a core structure in regulating cognitive suppression of maladaptive health behavior such as overeating (Cohen et al., 2011) and addiction (Volkow and Fowler 2000), deficits in the OFC may cause unhealthy lifestyles, which increase the chance of MetS. That brain abnormalities in the frontal lobe are associated with MetS in schizophrenia has also been indirectly demonstrated by the finding of an association of MetS with (premorbid) cognitive deficit (de Nijs et al., 2016) and worse executive functioning (Boyer et al., 2014). This may indicate that poor frontal lobe integrity, reflected by poor cognitive functioning, present before schizophrenia onset is a risk factor for metabolic complications.

Insula abnormalities may be implicated in high MetS prevalence, since this structure regulates craving (Pelchat et al., 2004; Del Parigi et al., 2002) and homeostatic feedback (Critchley et al., 2004). Insula abnormalities may therefore cause maladaptive perception of hunger and unawareness of satiety, increasing the change of unhealthy behavior.

Since the association between OFC and insula abnormalities and MetS appear to be mediated by cognitive deficits, cognitive remediation, aiming to diminish unhealthy lifestyles might be of help. Cognitive remediation has shown improvements in eating behavior and weight reduction (Raman et al., 2018) and reductions in substance use (Eack et al., 2016), although these associations have not been investigated yet in relation to MetS. In addition, in the former study, the association between cognitive

remediation and substance use was not specifically investigated in patients with schizophrenia. We found that volume reductions in OFC and insula in patients with schizophrenia and MetS compared to those without MetS are predominantly reflected in diminished cortical surface area, which indicates that cortical surface area may be an important factor in relation to MetS prevalence. Also, these results emphasize the importance of investigating cortical thickness and surface area as separate measures. Cortical surface area and thickness are thought to have a unique developmental trajectory (Wierenga et al., 2014), which is explained by independent genetic processes (Panizzon et al., 2009). Cortical thickness is shown to reach its peak earlier than cortical surface area (Wierenga et al., 2014). As cortical surface area peaks later in life and cortical thickness is more established at birth (Lyall et al., 2015), cortical surface area may be more susceptible to environmental factors occurring later in life, especially in the frontal lobe, since this area is relatively late to develop (Sowell et al., 2001). Health behavior and metabolic complications may be such environmental factors. It has been suggested that cortical surface area may be dependent on underlying WM expansion (Seldon, 2005). In line with our finding of reduced surface area in the frontal lobe, it has been shown with DTI that in non–psychiatric subjects, MetS is related to decreased WM integrity in the frontal lobe (Shimoji et al., 2013). Further exploration of the association between MetS in schizophrenia and specific structural deficits in multiple imaging modalities is recommended.

We also showed that MetS in patients with schizophrenia is associated with smaller global volumes of TB and GM and a larger ventricular volume. This is in line with other studies in non–psychiatric samples who showed smaller global volumes associated with MetS, with comparable volume reductions (Tiehuis et al., 2014; Yau et al., 2012). Possible explanations for these smaller global brain volumes are vascular abnormalities, neuroinflammation and oxidative stress associated with MetS (Yates et al., 2012). We found no difference in WM volume between the MetS groups. In DTI studies WM integrity abnormalities were found in non–psychiatric subjects with MetS compared to those without MetS (Shimoji et al., 2013; Segura et al., 2009). It may be possible that WM integrity measured by *diffusion tensor imaging* is more sensitive to MetS than WM volume.

Cerebrovascular integrity is reduced by MetS, causing atrophy as well as reduced blood flow (Yates et al., 2012). Therefore, besides structural deficits, functional deficits are expected as well in relation to MetS. Indeed, functional MRI deficits have been found in MetS (Boyer et al., 2014; Hoth et al., 2011). Genetic variations may influence the individual risk of the development of MetS (Suetani et al., 2017), and may also serve as a mediator between aberrant brain structure and MetS risk in schizophrenia, since

brain structure is influenced by genetic variations as well in schizophrenia (Harari et al., 2017). Future research in larger samples could identify these genetic variations and potentially apply these as predictors in an individualized prediction model for risk of MetS development. From a public health perspective, individualized prediction models using machine learning techniques, containing genetic and imaging related predictors might be an important starting point for future research, unraveling vulnerability for the development of MetS at an individual level.

Limitations of this study are the limited power, given the modest sample size, and the cross–sectional study design. Longitudinal studies are necessary to determine how changes in MetS are associated to change in brain reward structures. Also, we did not collect information on physical activity and food intake. These might be mediating factors, since it is known that better physical fitness and healthy dietary habits are related to larger brain volumes (Scheewe et al., 2013; Luciano et al., 2017). Also we did not assess reward functioning. Future studies should also include a control group with participants with and without MetS.

In summary, we were the first to find that patients with schizophrenia and MetS as compared to those without MetS had smaller brain volumes including a reduced reward circuit. The reward circuitry is involved in reward and risk processing and health behavior, implicating that abnormalities herein may lead to an increased MetS rate in schizophrenia. Future research in schizophrenia should focus on underlying mechanisms of poor cognition (i.e. reward processing deficits) in relation to MetS development.

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CHAPTER 8

SUMMARY AND GENERAL DISCUSSION

1. OBJECTIVES

By examining the factors that play a role in mental health and physical outcomes of schizophrenia, it becomes clear that the underlying mechanisms are multifaceted. At present little is understood of these mechanisms– as the scientific evidence falls short. In this thesis schizophrenia outcomes were examined from various angles. In part I, the medium and long–term mental health outcomes of the GROUP cohort were examined using longitudinal retrospective and prospective study designs. In addition outcomes were predicted on a group level as well as on an individual level. In part II olfactory and metabolic outcomes were investigated using longitudinal retrospective and cross–sectional study designs. In addition to mental health variables, various cognitive and brain measurements were used to predict these physical outcomes.

2. MAIN FINDINGS

PART I: MENTAL HEALTH OUTCOMES

In **chapter 2** we explored predictors of three–year outcome of remission of psychotic symptoms and compulsory hospitalization. Predictors included a comprehensive test–battery of cognitive domains, demographic and clinical information and comorbid substance abuse. This three–year longitudinal study showed that higher verbal IQ and lower number of psychotic episodes are protective factors for a poor outcome of schizophrenia. Memory deficits and higher number of psychotic episodes are risk factors for a poor outcome of schizophrenia, however with modest accuracies. This suggests that further research is needed before prediction tools can be developed.

Chapter 3 begins where **chapter 2** ends by employing individualized prediction, instead of group level prediction. In this chapter we use demographic, clinical, genetic, environmental, (premorbid) cognitive, social cognitive and extrapyramidal predictors of medium– and long–term (three–year and six–year respectively) symptomatic and global functioning outcomes, to classify good versus poor clinical outcome at an individual level with a machine learning algorithm. We found that it is possible to predict medium– and long–term symptomatic and global functioning outcomes with reasonable accuracies of up to 68%. Training a machine learning algorithm revealed that present state and past level of positive, negative and general symptoms, need of care features and clinical and demographic characteristics, such as educational level and quality of life, predicted our multiple endpoints best, suggesting these factors should be included in successful prediction of outcome. As a replication of the European First Episode Schizophrenia Trial (EUFEST), which successfully predicted

short–term outcome at an individual level (Koutsouleris et al., 2016), we found similar best performing predictors compared to EUFEST predictors. We also showed that short–term outcome predictors of EUFEST are, to certain extent (up to 66%), also predictive of medium– to long–term outcomes in the GROUP study. Our study is a promising step in pursuit of personalized medicine applicability in mental care institutes. However, our model needs replication in independent samples, before the step of practical implementation in the clinic can be made.

In **chapter 4** we examined whether connectome wiring integrity is predictive of outcome. We assessed level of present state symptomatology, global functioning and IQ as outcomes after three years following baseline MRI assessment. We showed that more prominent impairments of connectivity among key brain hubs of rich club herald progressive decline in global functioning. On the other hand, relative sparing of rich club connections was more likely to precede stable or even improved global functioning. Also, we found that more severe disruptions in network clustering are particularly associated with subsequent increases in symptom severity and decreases in total IQ. To examine whether these associations were just normal age–related changes, we investigated whether baseline connectome organization predicted subsequent changes in IQ and subclinical symptoms in healthy controls and unaffected siblings of the patients. Since we found no such associations, we propose that our findings in schizophrenia patients represent effects of ongoing illness. Our findings suggest that connectome wiring has an influential role on the course of illness in schizophrenia.

PART II: PHYSICAL OUTCOMES

Chapter 5 explored associations of cognition with present state olfactory identification (OI). We described a study examining olfactory identification differences in a group of schizophrenia patients and healthy controls, related to cognitive and social functioning in childhood and adolescence, to present state cognition and to present state social cognition. We focused in particular on these (social) cognitive domains, because olfactory and (social) cognitive development are thought to be dependent on similar neural substrates. We confirmed and extended existing literature on associations between olfactory identification and (social) cognitive functioning. We further showed that olfactory identification was positively associated with childhood/adolescence cognitive as well as childhood/adolescence social functioning, and with a range of present state social cognitive domains (i.e. face recognition, emotion recognition and theory of mind). This association was found not only in patients with schizophrenia but also in healthy controls, however, with the notion that patients scored worse in all the assessed domains. These results indicate that the underlying mechanism causing

OI deficits and cognitive/social impairment may share similar neural substrates, in particular of the frontotemporal structures, not specific to schizophrenia.

In **chapter 6** we describe a study examining the cognitive trajectory during childhood and adolescence in patients with schizophrenia. We found an early cognitive decline (before the age of 16) in those schizophrenia patients with established co–morbid MetS as compared to schizophrenia patients without MetS. MetS prevalence as well as lower cognition might be influenced by a lower socioeconomic status (Loucks et al.,2007; Greenfield and Moorman, 2018), but interestingly, the early cognitive decline we found in schizophrenia patients with MetS could not be explained by socioeconomic status. Identifying risk factors of developing MetS in schizophrenia is an important goal in improving health and life expectancy after a first psychotic episode. The results of this study are clinically relevant and suggest the cognitive trajectory is an essential factor in relation to MetS prevalence and could underlie future risk of metabolic complications later in life in schizophrenia. Future research on improving health in schizophrenia should include the effects of cognitive treatment.

In **chapter 7** we performed a study examining the relationship between MetS, which is highly prevalent is schizophrenia, and structural MRI brain volumes of reward areas in schizophrenia patients and controls. We included schizophrenia patients with MetS and without MetS and healthy controls. We focus in particular on these reward related brain areas in relation to MetS since the reward circuitry is involved in reward and risk processing and health behavior, and MetS is often a consequence of unhealthy behavior. We were the first to find that patients with schizophrenia and MetS as compared to those without MetS had a reduced reward circuit, implicating that abnormalities herein may lead to an increased MetS rate in schizophrenia.

Findings of **chapter 6** and **chapter 7** suggest that brain volume and associated cognitive deficits might predate the development of the metabolic syndrome (MetS).

CONCLUSION

Outcome prediction is multifaceted. Taken together, this thesis shows that predictors of mental health and physical health outcomes include an interaction of many factors concerning the (endo)phenotype such as structural brain integrity (grey matter and white matter pathways wiring), premorbid functioning, demographic characteristics, psychiatric symptomatology, need of care, and (social) cognitive functioning. Some predictor modalities hold special promise, such as reward processing in health outcome prediction; premorbid functioning and (social) cognition in predicting metabolic syndrome and olfactory identification deficit; connectome organization,

patients' needs and baseline symptoms in symptomatic and global functioning outcome prediction.

Furthermore, it can be concluded that mental health and physical wellbeing are not separable in schizophrenia. Much of the same predictive factors of mental health outcomes might also apply to physical outcomes, and the other way around (figure 1 summarizes the associations between predictors and outcomes).

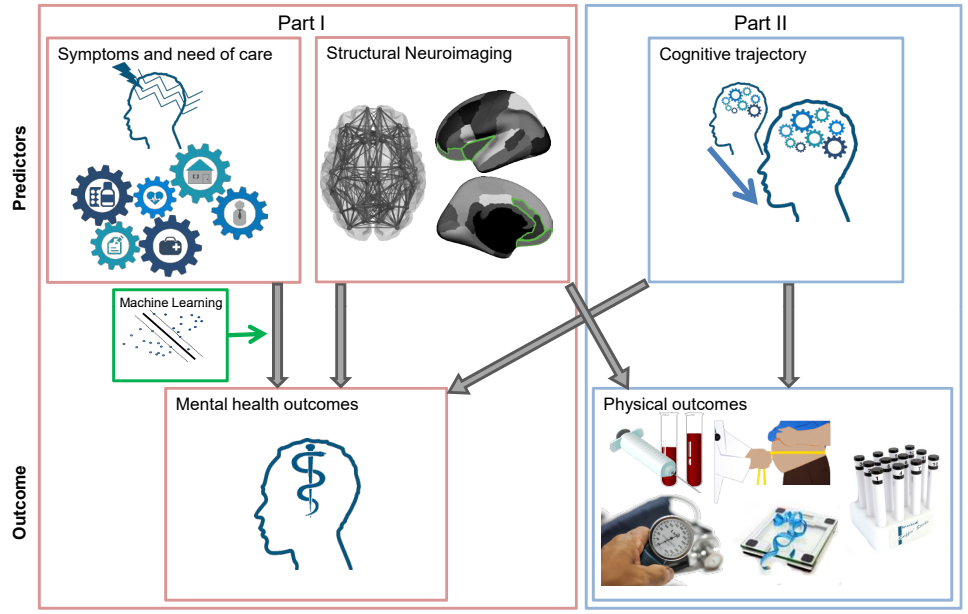

FIGURE 1.

3. METHODOLOGICAL CONSIDERATIONS

While a wide variety of methods was used in this thesis (retrospective and prospective longitudinal design, machine learning, structural neuroimaging of brain volume, cortical surface area, cortical thickness and connectome organization) as a means to investigate outcomes, there are several methodological limitations that are shared among the studies, including loss to follow–up, selection bias, retrospective assessment and missing data. Medication use of patients might be a limitation as well. Below, it is discussed how these limitations may have influenced the results.

BIAS

Attrition bias is one of the major methodological limitations of a longitudinal study design, affecting the generalizability of the results in the GROUP study. Patients with unfavourable baseline characteristics were more likely to be lost to follow up, as was concluded in **chapter 2**. However, as indicated by Wolke et al (2009), it is possible that the prediction is only marginally affected by selective drop–out.

Furthermore, a selection bias/participation bias may have occurred, because of the prerequisite for patients to have (a) family member(s) to be included in the study, which may have excluded patients that were more isolated and had lower functioning.

In **chapter 6** and **7**, concerning MetS assessment, a selection bias may have occurred, since not all participants included in the GROUP study consented to physical examination, venipuncture and/or MRI scanning. However, no differences were found in illness severity between GROUP participants who were and were not included in these studies.

Retrospective assessment, as was applied in **chapter 5** and **6**, may cause a recollection bias, although Brill et al. (2008) confirm predictive and concurrent validity of the retrospective method used in this thesis, in schizophrenia patients. Also, it was shown by Fisher and colleagues (2001) that patient reports of childhood events have good reliability and validity in psychosis.

Since the GROUP study is a multicentre study there are many raters, which may decrease the consistency of the data collection. However, all the GROUP raters were trained in patient assessment in the same way. Also, inter–rater reliability was high concerning symptom ratings, suggesting raters did well (Korver et al., 2012).

MEDICATION USE

In the GROUP study the majority of patients used medication at baseline (92%). Antipsychotic medication may negatively influence white matter connectivity (Szeszko et al., 2014), OI (Moberg et al., 2014), metabolic symptoms (Bak et al., 2014) and structural brain volume (Haijma et al., 2013). However, deficit in these predictors have also been found in drug–naïve patients (Mandl et al., 2013; Moberg et al., 2014; Enez Darcin et al., 2015; Haijma et al., 2013 respectively). Furthermore in the studies presented in **chapter 4**, **5**, **6** and **7** results did not change when antipsychotic drug use was accounted for.

Finally, despite careful selection of genetic information as predictor modality in the prediction of mental health outcome (**chapter 3**; i.e. polygenic risk score for schizophrenia), we cannot exclude the possibility of specific gene × environment interactions influencing the outcome of psychosis. In other words, the degree of environmental impact on outcome may depend on genetic vulnerability. For example, not all people who use cannabis develop worse psychotic symptoms, and Caspi et al. (2005) found a moderating effect of a specific gene on this relationship. Similarly, van Winkel and colleagues (2015) found that cannabis exposure induced higher psychotic expression in patients with higher level of familiar vulnerability. Another recent example, further underlining the complexity of interactions, shows that a genetic disposition for schizophrenia development had causal pathways for the use of cannabis (Pasman et al., 2018). Gene × environment interactions could also be relevant for the prediction of physical outcomes. Unhealthy lifestyle factors (i.e. reduced physical activity: Lott et al., 2013; smoking: Yevtushenko et al., 2008), and the use of antipsychotics (Risselada et al., 2012) were found to interact with specific genes to increase the chance of MetS in schizophrenia.

4. FUTURE DIRECTIONS AND IMPLICATIONS

The results presented in the studies give rise to new research:

– Genetic contribution, using polygenetic risk score, was not found to predict mental health outcomes at an individual level in **chapter 3**. However, a possible way to improve the genetic prediction model is the inclusion of genetic data derived from the genome wide association studies. Extensive genetic assessment could further create enriched models, containing even more relevant information for outcome prediction.

– Cognitive functioning as a predictor for mental health outcomes was not convincing, however it did result in significant models in the prediction of mental health outcomes (**chapter 2** and **3**; with a comparable area under the curve between 50 and 60). Previous research on psychosocial approaches in treatment of schizophrenia has yielded incremental evidence of efficacy of cognitive remediation in outcome (Barlati et al., 2013). Cognitive functioning was a convincing determinant of physical outcomes (**chapter 5** and **6**). Also, cognitive remediation was found to be effective in reducing unhealthy lifestyles (Raman et al., 2018; Eack et al., 2016) in non–psychotic subjects. In summary, research aimed to investigate beneficial effects of cognitive remediation in outcome could be a fruitful endeavour.

MACHINE LEARNING

Previous studies have identified multiple predictors of psychosis outcome, mostly at group level, with inconsistent contribution (Gaebel et al., 2014; Lambert et al., 2010; Alvarez–Jimenez 2012). Thus far, studies have not been able to make meaningful prediction models for individual patients in the long term (Millan et al., 2016). The choice of predictors is subjective, however, prediction accuracy might be improved when considering larger number of predictors, since the chance becomes smaller to miss an important predictor for outcome. Furthermore, in case of large datasets, machine learning is highly suitable for calculating complex interactions.

Notwithstanding the fact that machine learning is a powerful technique in prediction when considering large heterogeneous datasets, external validation of the results presented in **chapter 3** is necessary when the aim is to implement an outcome prediction tool in the clinical practice. New data in similar patient samples is needed before a tool could be developed.

Also, individualized prediction with a multimodality modelling setup with machine learning techniques as applied in **chapter 3** could be applied for the prediction of MetS, enriched with neuroimaging parameters and elaborate genetic assessment.

The search for predictive factors in schizophrenia has been hampered by phenotypic heterogeneity. Methods such as machine learning are very suitable to mitigate this (Schnack, 2017). In this thesis we included schizophrenia patients as well as schizophrenia spectrum patients, with recent onset, but also more chronic cases. Since in the daily practice, heterogeneity of first mental health contact presentation is the reality, personalized medicine research, using machine learning is very suitable.

Despite the research that is still necessary, the results of this thesis could influence clinical practice. A comprehensive evaluation of predictors of mental health outcomes as well as physical outcomes can assist clinicians to develop a collaborative relationship with patients and their families to generate more informed expectations for medium– and long–term outcomes, based on a baseline psychotic presentation. Once prediction tools are developed, individualized outcome could aid psychiatrists to choose the most appropriate next steps in treatment, and to map risks and resilience factors in each individual patient.

CONCLUDING REMARKS

Outcome is an important measure in health care planning. Moreover, patients (and their families) presenting with a psychotic episode at the clinic want to know what to expect regarding the course of the disease. Research presented in this thesis highlights that the investigated predictors can be used in a meaningful way to predict mental health and physical outcomes in psychosis. The studies presented in this thesis confirm the necessity of a multidisciplinary approach in health care, using mental health and physical outcome as integral treatment target. Future focus should be on personalized outcome prediction. Although our results are promising, schizophrenia outcome prediction remains complex, and higher classification performance is necessary. The need for even more elaborate sets of predictors is necessary, as well as the need for larger multicentre prospective cohort studies for replication, before individualized prediction tools can be developed, tested and implemented.

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APPENDICES

LIST OF PUBLICATIONS
NEDERLANDSE SAMENVATTING
DANKWOORD
CURRICULUM VITAE

LIST OF PUBLICATIONS

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NEDERLANDSE SAMENVATTING

Hoofdstuk 1 van dit proefschrift geeft een algemene introductie over schizofrenie en het doel van het proefschrift.

Schizofrenie–spectrumstoornissen, geclassificeerd als psychotische stoornissen, behoren tot de meest ernstige psychiatrische aandoeningen wereldwijd, op een persoonlijk, familiaal en maatschappelijk vlak. Schizofrenie manifesteert zich doorgaans in de jongvolwassenheid en wordt gekenmerkt door positieve psychotische symptomen (zoals wanen en hallucinaties), negatieve symptomen (zoals verminderde motivatie en sociale interactie), en cognitieve problemen. Schizofrenie is een heterogene ziekte, met een klinisch beloop dat gekenmerkt wordt door ofwel een chronisch beeld, terugkerende psychotische episodes, of een enkele episode met (deels) herstel van psychotische positieve symptomen, negatieve symptomen en/of cognitieve problemen.

Er zijn veel omgevings en genetische factoren die het beloop en de uitkomst van de ziekte beïnvloeden, wat het moeilijk maakt uitspraken te doen over de prognose na het hebben van een psychose. Het vinden van voorspellers van de uitkomst van psychose kan bijdragen aan het verklaren van de complexiteit van de ziekte en aan het verbeteren van prognostische uitspraken, en mogelijk bijdragen aan het veranderen van het pathologische beloop dat vaak wordt geassocieerd met schizofrenie.

Het algemene doel van het onderzoek in dit proefschrift is om factoren in de kindertijd, adolescentie en na de start van de ziekte te onderzoeken die geassocieerd kunnen zijn met klinische en fysieke uitkomsten van psychose. Het proefschrift is onderverdeeld in twee delen. In het eerste deel worden studies gepresenteerd waarin precursoren (in de kindertijd en adolescentie, en na de start van de ziekte) van klinische uitkomsten worden onderzocht– dit betreft korte termijn uitkomsten, onderzocht op groepsniveau, en lange termijn uitkomsten, onderzocht op individueel niveau. In het tweede deel ligt de nadruk op fysieke prognose op het gebied van olfactorische en metabole uitkomsten, met longitudinale retrospectieve en cross–sectionele onderzoeksdesigns. Er is gekeken naar de associatie tussen fysieke uitkomsten met klinische variabelen, cognitie en structurele MRI.

GEESTELIJKE GEZONDHEID UITKOMSTEN

In **hoofdstuk 2** is op groepsniveau onderzocht welke voorspellers relevant zijn voor korte termijn (drie jaar follow–up) uitkomsten van remissie van psychotische symptomen en gedwongen ziekenhuisopname in schizofrenie patiënten. Onderzochte voorspellers omvatten een uitgebreide testbatterij van cognitieve domeinen, baseline

demografische en klinische informatie van schizofrenie patiënten, en comorbide misbruik van middelen. Deze longitudinale studie heeft aangetoond dat een hoger verbaal IQ en een lager aantal psychotische episodes beschermende factoren zijn, en dat een slechter geheugen en een hoger aantal psychotische episodes risicofactoren zijn voor een nadelige klinische uitkomst van schizofrenie. Echter, de voorspellingen hebben een bescheiden nauwkeurigheid. Meer onderzoek is nodig voordat er voorspellingsinstrumenten kunnen worden ontwikkeld voor in de klinische praktijk. De resultaten van dit onderzoek suggereren dat toekomstig onderzoek naar voorspelmodellen voor de uitkomst van schizofrenie de beoordeling van (verbaal) IQ en geheugen kan laten meewegen.

In **hoofdstuk 3** onderzochten we demografische, klinische, genetische, omgevings–, (premorbide) cognitieve, (premorbide) sociaal–cognitieve en extrapiramidale baseline voorspellers van medium en lange termijn (follow–up na drie en zes jaar na de baseline meting respectievelijk) symptomatische en globale uitkomst na het hebben van een psychose. Het doel was om goede versus slechte uitkomst te classificeren op een individueel patiënt niveau, aan de hand van een machine learning–algoritme. Onze resultaten laten zien dat het voorspellen van symptomatische en globale uitkomsten met een redelijke nauwkeurigheid, tot 68% mogelijk is. Het trainen van een machine learning–algoritme toonde aan dat huidige en vroegere mate van positieve, negatieve en algemene psychiatrische symptomen, alsook zorgbehoeften, klinische en demografische eigenschappen van de patiënt, zoals opleidingsniveau en kwaliteit van leven, de symptomatische en globale uitkomsten het best voorspelden. Dat suggereert dat deze factoren moeten worden meegenomen in de ontwikkeling van een succesvol voorspellingsinstrument voor de uitkomst van schizofrenie. Als replicatie van de European First Episode Schizophrenia Trial (EUFEST), waarin globale uitkomst van schizofrenie op korte termijn op individueel niveau met succes werd voorspeld, toonden we aan dat EUFEST–voorspellers vergelijkbaar waren met onze voorspellers. We hebben ook aangetoond dat voorspellers van korte–termijn globale uitkomst, die gevonden werden in EUFEST tot op zekere hoogte (tot 66%) ook voorspellend zijn voor lange–termijn uitkomsten in onze studie. Onze studie is een veelbelovende stap in gepersonaliseerde voorspelling van uitkomst voor patiënten in de geestelijke gezondheidszorg. Ons model moet echter in een onafhankelijke groep nieuwe deelnemers worden gerepliceerd voordat het in de kliniek kan worden geïmplementeerd.

In **hoofdstuk 4** werd onderzocht of de bedradingsorganisatie van het netwerk van witte stofverbindingen in het brein, ofwel het connectoom hersennetwerk, voorspellend is voor symptomatische en globale uitkomst in schizofrenie. We hebben het niveau van

huidige symptomatologie, algemeen functioneren (het hebben van werk en zelfstandig kunnen wonen) en cognitieve prestaties drie jaar na de baseline (MRI) meting beoordeeld bij een groep schizofrenie patiënten. We vonden dat patiënten met grotere afwijkingen in connectoom bedrading op baseline– in het bijzonder verstoringen van rich–clubverbindingen (een kern van sterk met elkaar verbonden gebieden die een centrale rol in het gehele breinnetwerk hebben) – een afname in functionele uitkomst lieten zien in de drie jaar die volgde na de baseline MRI–deelname, terwijl relatief gespaarde baseline rich–clubverbindingen voorspellend waren voor stabiel of zelfs verbeterd functioneren. Daarnaast vonden we dat ernstigere verstoringen in de globale connectoom organisatie (voornamelijk de totale mate van clustering) voorspellend waren voor toename in ernst van de symptomen en daling van het totale IQ. Om te onderzoeken of deze associaties mogelijk normale leeftijdsgerelateerde veranderingen weerspiegelen, hebben we onderzocht of baseline connectoom organisatie ook veranderingen in IQ en subklinische symptomen bij gezonde controles en gezonde broers en zussen van patiënten voorspelde. Aangezien we dergelijke associaties niet vonden, stellen we dat de bevindingen bij patiënten de effecten zijn van de ziekte. De bevindingen van onze studie suggereren dat de organisatie van de bedrading van de hersenen voorspellende waarde kan hebben voor symptomatische en globale uitkomst.

FYSIEKE UITKOMST

In **hoofdstuk 5** zijn de associaties tussen premorbide functioneren in de kindertijd en adolescentie met het huidige olfactorisch functioneren (de mate waarin men in staat is geuren te identificeren) onderzocht in schizofrenie patiënten. We repliceerden dat premorbide sociaal en premorbide cognitief functioneren afwijkt van het normale ontwikkelingstraject bij kinderen en adolescenten die later in het leven schizofrenie ontwikkelen. Eveneens repliceerden we verminderingen in het reuk vermogen en in het huidig cognitief functioneren in alle geteste cognitieve domeinen bij schizofrenie patiënten in vergelijking met gezonde deelnemers. Bovendien vonden we associaties tussen slechtere geur identificatie en een breed spectrum aan cognitieve gebreken (in het IQ, geheugen, aandacht en executief functioneren). Verder toonden we aan dat verminderde geur identificatie geassocieerd is met slechter cognitief en sociaal functioneren in de kindertijd en adolescentie en met een slechtere huidige sociale cognitie (gezicht recognitie, emotie recognitie en theory of mind). Deze associaties werden niet alleen gevonden bij patiënten met schizofrenie, maar ook bij gezonde controles, echter met de kanttekening dat patiënten slechter scoorden op alle beoordeelde domeinen. Deze resultaten geven aan dat een geuridentificatie tekort een risicomarker zou kunnen zijn voor cognitieve/sociaal cognitieve problemen, aangezien

het onderliggende mechanisme dat geur identificatie tekorten en (premorbide) cognitieve/sociaal cognitieve problemen veroorzaakt, afhankelijk is van overlappende neurale substraten, in fronto–temporale hersenstructuren. Dit is niet specifiek voor schizofrenie.

In **hoofdstuk 6** beschrijven we onderzoek naar het premorbide (sociaal) cognitief functioneren in de kindertijd en adolescentie bij patiënten met schizofrenie, in relatie tot het metabool syndroom (MetS – een cluster van veel voorkomende aandoeningen: overgewicht/obesitas, hoge bloeddruk, verstoorde vetstofwisseling, verstoorde suikerstofwisseling – dat relatief vaak voorkomt bij schizofrenie patiënten, met name door een ongezondere leefstijl en genetische kwetsbaarheid). We vonden een vroege cognitieve achteruitgang, vóór de leeftijd van 16 jaar, bij schizofrenie patiënten met co–morbide MetS in vergelijking met schizofrenie patiënten zonder MetS. Interessant is dat deze vroege cognitieve achteruitgang bij patiënten met MetS ten opzichte van patiënten zonder MetS niet kon worden verklaard door verschillen in de sociaaleconomische status van de ouders. Het identificeren van risicofactoren voor het ontwikkelen van MetS bij schizofrenie patiënten is een belangrijk doel bij het verbeteren van de gezondheid en de verminderde levensverwachting, geassocieerd met schizofrenie, na het hebben van een eerste psychotische episode. De resultaten van dit onderzoek suggereren dat naast leefstijl en genetische factoren het cognitieve traject een essentiële factor is in relatie tot de prevalentie van MetS en mogelijk de basis vormt voor het toekomstige risico op metabole complicaties later in het leven, als schizofrenie is vastgesteld. Toekomstig onderzoek naar het verbeteren van de gezondheid van schizofrenie patiënten zou cognitief functioneren, en het verbeteren ervan in patiënten in acht moeten nemen.

In **hoofdstuk 7** hebben we een onderzoek uitgevoerd naar de relatie tussen MetS en structurele MRI–hersenvolumes, en specifiek van beloningsgebieden, bij schizofrenie patiënten. Schizofrenie patiënten met co–morbide MetS, schizofrenie patiënten zonder MetS en gezonde controles zijn geïncludeerd in de studie. We hebben ons met name gefocust op deze beloningsgerelateerde hersengebieden in relatie tot MetS in schizofrenie, aangezien het belonings–hersencircuit betrokken is bij beloning en risicoverwerking in gezondheidsgedrag, omdat MetS vaak een gevolg is van ongezond gedrag en omdat schizofrenie patiënten cognitief kwetsbaar zijn op het gebied van beloningsverwerking. We repliceerden dat patiënten kleinere hersenvolumes hadden in vergelijking met gezonde controles. Verder vonden we dat patiënten met schizofrenie en co–morbide MetS in vergelijking met degenen zonder MetS verkleinde belonings–hersengebieden hadden, wat suggereert dat afwijkingen in het brein gerelateerd kunnen zijn aan een verhoogde MetS prevalentie in schizofrenie.

De bevindingen van **hoofdstuk 6** en **hoofdstuk 7** doen vermoeden dat het verminderde hersenvolume en de bijbehorende cognitieve stoornissen hun oorsprong kunnen hebben vóór de ontwikkeling van het metabool syndroom in schizofrenie.

Hoofdstuk 8 vormt de samenvatting en discussie van de bevindingen van **hoofdstuk 2** tot en **7**. In dit proefschrift werden meerdere factoren gerelateerd aan uitkomst van psychose. Samenvattend is het duidelijk geworden dat voorspellers van symptomatische, algemene en fysieke uitkomsten een interactie van vele factoren betreft, met betrekking tot structurele hersenintegriteit (grijze en witte stof), premorbide functioneren, demografische eigenschappen, huidige en vroegere ernst van psychiatrische symptomen en co–morbiditeit (depressie), zorgbehoeften en (sociaal) cognitief functioneren. Sommige voorspellende modaliteiten leveren een veelbelovende bijdrage, zoals beloning–verwerking in het voorspellen van gezondheidsuitkomst; premorbide functioneren en (sociale) cognitie in het voorspellen van metabool syndroom en olfactorische identificatie; connectoom organisatie, zorgbehoeften, en huidige en vroegere ernst van symptomen in het voorspellen van symptomatische en globale uitkomst. Verder kan worden geconcludeerd dat geestelijke gezondheid en lichamelijke gezondheid niet te scheiden zijn in schizofrenie. Veel van dezelfde factoren die gerelateerd zijn aan geestelijke gezondheid uitkomsten waren ook van toepassing op fysieke uitkomsten, en omgekeerd. In **hoofdstuk 8** worden eveneens de klinische implicaties en potentieel toekomstig onderzoek besproken.

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CURRICULUM VITAE

Jessica de Nijs was born on July 12th 1984 in 's–Hertogenbosch. After graduating high school in 2002 (Gymnasium at the Jeroen Bosch College in 's–Hertogenbosch) she started a bachelor communication at the University of Nijmegen in 2002. After finishing the first year she switched to psychology at the University of Utrecht in 2004. In the bachelor she became interested in the field of neuropsychology and started her masters neuropsychology at the University of Utrecht. During this year she did an internship at the department of experimental psychology of the University of Utrecht, under the supervision of dr. Tanja Nijboer. After graduating in 2008, and after pursuing a carrier out of academia, in 2010, she started working as a research assistant and research coordinator at the Genetic Risk and Outcome of Psychosis study under the supervision of Wiepke Cahn and René Kahn at the psychiatry department of the University Medical Center Utrecht. In 2013 Jessica started her PhD research at the UMC Utrecht Brain Center, with Wiepke Cahn, René Kahn and Hugo Schnack as supervisors, which resulted in this thesis.