Understanding cognitive heterogeneity in psychosis and high risk individuals
Meijer, J.H.

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Although sub-acute effects of cannabis use may impair processing speed and working memory, lifetime cannabis using patients with psychosis seem to have a higher cognitive potential.

Cognitive deficits associated with lifetime stimulant use are dependent on the frequency of use in patients with psychosis, their unaffected relatives and controls.

While half of genetic high risk individuals experience some degree of cognitive impairment relative to controls, severe impairment seems to be restricted to a minority.

Olfactory identification deficits may reflect dopaminergic imbalance and therefore could be a risk marker in psychosis prediction.

Poor premorbid academic functioning before the age of nineteen is predictive of a broad-based cognitive impairment after psychosis onset.

The MATRICS is a valuable initiative to standardize cognitive assessment in patients with psychosis and possibly in UHR individuals, although the inclusion of tasks with less cognitive density would promote clinical utility.

Combining cognitive measures such as verbal fluency with structural brain imaging techniques may improve psychosis prediction in UHR individuals.
UNDERSTANDING COGNITIVE HETEROGENEITY IN PSYCHOSIS AND HIGH RISK INDIVIDUALS

JULIA H. MEIJER
Understanding Cognitive Heterogeneity in Psychosis and High Risk individuals

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit van Amsterdam op gezag van de Rector Magnificus prof. dr. D.C. van den Boom
ten overstaan van een door het college voor promoties ingestelde commissie, in het openbaar te verdedigen in de Aula der Universiteit op woensdag 19 september 2012, te 13:00 uur

doors

Julia Helene Meijer

geboren te Amsterdam
PROMOTIECOMMISSIE

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Faculteit der Geneeskunde
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INTRODUCTION
1. INTRODUCTION

1.1 The schizophrenia concept

Schizophrenic disorders are chronic and severe mental conditions that affect 26 million people worldwide and are the cause of moderate to severe disability in 60% of cases (Eaton et al., 2008). Due to their early onset and debilitating effects, schizophrenic disorders rank fifth among men and sixth among women as a leading cause of years lived with disability (Lora et al., 2012). Despite the diversity in pathogenesis, symptoms and course, the syndrome is invariably characterized by recurrent distortions in reality testing. These so-called “positive symptoms” relate to experiences such as hallucinations, delusions, bizarre behaviour and disorganization (APA, 2000). In addition, the clinical presentation of schizophrenia is characterized by the occurrence of (i) negative symptoms including avolition, affective flattening and social withdrawal, (ii) cognitive symptoms and (iii) affective symptoms (van Os and Kapur, 2009). Lifetime prevalence of schizophrenia is about 0.8-1% and incidence is 0.2-0.4 per 1000, with peak incidence during the third decade of life (Mueser and McGurk, 2004). Although prevalence is roughly equal in both sexes, women tend to have a later disease onset, better social functioning and a more favourable illness course (Mueser and McGurk, 2004). The high heritability (80%) of schizophrenia is not due to genetic influences per se but also to genotype-environment interactions that can be defined as “genetic control of sensitivity to environmental factors”, or as “environmental control of gene expression” (Kendler and Eaves, 1986). In a genotype–environment interaction, the disorder will tend to cluster in families not because of a direct genetic effect, but because relatives are more vulnerable to the risk-increasing effect of a prevalent environmental factor (van Os and Marcelis, 1998). Known environmental risk factors include pre- and perinatal factors, cannabis use, urbanicity and social isolation (Mueser and McGurk, 2004; van Os et al., 2010).

1.2 Cognitive functioning as core deficit in schizophrenia

Although cognitive deficits are not yet included in the diagnostic criteria for schizophrenia (APA, 2000), they are considered a core feature of schizophrenia symptomatology (Elvevag and Goldberg, 2000). More than a century ago, when schizophrenia was first defined in its current form, it was called dementia praecox, the focus being on the intellectual deterioration that accompanied the syndrome (Kraepelin, 1919). In the following years, the focus shifted to the more easily identifiable positive symptoms. During the past decade however, there has been a resurgence of interest in the cognitive alterations in patients with schizophrenia. This development may be explained by the notion that cognitive deficits are better predictors of functional outcome such as work performance and independent living than positive symptoms (Green et al., 2000; Harvey et al., 1998).

It has been found repeatedly that patients with a diagnosis of schizophrenia show a generalized impairment across a range of cognitive abilities including attention, processing speed, verbal learning and memory, working memory and executive functions (Elvevag and Goldberg, 2000; Mesholam-Gately et al., 2009; Heinrichs and Zakzanis, 1998). The degree of
impairment depends on the domain measured, with verbal memory and processing speed showing the largest deficits with effect sizes ranging from 1.3 to 1.6 (Heinrichs and Zakzanis, 1998; Mesholam-Gately et al., 2009).

The neurodevelopmental model of schizophrenia suggests that cognitive deficits are a proximal manifestation of aberrant brain maturational processes that occur prior to the onset of the full clinical syndrome (Marenco and Weinberger, 2000). Likewise, children who will eventually develop schizophrenia exhibit subtle cognitive deficits of around -0.5 SD relative to their peers as early as seven years of age (Seidman et al., 2006; Keefe and Fenton, 2007). These cognitive deficits become more pronounced (around -1 SD) during the prodromal phase and first psychotic episode, after which they stabilize over the long-term course of the illness (Hoff et al., 2005; Lewandowski et al., 2011). Cognitive deficits have been associated with higher levels of negative symptoms, are at best marginally influenced by antipsychotic medication, and often persist despite complete resolution of positive symptoms (Szoke et al., 2008). Therefore, strategies are currently being developed to improve cognitive functions, either through pharmacological treatment or cognitive rehabilitation programmes.

1.3 Cognitive functioning in Genetic High Risk studies

Two major types of “high risk” strategies exist to better understand the development of psychosis and to improve detection and treatment strategies. The first is the genetic high risk approach, focusing on unaffected first-degree relatives of schizophrenia patients who have around 4 to 10% chance of developing the disease themselves (Gottesman, 1991). Generally, unaffected relatives display cognitive functioning intermediate to probands and healthy controls, with effect sizes ranging from 0.3 to 0.6 (Snitz et al., 2006; Seidman et al., 2010; Szoke et al., 2005). Largest effect sizes have been found on domains of verbal learning, sustained attention and semantic verbal fluency (Snitz et al., 2006) and effect sizes are comparable for offspring, siblings and parents.

These subtle cognitive deficits in unaffected relatives are currently considered as putative endophenotypes that might facilitate the identification of genetic factors involved in the vulnerability to schizophrenia (Gur et al., 2007). The endophenotype approach proposes that strictly defined neurobiological features of schizophrenia may reflect more direct expressions of genetic polymorphisms than clinical manifestations such as positive symptoms (Joyce and Roiser, 2007). Although several studies have identified putative cognitive endophenotypes, genetically sensitive studies that test the validity of these concepts have been limited so far.

1.4 Cognitive functioning in Ultra High Risk studies

The second type of high risk studies is a clinical approach identifying help-seeking adolescents or young adults who have not yet manifest psychosis, but subthreshold schizophrenia-like symptoms or other potentially prodromal signs. During the prodromal period, mood, cognitive, psychosocial and mild positive symptoms may appear (Yung et al.,
The most widely applied set of inclusion criteria for these kind of studies is defined by the ultra high-risk (UHR) approach and consists of (i) attenuated psychotic symptoms, (ii) brief intermittent psychotic symptoms, or (iii) a substantial drop in social/role functioning in conjunction with schizotypal personality disorder or a first-degree relative with psychotic disorder (Yung et al., 2005). Individuals who fulfil the UHR criteria have a 12-50% risk of developing psychosis within the following years (Yung et al., 2007). Cross-sectional UHR studies have consistently documented that neuropsychological deficits are intermediate between controls and first-episode psychosis patients, with effect sizes in the moderate range (Seidman et al., 2010; Simon et al., 2007). These deficits appear to be associated with functional disability in a manner parallel to that observed in established psychosis (Niendam et al., 2006). Additionally, it has been found that individuals in late prodromal stages show greater deficits compared with those in early prodromal stages (Simon et al., 2007). The issue however remains whether cognitive functioning may predict future transition to psychosis. While some studies found that UHR individuals who subsequently developed psychosis had worse cognitive performance at baseline in comparison to non-converters (Seidman et al., 2010; Eastvold et al., 2007), other studies did not confirm these results (Keefe et al., 2006; Hawkins et al., 2008). Longitudinal studies that compare cognitive functioning in UHR individuals who do and do not convert to psychosis have been limited by small samples and brief follow-up periods, which may have accounted for inconsistent results (Seidman et al., 2010).

1.5 Aim of the thesis

The overall aim of the studies described in this thesis was to increase our understanding of the variation in cognitive disturbances in psychosis and high risk populations. While cognitive impairment is present in most persons with schizophrenia, there is substantial inter-patient heterogeneity and this also holds for clinical and genetic high risk samples. Clarifying this phenotypic heterogeneity in the cognitive domain is needed to identify putative endophenotypes that may help to unravel the genetic background of the disorder, to improve psychosis prediction in at-risk individuals and to better direct treatment approaches towards specific patient groups. In the first part of this thesis we will examine how cognitive functioning is associated with different clinical variables. More specifically, associations will be studied between cognitive functioning and the two most frequently used substances (cannabis and stimulants), obsessive compulsive symptoms, and extrapyramidal symptoms. In the second part of this thesis the focus shifts to genetic and clinical high risk populations. Here we will address the impact of the cognitive impairment in patients with psychosis compared to their unaffected siblings and parents. Additionally we will investigate how level of functioning before the age of nineteen is linked to adult cognitive functioning in patients and their relatives. Furthermore, we will examine the size of the cognitive impairment in UHR individuals by the use of a standardized cognitive battery developed for schizophrenia. Finally we will examine whether combining structural MRI with a verbal fluency task may be of additional value for psychosis prediction in UHR subjects.
The following research questions will be addressed in this thesis:

**PART I**

**Chapter 2:** What is the association between current and lifetime cannabis use and cognitive functioning in patients with non-affective psychosis, their unaffected siblings and controls?

**Chapter 3:** What is the association between current and lifetime stimulant use and cognitive functioning in patients with non-affective psychosis, their unaffected siblings and controls?

**Chapter 4:** Is comorbid obsessive-compulsive symptomatology in patients with non-affective psychosis and their unaffected relatives associated with cognitive functioning?

**Chapter 5:** Are odour identification deficits in patients with non-affective psychosis associated with symptoms of parkinsonism?

**PART II**

**Chapter 6:** What is the size of the cognitive deficit in patients with psychosis compared to their unaffected first-degree relatives and healthy controls?

**Chapter 7:** What is the association between current cognitive functioning and adjustment to social and academic situations before the age of nineteen years in patients with non-affective psychosis and their unaffected siblings?

**Chapter 8:** Is the Dutch translation of the Measurement And Treatment Response Initiative to Improve Cognition in Schizophrenia (MATRICS) able to differentiate between patients with psychosis, UHR patients and healthy controls?

**Chapter 9:** Is the association between semantic verbal fluency performance and grey matter density different between UHR subjects that do and do not develop a psychotic disorder during follow-up?

**REFERENCE LIST**


prediction: 12-month follow up of a high-risk ("prodromal") group. Schizophr Res. 60, 21-32.


CANNABIS AND COGNITIVE PERFORMANCE IN PSYCHOSIS: A CROSS-SECTIONAL STUDY IN PATIENTS WITH NON-AFFECTIVE PSYCHOTIC ILLNESS AND THEIR UNAFFECTED SIBLINGS

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GROUP investigators: René S. Kahn, Don H. Linszen, Jim van Os, Durk Wiersma, Richard Bruggeman, Wiepke Cahn, Lieuwe de Haan, Lydia Krabbendam and Inez Myin-Germeys

ABSTRACT

Background: Studies of the relationship between cannabis use and cognitive functioning in patients with psychosis have yielded contradictory findings. In individuals at genetic high risk for psychosis, information is sparse. The aim of this study was to assess the association between recency and frequency of cannabis use and cognitive functioning in patients with psychosis and their unaffected siblings.

Method: We conducted a cross-sectional study in 956 patients with non-affective psychosis, 953 unaffected siblings and 554 control subjects. Participants completed a cognitive test battery including assessments of verbal learning, set shifting, sustained attention, processing speed, working memory, acquired knowledge, reasoning and problem solving and social cognition. Cannabis use was assessed by urinalysis and by the Composite International Diagnostic Interview. Using random-effect regression models the main effects of cannabis (recency and frequency) and the interaction with status (patient, sibling, control) on cognitive functioning were assessed.

Results: Current cannabis use was associated with poorer performance on immediate verbal learning, processing speed and working memory (Cohen's d -0.20 to -0.33, p<0.005). Lifetime cannabis use was associated with better performance on acquired knowledge, facial affect recognition and face identity recognition (Cohen's d+0.17 to +0.33, p<0.005). There was no significant interaction between cannabis and status on cognitive functioning.

Conclusion: Lifetime cannabis-using individuals might constitute a subgroup with a higher cognitive potential. The residual effects of cannabis may impair short-term memory and processing speed.
INTRODUCTION

Cognitive impairment is recognized as a core feature of schizophrenia (Green, 1996; Palmer et al. 2009). Mild cognitive alterations are also observed in unaffected relatives of patients who are at increased risk to develop a psychotic disorder (Snitz et al. 2006). In both patients with psychosis and their unaffected siblings, cannabis use is more prevalent than in the general population (Barnes et al. 2006; Smith et al. 2008). In patients with psychosis, cannabis use has been associated with worse disease outcome (Linszen et al. 1994). In unaffected siblings the psychotomimetic effect of cannabis is increased compared to control subjects, suggesting that familial liability to psychosis is associated with sensitivity to cannabis (van Winkel, 2011; Genetic Risk and Outcome of Psychosis (GROUP) Investigators, 2011). Whether cannabis use is also associated with cognitive alterations in patients with psychosis and their unaffected relatives is however still a matter of debate.

Acute administration of the major psychoactive component in cannabis (Δ9-tetrahydrocannabinol; THC) has been shown to cause impaired attention and memory in schizophrenia patients and their unaffected siblings (D’Souza et al. 2005; Henquet et al. 2006). These impairments in patients and siblings were larger compared to those in healthy controls, suggesting an increased sensitivity to the adverse cognitive effects of acute cannabinoid administration. On the contrary, better cognitive functioning has also been reported in cannabis using patients compared to non-using patients on tasks of planning and reasoning, visual memory, processing speed, global cognition and working memory (Coulston et al. 2007a; Potvin et al. 2008; Loberg and Hugdahl, 2009; Yücel et al. 2010).

This superior cognitive functioning in cannabis using patients seems counterintuitive given the deleterious cognitive effects that have been reported in cannabis using control subjects (Solowij and Michie, 2007; Morrison et al. 2009). Two hypotheses attempt to explain these results. First, it has been suggested that cannabis improves cognition, either by counteracting a putative neurotoxic process related to schizophrenia, or by stimulating prefrontal neurotransmission (Verrico et al. 2003; Jockers-Scherubl et al. 2007; Coulston et al. 2007a; Coulston et al. 2007b; Potvin et al. 2008; Cohen et al. 2008). Secondly, it has been suggested that causality is the other way around. In this view, patients with psychotic disorder and lifetime cannabis use may form a subgroup with a relatively lower genetic vulnerability for psychosis and better premorbid functioning compared to patients who have never used cannabis (Schnell et al. 2009; de la Serna et al. 2010; Yücel et al. 2010).

Elucidating the association between cannabis use and cognitive functioning in patients and individuals at genetic high risk for psychosis is of both theoretical and clinical relevance (Loberg and Hugdahl, 2009). Whilst spared cognitive functioning through cannabis use would be relevant for the development of cognitive enhancing medication, a further cognitive decline associated with cannabis use should stimulate development of interventions aiming at a reduction of cannabis use.

It seems essential to account for the recency of cannabis use in studies on the association between cannabis and cognitive functioning, since contradictory findings between acute administration and lifetime cannabis use have been found (D’Souza et al. 2005; Henquet et al. 2006; Coulston et al. 2007a; Potvin et al. 2008; Loberg and Hugdahl, 2009; Yücel et al. 2010).
In addition, the frequency of cannabis use should be taken into account in order to investigate dose-response relationships (Coulston et al. 2007a). Thus, the aim of the present study was to investigate if cognitive performance differs between cannabis users and non-users depending on the recency and frequency of use. Moreover, we wanted to investigate whether these associations are different in patients with non-affective psychosis, their unaffected siblings and control subjects. Our first hypothesis was that current cannabis use would be associated with worse cognitive functioning in the three Status groups (patient, sibling, control), and that this association would be stronger with increasing frequency of use over the past year. Our second hypothesis was that there would be an interaction between Status and Cannabis in lifetime users. We expected lifetime cannabis use to be associated with better cognitive functioning in patients as suggested by Yücel et al. (2010), while we expected no such association in siblings and controls.

METHODS

Study design and population

Data pertain to baseline measures of a longitudinal study (Genetic Risk and Outcome in Psychosis [GROUP]) in the Netherlands and Belgium. In selected representative geographical areas, patients were identified through clinicians working in regional psychotic disorder services whose caseloads were screened for inclusion criteria. Subsequently, a group of patients presenting consecutively at these services as either outpatients or inpatients were recruited for the study. Controls were selected through a system of random mailings to addresses in the catchment areas of the cases.

Inclusion criteria for patients, siblings and controls were (1) age range of 16 to 50 years and (2) good command of the Dutch language. Patients had to meet DSM-IV-TR criteria for a non-affective psychotic disorder (APA 2000) which was assessed with the Comprehensive Assessment of Symptoms and History interview (CASH; Andreasen et al. 1992) or the Schedules for Clinical Assessment in Neuropsychiatry version 2.1 (SCAN; Wing et al. 1990). Exclusion criteria for healthy controls were a history of psychotic disorder or a first-degree family member with a history of psychotic disorder.

The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and subsequently by local review boards of each participating institute. All of the subjects gave written informed consent in accordance with the committee’s guidelines.

Substance use and clinical symptoms

Substance use was assessed with a short version of the Composite International Diagnostic Interview (CIDI; World Health Organization 1990) sections B (tobacco use), J (alcohol use) and L (substance use), and with urinalysis. Urine was screened for the presence of THC with a cut off of 50ng/ml, in order to infer a detection window of one month. Cannabis Recency was categorized as current (urinalysis positive for THC), lifetime (urinalysis negative AND
cannabis use ≥ 5 times lifetime based on the CIDI), and never (urinalysis negative and cannabis use < 5 times lifetime based on the CIDI). Although this latter group may have included subjects who had limited experience with cannabis, for simplicity this group is referred to as ‘never-users’. Cannabis Frequency over the past year was categorized as daily, weekly, or less than weekly, based on the CIDI. Severity of positive and negative symptoms in patients was rated with the Positive and Negative Syndrome Scale (PANSS) with total scores for positive, negative and general symptoms (Kay et al. 1987).

**Cognitive assessment**

The cognitive assessment took 90 to 120 minutes. Subjects were administered 10 cognitive tasks that yielded 13 outcome parameters which were used as dependent variables in the analyses. Verbal learning was assessed using the Word Learning Task (WLT; Brand et al. 1985) with outcome parameters of immediate recall (15-word list, 3 learning trials) and retention rate after 20 minutes. Set shifting ability was assessed using the Response Shifting Task (RST), a modified version of the Competing Programs Task (Bilder et al. 1992; Nolan et al. 2004) with outcome parameters of reaction time and accuracy. Sustained visual attention and vigilance was assessed using the Continuous Performance Task-HQ (CPT-HQ; Nuechterlein et al. 1984) with outcome parameters of reaction time and accuracy. The following subtests of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler 1997) were assessed: Digit-Symbol Coding as a measure of processing speed, Arithmetic as a measure of working memory, Information as a measure of acquired knowledge and Block Design as a measure of reasoning and problem solving. The Degraded Facial Affect Recognition Task (DFAR; Van ’t Wout et al. 2004) was used to assess recognition of neutral, happy, fearful and angry emotions. The Benton Face Recognition Task (BFRT; Benton et al. 1983) was used to assess visuospatial discrimination of unfamiliar faces. The Hinting Task (Versmissen et al. 2008) was used to assess theory of mind.

**Statistical procedures**

Differences in demographic and substance use characteristics between patients, siblings and controls were tested with one way analysis of variance (ANOVA) or $\chi^2$ tests. Differences in demographic and clinical characteristics between cannabis using patients (current and lifetime combined) and never using patients were tested with independent t-tests and $\chi^2$ tests. These tests were two-tailed with a significance level of 0.05.

Furthermore, we used a three step procedure to assess the effect of Status (patient, sibling, control) and Cannabis Recency (current, lifetime, never) on cognitive functioning in the entire study sample ($n=2463$). In the first step we built a random effect regression model for each cognitive functioning outcome. Cognitive functioning was the dependent variable and Status, Cannabis Recency, and the Status by Cannabis Recency interaction were independent variables as the fixed part of the model. To take dependency of the data into account, because of intra-family correlation between patients and siblings, family was entered as a random factor with a random intercept into this regression model. For the effect of Status, controls were set as the reference category, against which patients and siblings were compared. For the effect of Cannabis Recency, never users were set as the reference category, against which current and
lifetime users were compared. Additionally, regression analyses were repeated with current users as the reference category in order to test significant differences between current and lifetime cannabis user groups.

A similar model was built for the 612 subjects who had used cannabis in the preceding year to assess the effect of Cannabis Frequency (daily, weekly, less) on cognitive functioning. Frequency of use over the past year was chosen over frequency of lifetime use, because self report over a more recent period is less likely to be subject to recollection bias. Moreover, any frequency effects of cannabis use may be confounded by the time that has elapsed since the last use. While this timeframe may be highly variable in lifetime users (up to ten years or more), in past year users this is limited. Cognitive functioning was the dependent variable and Status, Cannabis Frequency, and the Status by Cannabis Frequency interaction were independent variables as the fixed part of the model. Family was entered as a random factor with a random intercept. Less than weekly users were set as a reference category, against which the more frequent user groups were compared.

In the second step we identified relevant confounders. Potential confounders that have been mentioned previously (Coulston et al. 2007b; Potvin et al. 2008) were entered separately into the regression models as covariates. A potential confounder was considered a true confounder if adding the confounder to the regression model changed the effect estimates by 10% or more. The following covariates were tested: age, gender, heavy alcohol use (>14 units weekly for women and >20 units weekly for men), current nicotine use, a history of illicit substance use other than cannabis over the past year (cocaine, amphetamines, XTC, opiates, inhalants, hallucinogens), and highest parental education (ranging from 1 = primary school to 8 = university). In analyses with the Degraded Facial Affect Recognition task as the dependent variable, the scores on the Benton Face Recognition Task were added to the covariate set in order to differentiate facial affect recognition from non-emotional face processing skills.

In the third step the covariate set was added to the fixed part of the random effect regression models. If the Status by Cannabis Recency (or Cannabis Frequency) interaction term was not statistically significant, it was removed from the model and analyses were repeated with the random effect model containing only the main effects and covariates.

Since the 13 cognitive outcome parameters came from 10 cognitive tests, we divided the alpha level for the statistical tests by 10. Adjustment for 13 comparisons was considered too conservative, since outcome parameters derived from the same test were strongly correlated (e.g. Accuracy and Reaction Time as two outcome parameters of the CPT-HQ and the RST). Due to the high power caused by the large n, effect sizes (Cohen’s d) were calculated to distinguish relevant effects from trivial but statistically significant effects.

Normality of the dependent variables (cognitive functioning) was checked visually with histograms and box plots and confirmed if the test-statistic W in the Shapiro Wilk test exceeded 0.90. Eleven out of thirteen dependent variables were normally distributed. Due to ceiling effects, parameters for CPT Accuracy and the Hinting Task were not normally distributed. Since a logarithmic transformation did not result in a normal distribution these scores were dichotomized into ‘affected’ and ‘unaffected’ individuals. ‘Affected’ for the CPT Accuracy (range 0-100%) was defined as <100% accurate responses (=51.6% of total sample) and for
the Hinting Task (range 0-20) as a score <20 (≈57.8% of total sample). Generalized estimating equations (GEE) analyses were used to assess the effect of the independent variables on these two dichotomous outcomes (Hanley et al. 2003). The GEE models were analyzed in addition to the random effect regression models and built in the same way. To minimize the risk of type I errors, the analysis yielding the most conservative results for these two cognitive outcomes was selected for the discussion. Analyses were performed using SPSS 17.0 for Windows.

RESULTS

Characteristics of the study sample

The GROUP sample consisted of 1120 patients with non-affective psychotic disorder, 1057 siblings of these patients and 590 unrelated controls. Subjects that had not performed cognitive testing (n=42) and subjects without a valid drug urine screening (n=255) were excluded from the current study. Seven subjects with a negative urine screening were excluded because information on lifetime cannabis use was missing. Analyses were performed on the remaining 2463 subjects (956 patients, 953 unaffected siblings, 554 controls). DSM-IV-TR diagnoses of the patients were as follows: schizophrenia (DSM-IV 295.1/ 295.2/ 295.3/ 295.6/ 295.9; n=681, 71.2%), schizoaffective disorder (DSM-IV 295.7; n = 111, 11.6%), other psychotic disorders (DSM-IV 297/ 298; n= 145, 15.2%) and psychotic illness in the context of substance-abuse or somatic illness (n=8, 0.8%). Eleven patients (1.2%) had a final diagnosis of affective psychosis although fulfilling criteria for a clinical diagnosis of non-affective psychosis at study entry.

As presented in Table 1, control subjects were older (30.2 years) than patients (27.3 years) and siblings (27.9 years). Males were overrepresented in the patient group (76.4%) compared to siblings (45.4%) and controls (45.5%). Parental educational degree and subject educational degree was lowest in patients. Of all subjects, 38.3% (n=943) had used cannabis lifetime and 10.5% (n=258) were current cannabis users. Patients and siblings were more likely to be current or lifetime cannabis users compared to controls. Regarding the frequency of cannabis use over the past year, patients and siblings were more likely to be daily users compared to controls. Patients were also more likely to be using nicotine or illicit substances compared to siblings and controls. Groups did not differ in the proportion of heavy alcohol users. Table 2 shows that patients with current or lifetime cannabis use were 2.4 years younger and more often male compared to never using patients. Current and lifetime cannabis using patients had lower functioning on the GAF disability scale (52.9 vs. 58.3), higher PANSS positive symptoms (14.6 vs. 12.4), but similar PANSS negative symptoms compared to patients who had never used cannabis. In both groups around 85% of patients received treatment with antipsychotics.

Cannabis Recency

In the current user group (n=258), 59.4% was using daily, 30.3% weekly and 10.3% less than weekly. The lifetime user group (n=943) consisted of 44.1% daily users, 25.7% weekly users and 30.2% less than weekly users. The never user group consisted of 1262 subjects. The interaction term between Status (patient, sibling, control) and Cannabis Recency (current,
Table 1. Demographic variables of patients, siblings and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 956)</th>
<th>Siblings (n = 953)</th>
<th>Controls (n = 554)</th>
<th>F (df) or χ² (df)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (S.D.)</td>
<td>27.3 (7.4)</td>
<td>27.9 (8.3)</td>
<td>30.2 (10.5)</td>
<td>21.6 (2, 2459)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>76.4</td>
<td>45.4</td>
<td>45.5</td>
<td>229.0 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Education, % lowest (% highest)</td>
<td>12.3 (4.3)</td>
<td>7.1 (12.0)</td>
<td>2.2 (9.4)</td>
<td>244.5 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parental education, % lowest (% highest)</td>
<td>6.7 (18.3)</td>
<td>5.1 (18.8)</td>
<td>4.3 (16.1)</td>
<td>35.22 (16)</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td>Nicotine use, %</td>
<td>66.4</td>
<td>37.5</td>
<td>25.5</td>
<td>282.4 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heavy alcohol use, %</td>
<td>10.9</td>
<td>9.0</td>
<td>7.7</td>
<td>4.6 (2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Other substance use, %</td>
<td>20.4</td>
<td>7.8</td>
<td>6.0</td>
<td>97.09 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cannabis recency (n = 2463)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current, %</td>
<td>16.3</td>
<td>7.9</td>
<td>4.9</td>
<td>60.16 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lifetime, %</td>
<td>49.8</td>
<td>33.4</td>
<td>26.9</td>
<td>93.82 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Never, %</td>
<td>33.9</td>
<td>58.7</td>
<td>68.2</td>
<td>200.49 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cannabis frequency past year (n = 612)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily, %</td>
<td>48.3</td>
<td>25.6</td>
<td>19.5</td>
<td>38.71 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weekly, %</td>
<td>26.6</td>
<td>28.3</td>
<td>30.5</td>
<td>0.57 (2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Less, %</td>
<td>25.1</td>
<td>46.1</td>
<td>50.0</td>
<td>32.12 (2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

df, degrees of freedom; S.D., standard deviation; n.s., non-significant.

Table 2. Demographic and clinical variables of patients with and without a lifetime history of cannabis use

<table>
<thead>
<tr>
<th></th>
<th>Cannabis use (lifetime + current) (n=632)</th>
<th>Never cannabis use (n=324)</th>
<th>t (df) or χ² (df)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (S.D.)</td>
<td>26.5 (6.4)</td>
<td>28.9 (8.7)</td>
<td>4.9 (954)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Gender, % male</td>
<td>86.1</td>
<td>57.4</td>
<td>97.5 (1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Education, % lowest (% highest)</td>
<td>15.2 (3.0)</td>
<td>6.8 (6.8)</td>
<td>34.1 (8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parental education, % lowest (% highest)</td>
<td>7.1 (19.0)</td>
<td>5.9 (17.0)</td>
<td>11.9 (8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mean GAF disability (S.D.)</td>
<td>52.9 (16.0)</td>
<td>58.3 (15.5)</td>
<td>4.8 (919)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean PANSS positive scale (S.D.)</td>
<td>14.6 (6.7)</td>
<td>12.4 (5.7)</td>
<td>-4.9 (930)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean PANSS negative scale (S.D.)</td>
<td>15.2 (6.6)</td>
<td>14.7 (6.4)</td>
<td>-1.2 (930)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Antipsychotic treatment, % yes</td>
<td>86.3</td>
<td>84.9</td>
<td>2.0 (2)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

df, degrees of freedom; S.D., standard deviation; n.s., non-significant; GAF, Global Assessment of Functioning; PANSS, Positive and Negative Syndrome Scale.
We illustrate this with an example. On the Word Learning Test—immediate recall (WLT-IR) patients score -0.95 SD from control mean (Figure 1c). Moreover, current cannabis users score -0.2 SD from never users (Figure 1a). Therefore, the mean score of current cannabis using patients lays -1.15 SD from the mean score of never using controls.

**Fig. 1.**
(a) Main effects of cannabis recency on cognitive functioning: ••--, current users; -■-, lifetime users; -A-, never-users. Effects that remained significant after correction for multiple comparisons (p<0.005) in current/lifetime users compared with never-users are circled. (b) Main effects of cannabis frequency on cognitive functioning: -■-, daily; - -•- -, weekly; -A-, monthly. (c) Main effects of status on cognitive functioning: --•--; -, patients; -■-, siblings; -A-, controls. WLT IR, Word Learning Task immediate recall; WLT RR, Word Learning Task retention rate; RST RT, Response Shifting Task reaction time; RST Acc, Response Shifting Task accuracy; CPT RT, Continuous Performance Task-HQ reaction time; CPT Acc, CPT-HQ accuracy; DS coding, Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) digit-symbol coding; Arithm, WAIS-III arithmetic; Inform, WAIS-III information; Block, WAIS-III block design; Affect Rec, Degraded Facial Affect Recognition total score; Face Rec, Benton Face Recognition; Hinting, Hinting task; F, test statistic from mixed-model regression analyses; df, degrees of freedom.
while siblings performed intermediate to patients and controls on selected tasks. Figure 1a demonstrates that, while taking the main effect of Status into account, current cannabis users performed significantly worse compared to never users on the Word Learning Task-immediate recall (d=−0.20), WAIS-III Digit-Symbol Coding (d=−0.22) and WAIS-III Arithmetic (d=−0.20). Lifetime cannabis users performed better than never users on WAIS-III Information (d=+0.17), the Degraded Facial Affect Recognition task (d=+0.33) and the Benton Face Recognition Task (d=+0.21). In addition, current cannabis users performed significantly better than never users on WAIS-III Information (d=+0.19). Repeating the analyses after changing the reference category to current users yielded significant differences between current and lifetime users for Digit-Symbol Coding (d=+0.15, p<0.011) and for the Word Learning Task-immediate recall (d=+0.18, p<0.001), the latter of which remained significant after adjusting for multiple comparisons.

GEE analyses confirmed the mixed-model regression results for the not normally distributed data. For CPT-accuracy, the proportion of ‘affected’ individuals was not significantly different within current (58.8%), lifetime (53.1%) and never users (49.0%), Wald χ²(2)=0.98, p=0.61. Also for the Hinting Task, the proportion of ‘affected’ individuals was not significantly different within current (64.0%), lifetime (60.0%) and never users (54.8%), Wald χ²(2)=0.35, p=0.84.

Cannabis Frequency

The interaction term between Status (patient, sibling, control) and Cannabis Frequency (daily, weekly, less) was not statistically significant for any of the cognitive variables and was therefore removed from the regression models. In the resulting model, including Status, Cannabis Frequency and relevant confounders, there was no significant effect of Cannabis Frequency on any of the cognitive parameters (Figure 1b). GEE analyses confirmed the mixed-model regression results for the not normally distributed data. For CPT-Accuracy, the proportion of ‘affected’ individuals was not significantly different within daily (57.1%), weekly (59.6%) and less frequent users (52.6%), Wald χ²(2)=1.87, p=0.39. For the Hinting Task, the proportion of ‘affected’ individuals was not significantly different within daily (70.7%), weekly (60.5%) and less frequent users (60.9%), Wald χ²(2)=1.74, p=0.42.

Status

Although not a primary aim of this study, the main effects of Status on cognitive functioning are outlined in Figure 1c in order to facilitate interpretation of the results. The main effects of Cannabis (Recency and Frequency) have been assessed in random effect regression models together with the main effect of Status and the interaction between Cannabis and Status. The interaction terms were nonsignificant and main effects of Cannabis and Status on cognitive functioning should thus be added. We illustrate this with an example. On the Word Learning Test-immediate recall (WLT-IR) patients score -0.95 SD from control mean (Figure 1c). Moreover, current cannabis users score -0.2 SD from never users (Figure 1a). Therefore, the mean score of current cannabis using patients lays -1.15 SD from the mean score of never using controls.
The aim of this cross-sectional study was to investigate how recency and frequency of cannabis use are associated with cognitive performance in patients with non-affective psychosis, their unaffected siblings and control subjects. In line with our first hypothesis, current cannabis use was associated with worse performance on immediate verbal learning, processing speed and working memory and this association did not differ between the three Status groups. However, against our expectations, an increasing frequency of cannabis use over the past year was not associated with worse cognitive performance. Our second hypothesis was partly supported. While lifetime cannabis use was indeed associated with better performance on acquired knowledge, affect recognition and face identity recognition in patients, this association also applied to unaffected siblings and controls. Effect sizes of these associations were in the small range which may explain why previous studies that included smaller sample sizes have found contradictory results (Coulston et al. 2007b). The interpretation of the results is discussed here. As the comparison of cognitive performance between patients, siblings and controls (Figure 1c) was not the primary aim of this study, we refer to our baseline study on cognitive assessment in GROUP for further interpretation of these results (Meijer et al. submitted).

A negative association between cognitive functioning and current- but not lifetime-cannabis use is likely to result from a residue of cannabinoids in the central nervous system. Worse immediate verbal learning in current cannabis users is in agreement with other studies in patients with psychotic illness (Liraud and Verdoux, 2002; Pencer and Addington, 2003; D’Souza et al. 2005; Sevy et al. 2007; Jockers-Scherubl et al. 2007; Coulston et al. 2007a; Yücel et al. 2010). Also in healthy controls, immediate verbal learning is one of the cognitive functions most affected by acute cannabis administration and congruent with our results, this effect appears to be transient after four weeks of abstinence (Grant et al. 2003; Solowij and Michie, 2007).

In contrast with our finding of worse processing speed in current users, the majority of studies in schizophrenia patients reported either absent, or even positive effects of both current and lifetime cannabis use on visual processing speed (Sevy et al. 2007; Jockers-Scherubl et al. 2007; Coulston et al. 2007a; Schnell et al. 2009; DeRosse et al. 2010). Positive associations in those studies might have been driven by higher premorbid cognitive functioning in cannabis using patients (Fried et al. 2005; Schnell et al. 2009). Our finding that current- but not lifetime-cannabis users show worse processing speed is however in agreement with evidence from studies in control subjects (Ehrenreich et al. 1999; Fried et al. 2005).

Similar to our findings, recent cannabis use in schizophrenia patients has been associated with worse working memory (Ringen et al. 2010), but absent or positive associations have also been reported (Sevy et al. 2007; Mata et al. 2008; Scholes and Martin-Iverson, 2010). Opposite findings may have resulted from differing sample sizes or the heterogeneity of working memory measures that have been used. WAIS-III Arithmetic may be regarded as a relatively complex measure of working memory, with split loadings on processing speed and verbal comprehension (Tellegen, 2003). Our findings are supported by studies in control subjects that reported impaired working memory following intravenous THC administration and cannabis
smoking (Ilan et al. 2004; Morrison et al. 2009), while lifetime cannabis use was not associated with working memory impairments (Scholes and Martin-Iverson, 2010).

Of those subjects who had used cannabis over the past year, daily or weekly users did not perform significantly different compared to less frequent users. Although these findings seem counterintuitive, they are corroborated by the literature in schizophrenia patients (Rodriguez-Sanchez et al. 2010) and in healthy subjects (Pope, Jr. et al. 2002). Tolerance for the adverse cognitive effects of cannabis in more frequent users might have accounted for the absence of a dose-response relationship on cognitive functioning (Ramaekers et al. 2009). Another explanation may be that the subdivision of frequency into daily, weekly and less frequent use was not sensitive enough to detect a dose-response relationship.

Our finding that lifetime cannabis use was not associated with worse cognitive functioning is in line with a recent review that reported no convincing evidence for sustained cognitive impairments in adult abstinent cannabis users (Van Holst and Schilt, 2011). On the other hand, both current and lifetime cannabis users performed better than never users on acquired knowledge. Better acquired knowledge in current users may reflect the fact that current users are also lifetime users, since it is unlikely that they started using cannabis in the past month. In addition, we found that lifetime cannabis users performed better than never users on tasks of facial affect recognition and face identity recognition. Research on the association between cannabis use and facial affect and identity processing is sparse in both patients and controls. One study reported that patients who had used cannabis prior to psychosis onset showed a relative sparing of face identity recognition at 10-12 year follow-up, but this difference was lost after co-varying for age at psychosis onset (Stirling et al. 2005). In non-psychotic polysubstance users, cannabis use was not associated with quality of facial affect recognition, but this association might have been confounded by differing effects of other substances (Fernandez-Serrano et al. 2011).

A positive association between lifetime cannabis use and cognitive functioning may seem counterintuitive given the detrimental effects in acute administration studies (D’Souza et al. 2005; Morrison et al. 2009). It has been suggested that substance using patients might need better cognitive and social skills in order to maintain an illicit substance use (Joyal et al. 2003; Potvin et al. 2005), but in the Netherlands cannabis is not illegal and can be purchased with lesser restrictions. In other words, subjects do not need superior social functioning to obtain cannabis. Our findings are however in correspondence with a recent meta-analysis reporting that superior neuropsychological functioning in cannabis using schizophrenia patients was largely driven by studies that included lifetime users rather than current or recent users (Yücel et al. 2010). Our results support the hypothesis that cannabis using patients might constitute a subgroup of patients that is intrinsically less vulnerable for schizophrenia than patients who have never used cannabis (Zubin et al. 1977; Mueser et al. 1998). Once triggered, a drug-induced non-affective psychotic illness may be indistinguishable from psychosis due to a sufficient amount of biological vulnerability, although premorbid functioning and cognitive resilience may be better.

This developmental model has been supported by various studies that investigated the order in which cannabis use and psychosis occur. Three studies found that cognitive functioning...
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was specifically preserved in patients who had started cannabis consumption before disease onset (Stirling et al. 2005; Rodriguez-Sanchez et al. 2010) or before the age of 17 (Jockers-Scherubl et al. 2007). These studies suggest that it is not the cognitive effect of cannabis per se, but the contribution of cannabis to disease onset that explains better cognitive functioning in cannabis using patients. Secondly, evidence from follow-up studies suggests that acutely admitted psychotic patients using cannabis have a higher recovery potential for both cognitive and clinical parameters, especially after cessation of cannabis use (Loberg and Hugdahl, 2009; Gonzalez-Pinto et al. 2009). Thirdly, studies focusing on neurodevelopmental and genetic factors have added credibility to the vulnerability hypothesis. Cannabis use before psychosis onset has been associated with less neurological soft signs after transition to psychosis, which is thought to reflect a lower genetic loading in those patients (Bersani et al. 2002; Stirling et al. 2005; Ruiz-Veguilla et al. 2009).

It should however be stressed that lifetime cannabis use in our patients was associated with a lower educational degree. In healthy individuals, adolescent cannabis use is known to increase the risk of poor school performance and in particular early school leaving (Lynskey and Hall, 2000). Cannabis use is also known to impact negatively upon later employment in control subjects (Fergusson and Boden, 2008) and the impact may be even more severe in a cognitively vulnerable population of psychotic patients.

Other than in patients with psychosis and healthy controls, evidence on the association between cannabis use and cognition in genetic high risk subjects is sparse. In agreement with our results, Henquet (2006) found that acute THC administration in unaffected siblings and control subjects was associated with a cognitive decline in domains of verbal memory and processing speed. In addition, preliminary evidence suggested that sensitivity to the cognitive effects of THC might be moderated by a functional polymorphism in the catechol-O-methyltransferase (COMT) gene that is also known to moderate the risk to develop psychosis in reaction to cannabis use (Henquet et al. 2006). The present study is to our knowledge the first observational study to assess the relationship between daily-life cannabis use and cognitive functioning in genetic high risk subjects.

Finally, a significant interaction term would have indicated that the association between cannabis use and cognitive functioning was different between patients, siblings and controls but this was not the case. Although there have been suggestions of an increased vulnerability to the cognitive adverse effects of acute THC administration in patients and their siblings (D’Souza et al. 2005; Henquet et al. 2006), we did not replicate this finding. A first explanation might be that such an interaction effect is restricted to the first hours following acute intoxication of cannabis and not applicable to effects resulting from a residue of cannabinoids in the brain. A second difference in study methodologies is the psychoactive substance of use. While previous studies found an interaction effect on cognitive functioning between psychosis vulnerability and THC, we assessed associations with current, daily-life cannabis use. Contrary to cannabis, THC is a synthetic preparation that is devoid of cannabidiol, which is a potential inhibitor of pharmacological effects of CB1 agonists (Pertwee, 2008). Further research needs to clarify the association between individual cannabis components and cognitive functioning in individuals with psychosis and their unaffected relatives.
Despite the absence of an interaction effect, our findings do not imply that campaigns to discourage cannabis use are without merit. The adverse effects of cannabis use on psychotic symptomatology are well acknowledged in both patients (Linszen et al. 1994; Macleod, 2007; Castle, 2008) and individuals at genetic risk for psychosis (Caspi et al. 2005; Genetic Risk and Outcome of Psychosis (GROUP) Investigators, 2011).

The following limitations should be taken into account. First, the cross-sectional design restricts the drawing of causal inferences between cannabis use and cognitive functioning. Second, we cannot fully exclude the possibility that some of the current users in our study were tested within less than 24 hours after cannabis consumption so that the effects measured were those of acute intoxication. However, instructing frequent users to abstain from cannabis use before testing could have a negative effect on cognition as well, similar to those of acute intoxication (Pope, Jr. et al. 2002). Third, it should be acknowledged that the amount of cannabis use in the lifetime user group could have been highly variable (ranging from 5 times to >100 times) which may have led to a dilution of cannabis effects. Hence, we cannot exclude that higher quantities of lifetime cannabis use may have had a significant harmful effect on cognitive functioning. On the other hand, using 5 times or more as a cut-off for lifetime use is likely to select out most of the users who have experimented with cannabis without proceeding into continued use. This is illustrated by Perkonigg et al. (2008), who refer to the use of cannabis of 5 times or more as ‘repeated use’. Their study on the long-term natural course of cannabis use in a community sample of adolescents revealed that these repeated users were almost three times more likely to report cannabis use at 10-year follow up (OR = 2.8, 95% CI = 1.6–4.7) compared with those who had used cannabis fewer than 5 times.

The strength of this study is that, due to the comprehensive database of the GROUP study, we were able to address recommendations that have been made in prior studies (Coulston et al. 2007b; Yücel et al. 2010), such as investigating both recency and frequency of cannabis use, the inclusion of a cannabis-using control group, biological validation of self-report cannabis measures by urine drug screening, the assessment of a broad range of cognitive measures and controlling for a range of possible confounders. Furthermore, the current study expanded on existing studies by the inclusion of unaffected siblings, so that we were able to draw conclusions on the association between cannabis and cognition in people at genetic high risk for psychosis.

Our findings implicate that cannabis use in patients, siblings and controls is associated with differences in cognitive performance, depending on the recency of use. Current cannabis users perform worse on tasks of short-term memory and processing speed which may reflect residual effects. Lifetime cannabis users perform better on social cognition and acquired knowledge, which is more likely to result from lower biological vulnerability and higher premorbid functioning rather than an effect of cannabis itself. This discrepancy between potential and actual performance is clinically relevant for those patients whose cannabis use might complicate a potentially less severe course of psychosis. Studies with a longitudinal, prospective design may optimally address this issue, as it permits within-subject comparisons of cognitive performance before initiation and after cessation of cannabis use.
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COGNITIVE FUNCTIONING ASSOCIATED WITH STIMULANT USE IN PATIENTS WITH NON-AFFECTIVE PSYCHOSIS, THEIR UNAFFECTED SIBLINGS AND HEALTHY CONTROLS

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ABSTRACT

Background: While cannabis use and its relationship with cognitive functioning has been studied extensively in patients with schizophrenia, little is known about the association between stimulant use (amphetamines, cocaine, ecstasy) and cognitive functioning. The current study examined (1) whether recency and frequency of stimulant use is associated with cognitive functioning, and (2) whether these associations differ between patients with psychotic disorder, their unaffected siblings and controls.

Method: This cross-sectional study included 1,077 patients with non-affective psychosis, 1,032 unaffected siblings and 582 healthy controls. Participants completed a comprehensive cognitive test battery. Stimulant use was assessed by urinalysis and by the Composite International Diagnostic Interview (CIDI). Using random-effect regression models the main effects of Stimulant Use (current, lifetime frequent, lifetime infrequent, never use) and the interaction with Diagnostic Status (patient, sibling, control) on cognitive functioning were assessed, while correcting for possible confounders.

Results: Patients were more often lifetime users of stimulants compared to non-affected siblings and controls (25.6% vs. 9.5% vs. 5.8%). The interaction term between Stimulant Use and Diagnostic Status was not significant for any of the cognitive outcome variables. Current stimulant users showed more errors in verbal learning in comparison to never users (Cohen’s d -0.60; p<.005). Lifetime frequent (i.e. daily to weekly) stimulant use was significantly associated with worse immediate and delayed verbal recall, working memory and acquired knowledge (Cohen’s d -0.22 to -0.29; p<.005). Lifetime infrequent (less than weekly) stimulant use was not associated with significant cognitive alterations in comparison to never use.

Conclusion: Findings suggest that the association between stimulant use and cognitive functioning is similar in patients with psychosis, unaffected siblings and controls. The presence of cognitive deficits associated with lifetime stimulant use is dependent on the frequency of use, with no observed deficits in infrequent users and modest negative effects in frequent users.
1. INTRODUCTION

Substance use and substance use disorder are common phenomena in patients with schizophrenia, with prevalence estimates ranging between 10 and 70% (Barnes et al., 2006; Dixon et al., 1991; Mazzoncini et al., 2010; Mueser et al., 1990; Regier et al., 1990). This increased prevalence may reflect some shared neurobiological vulnerability for substance use disorders and schizophrenia (Chambers et al., 2001). Comorbid substance use disorder among patients diagnosed with schizophrenia is associated with greater symptom severity, poorer prognosis and more hospital admissions (Linszen et al., 1994; Moore et al., 2007; Swofford et al., 2000; van Dijk et al., 2012). Higher rates of substance abuse have also been reported in unaffected relatives of schizophrenia patients compared to healthy controls (Smith et al., 2008; Varma & Sharma, 1993), suggesting that the liability to abuse substances may be partly familial.

Over the last two decades, cannabis use has been the main target in studies concerning substance use in patients with schizophrenia (Henquet et al., 2010; van Os et al., 2010). Many of these studies have specifically focused on the association between cannabis use and cognitive alterations (e.g. memory, attention, processing speed, learning and cognitive planning). The relationship between cannabis use in patients with schizophrenia and cognitive function seems to depend on differences in time and frequency of use and the domain of cognitive functioning (Coulston et al., 2007; D'Souza et al., 2005; Henquet et al., 2006; Loberg & Hugdahl, 2009; Potvin et al., 2008; Yucel et al., 2012).

Relatively little is known about the relationship between cognitive functioning and the use of illicit drugs other than cannabis, such as cocaine (Buckley, 1998), 3,4-Methylenedioxymethamphetamine (MDMA, ‘ecstasy’; Landry, 2002) and amphetamines (Fowler et al., 1998) in patients with schizophrenia. These stimulant drugs constitute the group of the second-most popular illicit substances in patients with schizophrenia (Coyle, 2006), with prevalence rates ranging from 18 up to 36% (Shaner et al., 1993; van Dijk et al., 2012). Cocaine and amphetamines are both known to influence the dopaminergic system. They increase the levels of free dopamine in the brain in a dose-dependent manner: higher dosages of stimulants lead to more dopamine available and greater feelings of elation, euphoria and satisfaction (Center for Substance Abuse Treatment, 1999). Although not directly, evidence suggests that MDMA also influences the dopaminergic system in the brain through the interaction with the serotonergic system. As a consequence, stimulant use may be associated with development of psychosis and with aggravation of psychotic symptoms in this patient group (Barnett et al., 2007; Estroff & Gold, 1985; Janowsky et al., 1973; Janowsky & Davis, 1976; Landabaso et al., 2002; Richard et al., 1985). Also in the general population, stimulant use has been found to produce brief psychotic reactions independent of the individual’s mental state prior to the use of stimulants (Curran et al., 2004).

In addition to these psychotomimetic effects, the use of stimulants has also been associated with cognitive alterations. In general population samples, most consistent deficits have been reported in working memory, attention, executive functioning, motor speed, verbal learning and information processing (Block et al., 2002; Fernandez-Serrano et al., 2011; Toomey et al., 2003; van Holst & Schilt, 2011). At the same time, stimulant use has been found to enhance performance on certain types of psychomotor and concentration tasks (Center for Substance
Abuse Treatment, 1999). In schizophrenia, contradictory findings have been reported, with both worse and superior cognitive performance associated with the use of stimulants. It therefore remains unclear whether the use of stimulants is associated with a further cognitive decline in patients diagnosed with schizophrenia and/or with an enhancement of performance in certain domains (Reichenberg & Harvey, 2007; Tuulio-Henriksson et al., 2011). In studies on the cognitive effects of substance abuse in schizophrenia, the effects of disease related factors like psychotic symptoms and medication need to be taken into account as possible confounders of the relationship between substance use and cognitive functioning. One way to address this problem is to evaluate the effect of substance use in unaffected siblings of patients with a psychosis.

The present study aims to examine the association between current and lifetime stimulant use and cognitive functioning in patients diagnosed with a non-affective psychotic disorder, their unaffected siblings and healthy controls while correcting for the possible confounding effects of cannabis, psychedelics, other illicit substance use and heavy alcohol use (Coulston et al., 2007). In addition, we used smoking as a covariate, since nicotine also exerts an effect on brain and cognition (Coulston et al., 2007). In short, we aimed to examine (1) whether recency and frequency of stimulant use is significantly associated with alterations in cognitive functioning and (2) whether the association between stimulant use and cognitive functioning is different in patients, their unaffected siblings and controls. We hypothesized that both current and lifetime stimulant use is associated with more impairments in cognitive functioning. Based on the findings in studies on cannabis, we expected this association to be stronger for current and lifetime frequent use compared to lifetime infrequent use. Because of previous inconsistent results with regard to cognitive functioning and stimulant use in schizophrenia patients and healthy controls, we did not expect to find an interaction effect between stimulant use and diagnostic status.

2. METHODS

2.1 Participants

In this cross-sectional study 2,691 subjects were included: 1,077 patients with non-affective psychosis, 1,032 siblings and 582 healthy controls. Data pertain to baseline measures of GROUP (Genetic Risk and Outcome of Psychosis), a longitudinal study in the Netherlands and Belgium (Korver et al., 2012). In selected representative geographical areas patients were identified through clinicians working in psychotic disorder services whose caseloads were screened for individuals meeting the inclusion criteria. Additionally, a group of patients presenting consecutively at these services as either outpatients or inpatients were recruited for the study. Patients were asked for permission to contact their siblings. Controls were selected through a system of random mailings to addresses in the catchment areas of the cases.

Inclusion criteria for patients, siblings and controls were (1) age 16-50 years and (2) good command of the Dutch language. Patients had to meet DSM-IV-TR criteria (APA, 2000) for a non-affective psychotic disorder which was assessed with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992) or the Schedules for Clinical Assessment in
Neuropsychiatry version 2.1 (SCAN; Wing et al., 1990). Exclusion criteria for siblings were a history of psychotic disorder or bipolar disorder. Exclusion criteria for healthy controls were a history of psychotic disorder or a first-degree family member with a history of psychotic disorder.

The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and subsequently by local review boards of each participating institute. All of the subjects gave written informed consent in accordance with the committee’s guidelines.

### 2.2 Cognitive Measures

Subjects were assessed with a neuropsychological test battery, which required 90 to 120 minutes to complete. The 10 cognitive tasks yielded 13 outcome parameters, which were used as dependent variables in the analyses.

Verbal learning was assessed making use of the Word Learning Task (WLT; Brand & Jolles, 1985) with outcome parameters of immediate recall (15-word list, 3 learning trials) and retention rate after 20 minutes. Set shifting ability was conducted with the Response Shifting Task (RST), a modified version of the Competing Programs Task (Nolan et al., 2004), with outcome parameters of reaction time and accuracy. Sustained visual attention and vigilance was assessed with a version of the Continuous Performance Task (CPT-AX; Nuechterlein & Dawson, 1984) with outcome parameters of reaction time and accuracy. The following subtests of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997) were administered: Digit Symbol-Coding as a measure of processing speed, Arithmetic as a measure of working memory, Information as a measure of acquired knowledge and Block Design as a measure of reasoning and problem solving. The Degraded Facial Affect Recognition Task (DFAR; van ’t Wout, Aleman, Kessels, Laroi, & Kahn, 2004) was employed to assess recognition of neutral, happy, fearful and angry emotions. The Benton Face Recognition Task (BFRT; Benton et al., 1983) was used to assess visuospatial discrimination of unfamiliar faces. The Hinting Task (Versmissen et al., 2008) was used to assess theory of mind.

### 2.3 Assessment of symptoms and substance use

Severity of psychotic symptoms in patients was rated with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). In relatives and controls, the Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2002) was used to examine (subclinical) positive, negative and depressive symptoms on both a frequency scale (0=never to 3=nearly always) and a distress scale (0=not distressed to 3=very distressed).

Substance use was assessed by means of the Comprehensive International Diagnostic Interview (CIDI; WHO, 1990) and with urinalysis. Stimulant use (ecstasy, cocaine, amphetamine) was categorized as either current use (urinalysis positive) or lifetime but no current use (negative urinalysis plus positive self report on the CIDI for amphetamines, cocaine or ecstasy with a frequency of 5 times or more). In order to investigate the possibility of a dose-response relationship, lifetime stimulant use was subdivided into lifetime frequent use (daily or weekly use on the CIDI) and lifetime infrequent use (less than weekly use on the CIDI). The detection period for the urinalysis was 2-4 days for cocaine and 1-2 days for amphetamines and ecstasy.
2.4 Statistical analyses

Differences in demographic and substance-use characteristics between patients, siblings and controls were tested with one-way analysis of variance and chi square tests. Differences in demographic and clinical characteristics between current, lifetime frequent, lifetime infrequent and never users were tested within patient, sibling and control groups by means of one-way analysis of variance and chi square tests with a significance level of .05.

The association between stimulant use and cognitive functioning was assessed with mixed-model regression analyses. In a first step we built random effect regression models with each cognitive outcome measure as dependent variable. Stimulant use (current, lifetime frequent, lifetime infrequent, never), Diagnostic Status (patient, sibling, control) and the Stimulant use by Status interaction term were entered as fixed part of the model. Because of intra-family dependency between patients and siblings, “family number” was entered into the regression model as a random factor with a random intercept. In the second step, the following covariates were entered into the model: age, gender, highest educational level (ranging from 1 = primary school to 8 = university), use of cannabis, psychedelics, or other illicit substances (e.g. sedatives, inhalants, PCP), smoking, and heavy alcohol use (with a cut-off for females and males of 14, respectively 21 units per week). In case the interaction term was not statistically significant, the model and analyses were repeated without the interaction term. Due to the high power caused by the large n, effect sizes (Cohen’s $d$) were calculated to distinguish relevant effects from trivial but statistically significant effects. All analyses were performed with SPSS (version 17.0). For the group comparisons the significance level was set at .05, for the random effect analyses a correction for multiple comparisons was applied by setting the alpha at .005.

3. RESULTS

3.1. Demographic and clinical variables

As presented in Table 1, patients and unaffected siblings were significantly younger than controls. Patients were more often male compared to siblings and controls. Highest level of education was significantly lower in patients compared to siblings and controls. Moreover, patients were more often than siblings and controls lifetime users of stimulants (25.6% vs. 9.5% vs. 5.8%), cannabis (64.6% vs. 39.0% vs. 28.0%), psychedelics (8.8% vs. 5.4% vs. 3.8%), other illicit substances (8.9% vs. 3.1% vs. 2.6%), and nicotine (66.0% vs. 37.9% vs. 24.7%). Heavy alcohol use was not significantly different between the diagnostic groups.

Table 2a shows demographic and clinical characteristics of current, lifetime frequent, lifetime infrequent and never stimulant using patients. Stimulant using patients were significantly younger, more often male and lower educated in comparison to never users. Age at onset of psychosis was younger in stimulant users compared to never users. Stimulant using patients were more often lifetime users of cannabis, psychedelics, other illicit substances, heavy alcohol and nicotine. Stimulant use was not significantly associated with remission rate, the use of antipsychotics, or illness duration.
Table 1. Demographic and substance use variables in controls, siblings and patients

<table>
<thead>
<tr>
<th></th>
<th>Patients N=1,077</th>
<th>Siblings N=1,032</th>
<th>Controls N=582</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (mean ± SD)</td>
<td>27.7 ± 8.1</td>
<td>27.8 ± 8.3</td>
<td>30.5 ± 10.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Gender</strong> (N, %male)</td>
<td>818 (76.0%)</td>
<td>474 (45.9%)</td>
<td>267 (45.9%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Education</strong> (mean ± SD)</td>
<td>4.1 ± 2.0</td>
<td>5.1 ± 2.1</td>
<td>5.4 ± 1.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Stimulant use</strong> (N, %yes)</td>
<td>276 (25.6%)</td>
<td>99 (9.5%)</td>
<td>34 (5.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LT frequent (N, %yes)</td>
<td>128 (11.9%)</td>
<td>29 (2.8%)</td>
<td>13 (2.2%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LT infrequent (N, %yes)</td>
<td>131 (12.1%)</td>
<td>57 (5.5%)</td>
<td>19 (3.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Current</strong> (N, %yes)</td>
<td>17 (1.6%)</td>
<td>13 (1.3%)</td>
<td>2 (0.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Cannabis LT</strong> (N, %yes)</td>
<td>696 (64.6%)</td>
<td>402 (39.0%)</td>
<td>163 (28.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Psychedelics LT</strong> (N, %yes)</td>
<td>202 (8.8%)</td>
<td>56 (5.4%)</td>
<td>22 (3.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Other LT</strong> (N, %yes)</td>
<td>96 (8.9%)</td>
<td>32 (3.1%)</td>
<td>15 (2.6%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Alcohol heavy</strong> (N, %yes)</td>
<td>113 (10.5%)</td>
<td>112 (10.9%)</td>
<td>58 (10.0%)</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Smoking</strong> (N, %yes)</td>
<td>711 (66.0%)</td>
<td>391 (37.9%)</td>
<td>144 (24.7%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Other: use of inhalants, phenylcyclohexylpiperidine (PCP), sedatives and other substances; LT: lifetime

Table 2b and 2c show characteristics of current, lifetime frequent, lifetime infrequent and never stimulant using siblings and controls. Stimulant using siblings were younger, more often male and lower educated. They were more often lifetime users of cannabis, psychedelics, other illicit substances, heavy alcohol and nicotine. Stimulant using controls were more often male and more often users of cannabis, psychedelics, other illicit substances and nicotine. Age, educational level and heavy alcohol use were not significantly different between stimulant using and non-using controls.

### 3.2. Associations between stimulant use and cognitive functioning

The interaction term between Stimulant use (current, lifetime frequent, lifetime infrequent, never) and Diagnostic Status (patient, sibling, control) was not significant for any of the cognitive outcome parameters, indicating similar effects of stimulant use in all three groups. Consequently, the interaction term was removed from the random effect regression models for the final analyses. The effects of stimulant use displayed in Figure 1 therefore apply to the total group of patients, siblings and controls.
Table 2a, b, c. Demographic and clinical variables in patients, siblings and controls categorized by level of stimulant use

<table>
<thead>
<tr>
<th>Patients</th>
<th>Current use</th>
<th>LT frequent</th>
<th>LT infrequent</th>
<th>Never</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=17</td>
<td>N=128</td>
<td>N=131</td>
<td>N=801</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>(mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25.5 ± 5.8</td>
<td>26.9 ± 7.2</td>
<td>26.3 ± 6.3</td>
<td>28.0 ± 8.4</td>
<td>&lt;.043</td>
</tr>
<tr>
<td>Gender</td>
<td>(N, %male)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>17 (100%)</td>
<td>108 (84.4%)</td>
<td>119 (90.8%)</td>
<td>574 (71.7%)</td>
<td>&lt;.001</td>
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<tr>
<td>Education</td>
<td>(mean ± SD)</td>
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</tr>
<tr>
<td></td>
<td>2.8 ± 1.7</td>
<td>3.3 ± 1.8</td>
<td>4.0 ± 2.0</td>
<td>4.2 ± 2.2</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>AOP</td>
<td>(mean ± SD)</td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>20.6 ± 4.4</td>
<td>21.0 ± 5.8</td>
<td>21.2 ± 5.2</td>
<td>22.9 ± 7.2</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>Illness duration</td>
<td>(mean ± SD)</td>
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<td></td>
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<tr>
<td></td>
<td>4.4 ± 3.3</td>
<td>5.1 ± 5.1</td>
<td>4.3 ± 3.6</td>
<td>4.3 ± 4.0</td>
<td>NS</td>
</tr>
<tr>
<td>Remission</td>
<td>(N, %yes)</td>
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<tr>
<td></td>
<td>7 (41.2%)</td>
<td>52 (41.0%)</td>
<td>49 (37.2%)</td>
<td>382 (47.7%)</td>
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<td>Antipsychotics</td>
<td>(N, %yes)</td>
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<tr>
<td></td>
<td>16 (94.1%)</td>
<td>117 (91.2%)</td>
<td>112 (85.7%)</td>
<td>683 (85.3%)</td>
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<tr>
<td>Cannabis LT</td>
<td>(N, %yes)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>11 (84.6%)</td>
<td>27 (93.1%)</td>
<td>49 (86.0%)</td>
<td>315 (33.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Psychedelics LT</td>
<td>(N, %yes)</td>
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<tr>
<td></td>
<td>6 (46.2%)</td>
<td>9 (31.0%)</td>
<td>19 (33.3%)</td>
<td>22 (2.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other LT</td>
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<td>2 (15.4%)</td>
<td>6 (20.7%)</td>
<td>5 (8.8%)</td>
<td>19 (2.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heavy alcohol</td>
<td>(N, %yes)</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>6 (46.2%)</td>
<td>8 (27.6%)</td>
<td>16 (28.1%)</td>
<td>82 (8.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nicotine use</td>
<td>(N, %yes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (69.2%)</td>
<td>22 (75.9%)</td>
<td>34 (59.6%)</td>
<td>326 (34.9%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Siblings</th>
<th>Current use</th>
<th>LT frequent</th>
<th>LT infrequent</th>
<th>Never</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=13</td>
<td>N=29</td>
<td>N=57</td>
<td>N=933</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>(mean ± SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26.3 ± 9.4</td>
<td>26.2 ± 7.1</td>
<td>25.1 ± 4.7</td>
<td>28.0 ± 9.4</td>
<td>&lt;.047</td>
</tr>
<tr>
<td>Gender</td>
<td>(N, %male)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>11 (84.6%)</td>
<td>17 (58.6%)</td>
<td>35 (61.4%)</td>
<td>411 (44.1%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Education</td>
<td>(mean ± SD)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>4.0 ± 1.5</td>
<td>3.9 ± 2.3</td>
<td>4.9 ± 2.2</td>
<td>5.1 ± 2.1</td>
<td>&lt;.004</td>
</tr>
<tr>
<td>Cannabis LT</td>
<td>(N, %yes)</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>11 (84.6%)</td>
<td>27 (93.1%)</td>
<td>49 (86.0%)</td>
<td>315 (33.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Psychedelics LT</td>
<td>(N, %yes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (46.2%)</td>
<td>9 (31.0%)</td>
<td>19 (33.3%)</td>
<td>22 (2.4%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other LT</td>
<td>(N, %yes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 (15.4%)</td>
<td>6 (20.7%)</td>
<td>5 (8.8%)</td>
<td>19 (2.0%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heavy alcohol</td>
<td>(N, %yes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 (46.2%)</td>
<td>8 (27.6%)</td>
<td>16 (28.1%)</td>
<td>82 (8.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nicotine use</td>
<td>(N, %yes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (69.2%)</td>
<td>22 (75.9%)</td>
<td>34 (59.6%)</td>
<td>326 (34.9%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
4. Discussion

In the present study, we examined the association between current and lifetime stimulant use and cognitive functioning in a large sample of patients diagnosed with a non-affective psychotic disorder, their unaffected siblings and healthy controls while taking into account important potential confounders such as age, gender, educational level and other substance use. In general our hypotheses were confirmed. First, similar associations between stimulant use and cognition were found in patients, siblings and controls. Second, both current and lifetime frequent stimulant use were associated with worse cognitive functioning in specific domains of immediate and delayed verbal learning (WLT), working memory (WAIS Arithmetic) and acquired knowledge (WAIS Information). Third, in the infrequent stimulant-using group, an insignificant trend for better cognitive functioning was observed.

Figure 1. Random effect regression model: associations between cognitive functioning and current/lifetime stimulant use in comparison to never use in patients, siblings and controls. Cognitive functioning in stimulant users (N=409) is compared against never users (N=2282) who are represented by the baseline. Single and double green squares denote significant associations before (p<.05) and after (p<.005) correction for multiple comparisons, respectively.

<table>
<thead>
<tr>
<th>Controls</th>
<th>Current use N=2</th>
<th>LT frequent N=13</th>
<th>LT infrequent N=19</th>
<th>Never N=548</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>33.5 ± 6.4</td>
<td>28.5 ± 8.9</td>
<td>27.7 ± 8.3</td>
<td>30.7 ± 10.7</td>
<td>NS</td>
</tr>
<tr>
<td>Gender (N, %male)</td>
<td>1 (50.0%)</td>
<td>9 (69.2%)</td>
<td>14 (73.7%)</td>
<td>243 (44.3%)</td>
<td>&lt;.025</td>
</tr>
<tr>
<td>Education (mean ± SD)</td>
<td>6.5 ± 0.7</td>
<td>4.6 ± 1.9</td>
<td>5.5 ± 1.6</td>
<td>5.4 ± 1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Cannabis LT (N, %yes)</td>
<td>1 (50%)</td>
<td>11 (84.6%)</td>
<td>18 (94.7%)</td>
<td>133 (24.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Psychedelics LT (N, %yes)</td>
<td>0 (0%)</td>
<td>8 (61.5%)</td>
<td>8 (42.1%)</td>
<td>6 (1.1%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other LT (N, %yes)</td>
<td>0 (0%)</td>
<td>2 (15.4%)</td>
<td>3 (15.8%)</td>
<td>10 (1.8%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heavy alcohol (N, %yes)</td>
<td>0 (0%)</td>
<td>3 (23.1%)</td>
<td>4 (21.1%)</td>
<td>51 (9.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Nicotine use (N, %yes)</td>
<td>0 (0%)</td>
<td>8 (61.5%)</td>
<td>13 (68.4%)</td>
<td>123 (22.4%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

AOP: age at onset of psychosis; Illness duration: in years; LT: lifetime; Other: use of inhalants, phenylcyclohexylpiperidine (PCP), sedatives and other substances
Current stimulant use was associated with a general pattern of non-significantly worse cognitive functioning compared to never use. Current stimulant users only performed significantly worse than never users on the number of incorrect words in the Word Learning Task ($Cohen's d = -0.60$; $F(3,2239)=6.28; p<.005$).

Lifetime frequent (i.e. daily to weekly) stimulant use was associated with significant worse performance on a range of cognitive tasks compared to never stimulant use, including associations with immediate recall in the Word Learning Task ($F(3,2573)=4.39; p<.005$), delayed recall in the Word Learning Task ($F(3,2540)=7.21; p<.005$), WAIS Arithmetic ($F(3,2535)=2.91; p<.005$) and WAIS Information ($F(3,2424)=6.19; p<.005$), although effect sizes were small ($Cohen's d$ -0.22 to -0.29). Associations with the number of incorrect words in the Word Learning Task, as well as the association with WAIS Digit Symbol-coding did not survive correction for multiple comparisons. Although lifetime infrequent (less than weekly) stimulant use was associated with a general pattern of better cognitive functioning in comparison to never use, these results did not reach statistical significance and effect sizes were small ($Cohen's d = +0.10$).

4. DISCUSSION

In the present study, we examined the association between current and lifetime stimulant use and cognitive functioning in a large sample of patients diagnosed with a non-affective psychotic disorder, their unaffected siblings and healthy controls while taking into account important potential confounders such as age, gender, educational level and other substance use. In general our hypotheses were confirmed. First, similar associations between stimulant use and cognition were found in patients, siblings and controls. Second, both current and lifetime frequent stimulant use was associated with worse cognitive functioning in specific domains of immediate and delayed verbal learning (WLT), working memory (WAIS Arithmetic) and acquired knowledge (WAIS Information). Third, in the infrequent stimulant-using group, an insignificant trend for better cognitive functioning was observed.

The finding that lifetime frequent stimulant use was associated with worse cognitive functioning in specific cognitive domains is consistent with several previous studies in patients with schizophrenia (Pencer & Addington, 2003; Serper et al., 2000; Serper & Copersino, 2000; Sevy et al., 1990) and healthy controls (Bolla et al., 1999; Gillen et al., 1998; Mittenberg & Motta, 1993; Rosselli & Ardila, 1996). Furthermore, our study indicates worse cognitive functioning in unaffected siblings who frequently use stimulants in comparison to never users. To our knowledge, this is the first time that this association has been investigated in unaffected siblings.

Additionally, our results in current stimulant using patients are in line with a previous study that reported an association between current stimulant use and impaired verbal memory in a sample of schizophrenia patients (Serper & Copersino, 2000). Although not significant, we found a trend for worse cognitive functioning in current users on several other cognitive domains. The lack of significant associations in this group could be the result of insufficient power, since only 32 subjects were current stimulant users. However, other studies neither found (additional) cognitive impairments in current stimulant using schizophrenia patients (Cooper et al., 1999;
Copersino et al., 2004; Goldberg et al., 1991; Pencer & Addington, 2003; Serper & Copersino, 2000; Smelson et al., 2003), or even reported superior cognitive functioning in current using patients (Pencer & Addington, 2003; Smelson et al., 2002). Likewise, the acute administration of stimulants has also been associated with positive effects on working memory and processing speed in patients with schizophrenia (Barch & Carter, 2005; Goldberg et al., 1991). This was not replicated in our study, although results are not directly comparable. We found a pattern of worse cognitive functioning in current users with a positive urine screen. Subjects included in the previous studies had no history of stimulant use and only took stimulants for the purpose of the study (Barch & Carter, 2005; Goldberg et al., 1991).

Unlike previous studies that reported better cognitive functioning in lifetime -but not current- cannabis using patients (Fernandez-Serrano et al., 2011; Joyal et al., 2003; Meijer et al., 2012; Potvin et al., 2005), the association between lifetime infrequent stimulant use and better cognition in our study was small and insignificant. It has been suggested that patients who use substances need better cognitive skills to obtain drugs, which may explain higher levels of premorbid adjustment in comparison to never using patients (Murray et al., 1992). However, in the Netherlands stimulants are relatively cheap and easy to obtain, which makes such a selection effect less likely.

Stimulant using and never using patients did not differ in illness duration, use of antipsychotics and number of relapses, suggesting that the effect on disease course may be limited in patients with a non-affective psychotic disorder. However, prospective studies are needed to confirm this preliminary impression.

Methodological differences are likely to have contributed to inconsistencies between our results and those previously reported. First, variation in the type of stimulants may explain some of the different findings. Second, in the abovementioned studies, different tests have been used to determine verbal learning, processing speed and working memory. This heterogeneity in neuropsychological testing is a general problem that limits comparability and requires the use of more standardized cognitive test batteries. Comparability between studies would be further advanced by formulating clearer definitions of recency and frequency of substance use. And finally, the use of urinalysis versus self-report measures may account for differences in study results.

Our findings should be interpreted in light of some limitations. Although we corrected for the use of other illicit substances, alcohol, and nicotine, it is possible that a group of ‘pure’ stimulant users would have shown different results regarding associations with cognition. However, this study was designed to take place in a naturalistic context in which single drug use is exceptional. In addition, we used a rather rough division into ‘daily’, ‘weekly’ and ‘less than weekly use’ for measuring the frequency of stimulant use conform the criteria in the CIDI (WHO, 1990). In future studies, the use of a continuous measure is recommended (e.g. number of times used, total amount used). Moreover, although the choice to combine amphetamine, cocaine and ecstasy into one measure increases power, it may restrict comparability to other studies. On the other hand, as results from previous studies indicate that individual stimulant drugs have similar effects, it seems justified to group them together (Kraemer & Maurer, 2002; Staack & Maurer, 2005). Another limitation is that due to the cross-sectional design of the
study, conclusions about causality between stimulant use and cognitive functioning can not be drawn. Longitudinal studies and intervention studies are needed to determine whether these associations are caused by stimulant use or represent a pre-selection effect. Finally, the group of current stimulant users was relatively small compared to the lifetime frequent and lifetime infrequent groups. Although we did find large effect sizes in this group, a lack of power could have resulted in the absence of statistically significant associations.

These limitations notwithstanding, this study allowed us to expand the existing literature on the relationship between stimulant use and cognition. We were able to investigate a large sample of patients with non-affective psychotic disorders and their unaffected siblings. Moreover, our sample consisted of stimulant using and non-using healthy controls, making it the first study to assess the relationship between stimulant use and cognition in these three groups simultaneously. Furthermore, because of the naturalistic nature of our study, results may be easily generalized to everyday practice. Lastly, we carried out an extensive clinical assessment and a broad range of cognitive tests, which allowed us to assess associations with several cognitive domains while controlling for relevant confounders.

In conclusion, this is the first study to assess the association between stimulant use and cognitive functioning in three groups of individuals with varying levels of psychosis vulnerability. We found that frequent stimulant use may equally affect cognitive functioning in patients with non-affective psychosis, their unaffected siblings and healthy controls. Subjects with a lifetime history of frequent stimulant use were especially impaired in verbal memory, acquired knowledge and processing speed, while current stimulant users were impaired in verbal memory. Infrequent stimulant use was not associated with cognitive impairment in patients, their unaffected siblings and healthy controls. On the base of our findings, frequent stimulant use should be discouraged. More research on stimulant use and cognition needs to be performed to clarify contradictory results on this topic. Longitudinal studies investigating changes in stimulant use and cognitive functioning could provide more insight into the causes and consequences, clarifying the issue whether associations represent a direct cognitive effect of stimulant use or a selection effect. Furthermore, longitudinal research should determine whether these alterations in cognitive functioning persist over time or normalize after cessation of use.

**REFERENCE LIST**


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IS A SCHIZO-OBSESSIVE SUBTYPE ASSOCIATED WITH COGNITIVE IMPAIRMENT? RESULTS FROM A LARGE CROSS-SECTIONAL STUDY IN PATIENTS WITH PSYCHOSIS AND THEIR UNAFFECTED RELATIVES

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ABSTRACT

Aim: The current study investigated whether candidate cognitive endophenotypes may be employed to validate a schizo-obsessive subtype.

Method: We evaluated the association between obsessive compulsive symptoms (OCS) and cognitive performance in 984 patients with non-affective psychosis (22.5% with OCS), 973 unaffected siblings (7.7% with OCS), 851 parents (4.2% with OCS) and 573 controls (4.5% with OCS) using within-subject random effect regression analyses and cross-trait cross-relative analyses.

Results: No significant within-subject associations between OCS and cognitive functioning were found for patients and siblings. Severity of OCS was associated with worse set shifting ability in parents and worse processing speed in controls, but effect sizes were small (.10 and .05 respectively). Cross-trait cross-relative analyses yielded no significant results.

Conclusion: Contrary to our expectations, neither within-subject analyses nor cross-relative analyses yielded a clear association between OCS and cognitive performance. Results do not support a schizo-obsessive subtype associated with cognitive impairment.
INTRODUCTION

Although schizophrenia and obsessive-compulsive disorder (OCD) belong to distinct diagnostic categories, there are substantial areas of overlap between the two disorders regarding affected brain areas, neurotransmitters and pharmacotherapy (Buchsbaum et al., 1997; Cunill et al., 2009). The higher-than-expected comorbidity of obsessive-compulsive symptoms (OCS) and psychosis suggests a special association between the two disorders, although the nature of this relation is still under debate (Bottas et al., 2005). Several explanatory hypotheses have been proposed.

Firstly, it has been hypothesized that OCS and psychotic symptoms could be concomitant but nevertheless unrelated pathological processes, as is the case with ‘co-morbidity’ (Berman et al., 1998; Patel et al., 2010). This co-morbidity may be caused by shared genetic and/or environmental factors that render the brain vulnerable to both schizophrenia and other psychopathology, including OCS. Reports that there is no typical temporal sequence of both disorders corroborate this hypothesis (Devulapalli et al., 2008). Secondly, OCS and psychosis might be regarded as different expressions of the same disorder on the schizo-obsessive spectrum (Bottas et al., 2005). This hypothesis emphasises the similarities between obsessions and delusions as being irrational thoughts, the first with insight and the latter lacking insight. Thirdly, the emergence of OCS in schizophrenia has been hypothesized to be induced by anti-psychotics, especially clozapine (de Haan et al., 2002; de Haan et al., 2004; van Nimwegen et al., 2008). However, observations that OCD was already present in up to 14% of first-episode, predominantly drug-naive schizophrenia patients (Poyurovsky et al., 1999) demonstrate that this cannot be the only explanation for their co-occurrence. Finally, it has been suggested that the co-expression of schizophrenia and OCS may mark a unique subset of schizophrenia patients whose condition might be referred to as the “schizo-obsessive subtype” (Berman et al., 1998; McGlashan, 1997; Ongur & Goff, 2005; Zohar, 1997). In this view, the high co-occurrence is accounted for by a distinct diagnostic entity, with a unique pathophysiology, treatment response and clinical course.

The study of cognitive impairments has been suggested to be a valuable method to determine whether or not the putative schizo-obsessive subtype represents a true diagnostic entity (Berman et al., 1998; Lysaker et al., 2009). Various researchers have investigated whether cognitive functioning may differentiate schizophrenia patients with OCS (OCS+ patients) from schizophrenia patients without OCS (OCS- patients). While some studies reported worse cognitive functioning in OCS+ patients compared to OCS- patients on visual memory, language and executive functioning domains (Berman et al., 1998; Hwang et al., 2000; Lysaker et al., 2000; Lysaker et al., 2002), others reported no differences in cognitive performance (Ongur & Goff, 2005; Tumkaya et al., 2009; Whitney et al., 2004). Remarkably, even better functioning in OCS+ versus OCS- patients has been reported on domains of visual reproduction, set shifting and verbal fluency (Borkowska et al., 2003; Lysaker et al., 2002).

The association between OCS and cognitive functioning in schizophrenia patients needs to be considered in the context of significant heterogeneity in the etiopathology, symptomatology and course of the disorder (Tandon et al. 2009). Likewise, interpretation of worse cognitive functioning in OCS+ patients may be confounded by the fact that these patients also express
higher levels of psychotic symptoms, receive different antipsychotic treatment and are more often hospitalized in comparison with OCS- patients (Hwang et al., 2000; Lysaker et al., 2000; Lysaker et al., 2002).

To exclude such disease-related confounding, the study of unaffected relatives may be a valuable approach. Unaffected first-degree relatives share about half of their genetic material with the proband, but do not suffer from clinical psychosis and do not receive antipsychotic treatment (Gur et al., 2007). Moreover, unaffected relatives of OCS+ patients may be more likely to display OCS, based on the suggested familial aggregation of OCS in the general population and in schizophrenia samples (Mataix-Cols et al. 2005; Poyurovsky et al., 2005). Likewise, in a recent review it was noted that an important step towards delineation of specific subgroups within the OCS-schizophrenia axis may be the use of candidate endophenotypic markers, including cognitive functioning (Poyurovsky & Koran, 2005).

In schizophrenia, impairments in domains of executive functioning, working memory, attention/vigilance and affect processing may provide a means to study endophenotypic traits more closely associated with specific neurobiological deficits than are psychotic symptoms (Gur et al., 2007). Also in OCD cognitive deficits have been suggested as potential endophenotypic markers that may be used to clarify genetic contributions, such as nonverbal memory, executive functioning and motor inhibitory control (Menzies et al., 2007; Rao et al., 2008). Therefore, if OCS+ patients can be distinguished from OCS- patients based on a cognitive pattern which is replicated in their unaffected relatives, this may support a shared genetic vulnerability for OCS and psychosis as would be expected in the case of a schizo-obsessive subtype (Poyurovsky & Koran, 2005).

The first aim of the present study was therefore to investigate whether OCS+ patients can be differentiated from OCS- patients based on their cognitive performance. Second, we wanted to investigate the association between OCS and cognitive functioning in unaffected relatives of patients with psychosis and control subjects. Since OCS have been associated with cognitive functioning in subjects with and without psychosis, we hypothesized that a negative association between OCS and cognitive functioning would be present in patients, relatives and controls. Third, as an exploratory analysis, we wanted to examine whether the level of OCS in patients was associated with cognitive functioning in their unaffected relatives. Based on the assumption that both cognitive deficits and OCS are more prevalent in genetic high risk subjects we expected a cross-trait cross-relative association for cognitive domains that are impaired in both OCD and schizophrenia, such as set shifting, processing speed and sustained attention (Chamberlain et al., 2005; Kuelz et al., 2004).

METHODS

Study design and population
Data pertain to baseline measures of GROUP (Genetic Risk and Outcome of Psychosis), a longitudinal study in the Netherlands and Belgium (Korver et al., in press). In selected representative geographical areas patients were identified through clinicians working in
psychotic disorder services whose caseloads were screened for inclusion criteria. Additionally, a group of patients presenting consecutively at these services as either outpatients or inpatients were recruited for the study. Controls were selected through a system of random mailings to addresses in the catchment areas of the cases.

Inclusion criteria for patients, siblings and controls were (1) age range of 16 to 50 years and (2) good command of the Dutch language. Patients had to meet DSM-IV-TR criteria for a non-affective psychotic disorder (APA, 2000) which was assessed with the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992) or the Schedules for Clinical Assessment in Neuropsychiatry version 2.1 (SCAN) (Wing et al., 1990). Exclusion criteria for healthy controls were a history of psychotic disorder or a first-degree family member with a history of psychotic disorder. The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and subsequently by local review boards of each participating institute. All of the subjects gave written informed consent in accordance with the committee’s guidelines.

Clinical Measures
Severity of psychotic symptoms in patients was rated with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). In relatives and controls, the CAPE (Community Assessment of Psychic Experiences) (Stefanis et al., 2002) was used to assess the prevalence of (subclinical) positive, negative and depressive symptoms on both a frequency scale (0=never to 3=nearly always) and a distress scale (0=not distressed to 3=very distressed).

The Yale–Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989) was used in all participants to measure the presence and severity of obsessive compulsive symptoms (OCS) over the previous week. The Y-BOCS addresses interference, distress and time spent on, resistance against and control over obsessions and/or compulsions. All ten severity items are rated on a five-point Likert-scale, ranging from 0 (no symptoms) to 4 (extreme symptoms). Total Y-BOCS score (range=0–40), which is the sum of all ten severity items, was used as predictor in the analyses. The Y-BOCS has been validated for the use in patients with non-affective psychosis (Boyette et al., 2011; de Haan et al., 2006).

Cognitive Measures
Subjects were administered a neuropsychological test battery, which required 90 to 120 minutes to complete. The 10 cognitive tasks yielded 13 outcome parameters which were used as dependent variables in the analyses. Verbal learning was assessed using the Word Learning Task (WLT) (Brand & Jolles, 1985) with outcome parameters of immediate recall (15-word list, 3 learning trials) and retention rate after 20 minutes. Set shifting ability was assessed using the Response Shifting Task (RST), a modified version of the Competing Programs Task (Nolan et al., 2004) with outcome parameters of reaction time and accuracy. Sustained visual attention and vigilance was assessed using a version of the Continuous Performance Task (CPT-AX) (Nuechterlein & Dawson, 1984) with outcome parameters of reaction time and accuracy. The following subtests of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) (Wechsler, 1997) were assessed: Digit Symbol-Coding as a measure of processing speed, Arithmetic as
a measure of working memory, Information as a measure of acquired knowledge and Block Design as a measure of reasoning and problem solving. The Degraded Facial Affect Recognition Task (DFAR) (van ‘t Wout et al., 2004) was used to assess recognition of neutral, happy, fearful and angry emotions. The Benton Face Recognition Task (BFRT) (Benton et al., 1983) was used to assess visuospatial discrimination of unfamiliar faces. The Hinting Task (Versmissen et al., 2008) was used to assess theory of mind. Cognitive performance within the GROUP study on this test battery has been described previously (Meijer et al., 2012). Patients performed worse than controls on all cognitive domains (z-range -.18 to -1.34), while unaffected siblings and parents showed intermediate performance on selected tasks (z-range -.01 to -.43 and +0.13 to -1.17, respectively).

**Statistical Analyses**

Demographic and clinical characteristics were compared between OCS+ and OCS- patients using one way analysis of variance (ANOVA) for continuous data and chi-square tests for categorical data. Tests were two-tailed with a significance level of .05. The association between OCS and cognitive functioning was assessed in three ways: by means of within-subject regression analyses, by means of cross-trait cross-relative analyses, and (within patients) by means of group comparisons.

Firstly, we built a random effect regression model for each of 13 cognitive functioning outcomes with the Y-BOCS scores (range 0-40) as the fixed part of the model and cognitive functioning as the dependent variable. Family was used as a random factor with a random intercept to correct for intra-family correlation, since some families contributed more than one parent, sibling, or control. These models were analyzed within each status group (patient, parent, sibling, control) separately. Covariates were added to the model in two steps. As a first step age, gender and educational level were entered at the same time (“enter method”). Educational level was categorized: varying from lowest (1=primary school) up to highest (8=university), with an ordinal increase in educational years. Subsequently, symptoms were entered as a covariate. For patients PANSS scores were used (PANSS positive, negative, general) while CAPE scores were used for the three non-clinical groups.

Secondly, cognitive functioning was compared between subgroups of patients based on their Y-BOCS scores. Based on the literature (Bedard & Chantal, 2011; Ongur & Goff, 2005) the following categories were created: no OCS (Y-BOCS 0), subclinical OCS (Y-BOCS 1-7), mild OCS (Y-BOCS 8-15), or moderate-severe OCS (Y-BOCS ≥16). Analyses were performed by means of analysis of covariance (ANCOVA) with age, gender, education and PANSS scores as covariates and family as a random factor.

Thirdly, cross-trait cross-relative analyses were performed in order to exclude possible disease-related confounding (Toulopoulou et al., 2010). Therefore, for each cognitive outcome measure a random effect regression model was built with Y-BOCS scores of the patient as independent variable and cognitive functioning of their relative (siblings and parents separately) as dependent variable. Analyses were co-varied for age, gender, education and CAPE scores of the relative.
All tests were two-tailed. To correct for multiple comparisons the alpha was set to .005. Significant effects were transferred into Cohen’s d as a measure of effect size, in order to differentiate between small (d’=.2), medium (d’=.5), and large (d’=.8) effects. All statistical analyses were performed with SPSS version 17.0 for Windows.

RESULTS

For the current study we excluded subjects who did not have the Y-BOCS assessed (n=273), as well as additional subjects who had not participated in any of the cognitive tasks (n=30), resulting in a study sample of 3381 subjects (984 patients, 973 siblings, 851 parents, 573 controls). Table 1 shows that subclinical, mild and moderate-severe OCS was more prevalent in patients compared to relatives and controls.

Table 1. Level of OCS in the subject groups

<table>
<thead>
<tr>
<th>Level of OCS (Y-BOCS score)</th>
<th>Patients n=984</th>
<th>Siblings n=973</th>
<th>Parents n=851</th>
<th>Controls n=573</th>
</tr>
</thead>
<tbody>
<tr>
<td>No OCS (0)</td>
<td>77.5%</td>
<td>92.3%</td>
<td>95.8%</td>
<td>95.5%</td>
</tr>
<tr>
<td>Subclinical OCS (1-7)</td>
<td>6.8%</td>
<td>3.9%</td>
<td>1.8%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Mild OCS (8-15)</td>
<td>10.2%</td>
<td>3.0%</td>
<td>1.9%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Moderate-Severe OCS (≥16)</td>
<td>5.5%</td>
<td>0.8%</td>
<td>0.5%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

Table 2 demonstrates that OCS+ patients were significantly younger than OCS- patients. The gender distribution was not significantly different between the OCS groups. Moreover, OCS+ patients had significantly more positive and general symptoms on the PANSS compared to OCS- patients, while negative symptoms did not differ. In addition, OCS+ patients were more often currently treated with clozapine compared to OCS- patients. Observed mean cognitive test scores for OCS subgroups are also demonstrated. ANCOVA between the four OCS patient groups did not yield significant differences for any of the 13 cognitive outcome parameters.

Table 3 shows the results of random effect regression analyses. Analyses were co-varied for age, gender and education in the first step, while symptom scores (PANSS or CAPE) were included in the second step. Since the results for step 1 and 2 did not differ significantly, only results for the final model are displayed. In patients, higher Y-BOCS score (independent variable) was significantly associated with better performance on the Hinting task (dependent variable; d’=+.02), but this result did not survive correction for multiple comparisons. In siblings, the Y-BOCS score was not significantly associated with any of the cognitive parameters. In parents, higher Y-BOCS score was significantly associated with worse performance on the RST accuracy (d’=−.10). In controls, higher Y-BOCS score was significantly associated with better performance on the WAIS-Information task (d’=+.03) and worse performance on the Digit Symbol-Coding task (d’=−.05), of which only the latter result survived correction for multiple
Table 2. Group comparisons of demographic, clinical and cognitive variables between patients with different levels of OCS

<table>
<thead>
<tr>
<th></th>
<th>Y-BOCS 0 n=763 Mean (SD)</th>
<th>Y-BOCS 1-7 n=67 Mean (SD)</th>
<th>Y-BOCS 8-15 n=100 Mean (SD)</th>
<th>Y-BOCS ≥16 n=54 Mean (SD)</th>
<th>F/χ²(df) p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>28.1 (8.3)</td>
<td>27.1 (6.4)</td>
<td>27.9 (8.4)</td>
<td>23.5 (6.6)</td>
<td>F(3, 980)=5.55 p&lt;.001</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>76.4%</td>
<td>76.9%</td>
<td>78.0%</td>
<td>75.0%</td>
<td>χ²(2)=1.80 p=.62</td>
</tr>
<tr>
<td>Mean Y-BOCS score</td>
<td>0.0 (0.0)</td>
<td>5.0 (1.8)</td>
<td>11.2 (2.2)</td>
<td>20.8 (4.2)</td>
<td>-</td>
</tr>
<tr>
<td>PANSS positive</td>
<td>12.1 (5.1)</td>
<td>13.0 (6.0)</td>
<td>14.2 (5.1)</td>
<td>16.1 (5.9)</td>
<td>F(3, 980)=12.76 p&lt;.001</td>
</tr>
<tr>
<td>PANSS negative</td>
<td>13.9 (6.1)</td>
<td>14.0 (5.3)</td>
<td>14.7 (5.1)</td>
<td>15.6 (6.4)</td>
<td>F(3, 980)=1.68 p=.26</td>
</tr>
<tr>
<td>PANSS general</td>
<td>27.0 (8.3)</td>
<td>28.9 (7.4)</td>
<td>31.1 (7.7)</td>
<td>33.3 (9.9)</td>
<td>F(3, 980)=15.19 p&lt;.001</td>
</tr>
<tr>
<td>Inpatients (%)</td>
<td>12.7%</td>
<td>13.4%</td>
<td>15.0%</td>
<td>24.1%</td>
<td>χ²(3)=5.71 p=.13</td>
</tr>
<tr>
<td>Clozapine use (%)</td>
<td>8.1%</td>
<td>13.4%</td>
<td>14.0%</td>
<td>18.5%</td>
<td>χ²(3)=10.17 p=.017</td>
</tr>
<tr>
<td>WLT Immediate Recall</td>
<td>25.2 (6.3)</td>
<td>24.8 (6.5)</td>
<td>24.2 (6.0)</td>
<td>23.6 (6.9)</td>
<td>F(3,951)=0.18 p=.91</td>
</tr>
<tr>
<td>WLT Retention Rate</td>
<td>0.8 (0.2)</td>
<td>0.8 (0.2)</td>
<td>0.8 (0.2)</td>
<td>0.8 (0.2)</td>
<td>F(3,951)=0.34 p=.79</td>
</tr>
<tr>
<td>Digit Symbol-Coding</td>
<td>73.6 (17.4)</td>
<td>73.9 (16.4)</td>
<td>67.7 (17.2)</td>
<td>67.2 (16.7)</td>
<td>F(3,957)=0.63 p=.60</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>13.7 (4.5)</td>
<td>13.2 (4.7)</td>
<td>12.8 (4.5)</td>
<td>11.6 (4.7)</td>
<td>F(3,949)=0.73 p=.54</td>
</tr>
<tr>
<td>Block Design</td>
<td>40.5 (16.2)</td>
<td>43.8 (16.2)</td>
<td>40.3 (16.7)</td>
<td>38.1 (16.6)</td>
<td>F(3,951)=0.77 p=.51</td>
</tr>
<tr>
<td>Information</td>
<td>17.4 (5.3)</td>
<td>17.3 (6.0)</td>
<td>17.0 (5.4)</td>
<td>15.7 (5.5)</td>
<td>F(3,952)=0.61 p=.60</td>
</tr>
<tr>
<td>CPT Reaction Time</td>
<td>0.4 (0.1)</td>
<td>0.4 (0.1)</td>
<td>0.4 (0.1)</td>
<td>0.4 (0.1)</td>
<td>F(3,891)=0.81 p=.49</td>
</tr>
<tr>
<td>CPT Accuracy</td>
<td>98.9 (4.2)</td>
<td>99.3 (1.3)</td>
<td>98.8 (4.1)</td>
<td>98.1 (5.8)</td>
<td>F(3,891)=0.32 p=.81</td>
</tr>
<tr>
<td>RST Reaction Time</td>
<td>0.2 (0.2)</td>
<td>0.2 (0.2)</td>
<td>0.2 (0.2)</td>
<td>0.2 (0.2)</td>
<td>F(3,837)=1.21 p=.31</td>
</tr>
<tr>
<td>RST Accuracy</td>
<td>0.1 (0.2)</td>
<td>0.1 (0.2)</td>
<td>0.1 (0.1)</td>
<td>0.1 (0.2)</td>
<td>F(3,837)=2.09 p=.10</td>
</tr>
<tr>
<td>DFAR</td>
<td>70.0 (10.0)</td>
<td>70.5 (10.6)</td>
<td>70.3 (9.9)</td>
<td>68.6 (11.0)</td>
<td>F(3,901)=0.96 p=.41</td>
</tr>
<tr>
<td>Hinting Task</td>
<td>18.5 (2.1)</td>
<td>18.6 (2.1)</td>
<td>18.4 (2.1)</td>
<td>18.2 (2.1)</td>
<td>F(3,829)=3.03 p=.03</td>
</tr>
<tr>
<td>BFRT</td>
<td>22.9 (2.3)</td>
<td>22.8 (2.2)</td>
<td>22.7 (2.4)</td>
<td>22.9 (2.3)</td>
<td>F(3,946)=1.95 p=.12</td>
</tr>
</tbody>
</table>

WLT: Word Learning Task; RST: Response Shifting Task; CPT: Continuous Performance Task; DFAR: Degraded Facial Affect Recognition; BFRT: Benton Face Recognition Task
comparisons. Finally, cross-trait cross-relative analyses did not yield significant associations between Y-BOCS scores in probands and any of the cognitive parameters in their siblings or parents (results not shown).

**DISCUSSION**

To the best of our knowledge, our study was the first to assess the association between OCS and cognitive functioning in patients with non-affective psychosis, their unaffected siblings and parents, and control subjects. Contrary to our hypothesis, neither within-subject analyses nor cross-relative analyses yielded a clear association between OCS and cognitive performance. While OCS were significantly associated with worse set shifting accuracy in parents and worse processing speed in controls, the effect sizes were too small to be clinically relevant. Cross-trait cross-relative analyses were performed to exclude possible disease-related confounding, but failed to demonstrate an association between level of OCS in patients and their relatives’ cognitive performance. Our results do therefore not support the existence of a schizo-obsessive subtype from a neurocognitive perspective. Possible implications of the findings, together with suggestions for future research, are provided here.

In case of negative findings as in our study, it is important to evaluate differences with other study designs in the field to reflect on whether we might have missed an association between OCS and cognition in schizophrenia that is actually present. In contrast to our study seven studies reported a negative association between OCS and cognitive functioning in schizophrenia (Berman et al., 1998; Hwang et al., 2000; Kumbhani et al., 2010; Lysaker et al., 2000; Lysaker et al., 2002; Lysaker et al., 2009; Patel et al., 2010). Alternatively, seven studies corroborated our results, with OCS+ patients demonstrating similar, or even slightly better cognitive functioning compared to OCS- patients (Borkowska et al., 2003; Hermesh et al., 2003; Lee et al., 2009a; Ongur & Goff, 2005; Tiryaki & Ozkorumak, 2010; Tumkaya et al., 2009; Whitney et al., 2004).

**Table 3. Test statistics and effect sizes of significant random effect regression results with Y-BOCS score as independent variable and cognitive functioning as dependent variable**

<table>
<thead>
<tr>
<th></th>
<th>F(df)</th>
<th>p-value</th>
<th>Effect Size (Cohen’s d)</th>
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<tbody>
<tr>
<td><strong>Patients</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hinting Task</td>
<td>F(1, 947) = 4.47</td>
<td>&lt;.04</td>
<td>+.03</td>
</tr>
<tr>
<td><strong>Siblings</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>No significant results</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Parents</strong></td>
<td></td>
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<td></td>
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<tr>
<td>RST Accuracy</td>
<td>F(1, 658) = 14.63</td>
<td>&lt;.01**</td>
<td>-.10</td>
</tr>
<tr>
<td><strong>Controls</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Information</td>
<td>F(1, 529) = 3.99</td>
<td>&lt;.05</td>
<td>+.03</td>
</tr>
<tr>
<td>Digit Symbol-Coding</td>
<td>F(1, 525) = 7.04</td>
<td>&lt;.01**</td>
<td>-.05</td>
</tr>
</tbody>
</table>

** denotes significance after correction for multiple comparisons (p<.005)
It may be argued that an association between OCS and cognitive functioning in schizophrenia is only to be detected if the level of OCS is considerably high and the sample size is large enough. The mean Y-BOCS score of 11.6 in our OCS+ sample was relatively low due to the fact that patients with subclinical OCS were also included. In comparison, studies that did report an association between OCS and worse cognitive functioning included OCS+ patients with a higher Y-BOCS score (weighted mean = 21.6) (Berman et al., 1998; Hwang et al., 2000; Lysaker et al., 2002; Patel et al., 2010). However, apart from patients with subclinical (Y-BOCS 1-7) and mild (Y-BOCS 8-15) OCS, we also included a group with moderate to severe OCS (Y-BOCS ≥16; mean=20.8). Although this group represented only 5.5% of the patients, due to our large sample size the number of OCS+ patients was still considerable (n=54). In comparison, studies that did demonstrate an association between OCS and worse cognitive functioning were performed in a weighted mean number of 18.2 OCS+ patients (Berman et al., 1998; Hwang et al., 2000; Lysaker et al., 2000; Lysaker et al., 2002; Lysaker et al., 2009; Patel et al., 2010). Consequently, our negative results cannot be merely attributed to relatively mild OCS, or to insufficient numbers of OCS+ patients.

Moreover, it has been suggested that the association between OCS and cognition in schizophrenia is age-dependent (Borkowska et al., 2003). Although our patients were younger (mean age = 27.8) compared to studies that demonstrated worse cognitive functioning in OCS+ patients (weighted mean age = 42.6) (Berman et al., 1998; Hwang et al., 2000; Kumbhani et al., 2010; Lysaker et al., 2000; Lysaker et al., 2002; Lysaker et al., 2009; Patel et al., 2010), they were also considerably younger compared to patients in studies that failed to demonstrate such an association (weighted mean age = 38.1) (Borkowska et al., 2003; Hermesh et al., 2003; Lee et al., 2009a; Ongur & Goff, 2005; Tiryaki & Ozkorumak, 2010; Tumkaya et al., 2009; Whitney et al., 2004). Together with the fact that age differences were controlled for in our analyses, it is unlikely that our negative findings are the result of the inclusion of younger patients.

Another possibility is that we did not assess the right cognitive domains. In the case of a schizo-obsessive subtype, OCS+ patients would be expected to differ from OCS- patients on cognitive domains that show impairments in non-schizophrenic OCD patients (Berman et al., 1998; Whitney et al., 2004). The neurobiology of OCD is believed to be characterized by structural and functional abnormalities in the orbitofrontal cortex, anterior cingulate gyrus and basal ganglia. Accordingly, OCD patients have shown impaired performance on neurocognitive tasks sub-served by these brain regions, including verbal memory, processing speed, set shifting and sustained attention (Chamberlain et al., 2005; Kuelz et al., 2004). We did not find an association between performance on these domains and OCS in our study sample.

On the other hand, three cognitive domains that are known to be associated with OCD were not assessed in our study; decision making, response inhibition and visual memory (Chamberlain et al., 2005; Kuelz et al., 2004). Only two out of 14 previously mentioned studies used a gambling task to assess decision making performance and failed to report an association with OCS (Patel et al., 2010; Whitney et al., 2004). Response inhibition was also assessed in two studies, with one reporting a negative association with OCS (Lysaker et al., 2009) that could not be replicated in the second study (Patel et al., 2010). Visual memory was assessed in five studies, with mixed results of worse, equal, and even better performance in OCS+ patients.
Results demonstrate that, so far, it has not been possible to identify a unique pattern of cognitive impairment that distinguishes OCS+ from OCS- patients.

Likewise, the only cognitive test domain that has shown impairments in OCS+ patients more than once is cognitive flexibility assessed with the Wisconsin Card Sorting Test (WCST) (Hwang et al., 2000; Lysaker et al., 2000; Lysaker et al., 2002). Impairment in the WCST has been described to be typical for dorsolateral prefrontal cortex dysfunction in schizophrenia (Abbruzzese et al., 1995). On the other hand, Goldberg and Weinberger (Goldberg & Weinberger, 1994) have cautioned against an over-interpretation of the WCST as a specific measure of focal (schizophrenia-related) prefrontal dysfunction because, due to task complexity, it addresses many cognitive domains and may therefore merely represent a final common cognitive pathway. This is in line with the statement that the cognitive profile of OCS+ patients is more likely to represent a ‘pathophysiological double jeopardy’ (i.e. having two conditions instead of one), rather than a unique pattern of cognitive deficits (Whitney et al., 2004).

In addition to this lack of consistency in the cognitive domain, some methodological issues of previous studies should be taken into consideration. Despite the argument that cognitive impairment on a single domain is regarded as insufficient ground to label a patient (or a group of patients) as cognitively impaired (Palmer et al., 1997), four out of seven studies concluded OCS+ patients to be ‘impaired’ in comparison to OCS- patients based on deficits in one domain (Kumbhani et al., 2010; Lysaker et al., 2000; Lysaker et al., 2009; Patel et al., 2010). Moreover, the majority of studies did not adequately minimize the risk of a type I error by maintaining an alpha level of <.05 despite the performance of multiple statistical comparisons (Berman et al., 1998; Kumbhani et al., 2010; Lysaker et al., 2000; Patel et al., 2010). Thirdly, although cognitive performance in schizophrenia is known to be affected by the level of psychotic symptoms, some studies did not correct their analyses for the fact that positive (Lysaker et al., 2000; Lysaker et al., 2002) and negative (Hwang et al., 2000; Lysaker et al., 2002) symptoms were significantly higher in the OCS+ patients compared to OCS- patients. Hence, in those studies worse cognitive functioning may have been erroneously attributed to OCS.

Our study extended upon previous research by the inclusion of subjects at increased genetic risk for psychosis. Unaffected relatives have been used in the search for cognitive endophenotypes in schizophrenia (Gur et al., 2007) and OCD (Menzies et al., 2007), but not for the combination of both disorders. In case of an association between OCS and cognitive functioning in patients, replication of this result in their unaffected relatives would indicate i) that this association is not merely state-related and ii) that there may be a shared genetic vulnerability for both schizophrenia and OCD (Poyurovsky & Koran, 2005). In our case, no distinct cognitive pattern in the patients emerged and thus the analysis of relatives was not necessary to exclude any psychosis-related confounding. However, the inclusion of unaffected relatives was still valuable to investigate whether subjects at increased genetic risk for both psychosis and OCS display an additional cognitive vulnerability compared to relatives of OCS- patients, which could not be confirmed. Moreover, unaffected relatives did not display higher levels of OCS compared to controls. These results do not corroborate previous results of a strong familial-genetic component in OCD (Mataix-Cols et al., 2005), at least not in families with genetic loading for psychosis.
The results of this study should be viewed in the light of some limitations. Since the same researchers administered both the PANSS and the Y-BOCS, rater bias cannot be excluded. What makes rater bias less likely though is that the cognitive and OCS assessments were part of a large test battery in a group of patients and relatives that were unselected for the presence of OCS. Secondly, although the heterogeneity of our sample in age, illness duration and psychotic severity enhanced generalizability, it may have equalled out cognitive differences in specific subgroups of patients. Thirdly, we did not include all cognitive measures that were found to be associated with OCS comorbidity in former studies.

CONCLUSIONS

Despite the large sample size and the inclusion of unaffected relatives this study could not confirm the existing premise that OCS+ patients may be differentiated from OCS- patients based on their cognitive performance. Although OCS+ patients displayed a more severe clinical profile, our results do not validate a schizo-obsessive subtype from a cognitive perspective. While OCS+ patients in previous studies demonstrated a rather nonspecific cognitive profile, the majority of results was either marginally significant, present in a single cognitive domain, or possibly confounded by higher levels of psychotic symptomatology. Hence, future research including patients and their unaffected relatives is warranted to clarify the nature of genetic and environmental factors that predispose individuals with psychosis to OCS co-morbidity.

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ASSOCIATION BETWEEN OLFATORY IDENTIFICATION DEFICITS AND PARKINSONISM IN PATIENTS WITH NON-AFFECTIVE PSYCHOSIS

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In progress
ABSTRACT

Background: Olfactory identification deficits (OIDs) are present in schizophrenia patients and individuals at increased risk for psychosis but its pathophysiology remains unclear. While dopaminergic imbalance is known to lie at the core of schizophrenia symptomatology, its role in the development of OIDs has not been elucidated yet. This study investigated the association between OIDs and symptoms of parkinsonism as a derivative of dopaminergic functioning.

Methods: In 320 patients diagnosed with non-affective psychosis, olfactory identification performance was assessed by means of the Sniffin’ Sticks task. Level of parkinsonian symptoms was assessed by means of the Unified Parkinson’s Disease Rating Scale (UPDRS-III). By means of linear regression, the association between UPDRS and Sniffin’ Sticks score was investigated while correcting for possible confounders.

Results: Higher UPDRS scores significantly predicted worse olfactory identification in patients with non-affective psychosis (beta -0.19; p<0.001). The other covariates significantly associated with olfactory identification were negative symptoms (beta -0.22; p<0.001) and estimated IQ (beta 0.14; p<0.012). Together, they accounted for 15% of the variance in olfactory identification.

Conclusion: Results provide preliminary evidence that the same dopaminergic vulnerability may underlie the development of motor symptoms and OIDs in patients with non-affective psychosis. Further investigation should evaluate the clinical value of OIDs as a marker of dopaminergic imbalance that may predict psychosis.
1. INTRODUCTION

Olfactory identification deficits (OIDs) are consistent features in patients with non-affective psychosis that already exhibit in first episode psychotic patients (Nguyen et al., 2010). The pathophysiological mechanism underlying OIDs in schizophrenia however remains unclear. What has been elucidated so far is that the variance in OIDs in schizophrenia patients may not be explained by a range of state-related factors such as level of positive symptomatology, neurocognitive functioning, the use of nicotine and cannabis, or illness duration (Nguyen et al., 2010; Moberg et al., 1999). The prevailing explanation for olfactory problems in patients with schizophrenia is that brain abnormalities in schizophrenia and olfactory processing involve overlapping neuroanatomic structures, including temporolimbic and prefrontal regions (Nguyen et al., 2010; Cohen et al., 2012; Turetsky et al., 2009).

Despite the variety of behavioural and biological research in the field of OIDs in patients with schizophrenia, the putative role of dopamine in its pathophysiology has received very little attention. This is surprising since a relationship between OIDs and dopamine seems plausible for various reasons. Disruptions in corticostriatal circuitry and dopamine neurotransmission are often regarded as central to the positive, negative, and cognitive symptoms observed in schizophrenia (Howes and Kapur, 2009; Hovington and Lepage, 2012) and may also contribute to OIDs. Additionally, both human and animal studies have provided evidence that dopaminergic neurotransmission may play a central role in the synaptic organization, neural circuitry and biochemistry of the olfactory system (McLean and Shipley, 1988; Feron et al., 1999; Kamath et al., 2012). Finally, studies in non-psychotic populations, including patients with Parkinson’s disease, attention deficit hyperactivity disorder (ADHD), and drug-induced parkinsonism have indicated an association between olfactory performance and dopaminergic status (Kruger et al., 2008; Deeb et al., 2010; Schecklmann et al., 2011). Olfactory performance may therefore provide a unique model to investigate the effects of altered dopamine-mediated processes in patients with psychotic disorders.

Elucidating the putative dopaminergic contribution to OIDs in psychosis would not only shed light on pathophysiological mechanisms, but would also offer possible directions for early detection in at-risk subjects. For example, olfactory testing might be used to improve psychosis prediction similar to the prediction of Parkinson’s disease. Recent data indicate that more than 95% of patients with Parkinson’s disease present with significant olfactory loss that may precede clinical motor symptoms by years (Haehner et al., 2011). Likewise, several studies have demonstrated how a simple olfactory test was able to differentiate between asymptomatic subjects who would and would not develop Parkinson’s disease during follow-up (Landis et al., 2012).

Previous studies on the association between olfaction and dopaminergic functioning in different patient populations have used either Single Photon Emission Computed Tomography (SPECT) or motor abnormalities as a derivative of dopaminergic functioning (Ponsen et al., 2010; Berendse and Ponsen, 2009; Bovi et al., 2010). The aim of the current study was to assess the association between OIDs and parkinsonian symptoms in a cross-sectional sample of patients with non-affective psychosis. These motor abnormalities may have arisen either spontaneously (Pappa and Dazzan, 2009) or in response to antipsychotic treatment (Kruger et al., 2008; Bovi
et al., 2010) and are considered as a clinically relevant marker of dopaminergic imbalance. We hypothesized that the presence of OIDs would be associated with higher levels of parkinsonian symptoms.

2. METHODS

Study design and population
Data pertain to a subsample of the Genetic Risk and Outcome of Psychosis (GROUP) project, a longitudinal multicenter study in the Netherlands and Belgium (Korver et al., 2012). GROUP included patients with psychosis, their unaffected first-degree relatives, and control subjects. The present study investigated the association between OIDs and motor symptoms in the patient group exclusively.

Inclusion criteria were (1) age range of 16 to 50 years and (2) good command of the Dutch language. Patients had to meet DSM-IV-TR criteria for a non-affective psychotic disorder (APA, 2000) which was assessed with the Comprehensive Assessment of Symptoms and History interview (CASH; Andreasen et al., 1992) or the Schedules for Clinical Assessment in Neuropsychiatry version 2.1 (SCAN; Wing et al., 1990). The study protocol was approved centrally by the Ethical Review Board of the University Medical Centre Utrecht and subsequently by local review boards of each participating institute. All subjects gave written informed consent in accordance with the committee’s guidelines.

Olfactory Identification
Olfactory identification was assessed with a commercially available and comprehensively evaluated test battery called the Sniffin’ Sticks Test that is based on pen-like odour dispensing devices (Hummel et al., 2001). Participants had to identify 16 common odours by means of forced multiple choice from a list of four descriptors. Odour sticks were presented birhinally in a fixed order by a trained researcher. The interval between odour presentations was 30 seconds. Although tests of odour threshold and discrimination are also available, due to time constraints only odour identification was assessed as the olfactory domain most commonly affected in schizophrenia patients (Cohen et al., 2012). The Sniffin’ Sticks have been employed previously to assess olfactory identification in patients with psychosis and their unaffected twins (Ugur et al., 2005).

Parkinsonism and clinical variables
Parkinsonian symptoms such as bradykinesia, rigidity and tremor were assessed using the Unified Parkinson’s Disease Rating Scale (UPDRS-III; Ramaker et al., 2002). Severity of psychotic symptoms in patients was rated with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). Level of symptoms and disabilities was assessed with the Global Assessment of Functioning scale (GAF; APA, 2000). Substance use was assessed with a short version of the Composite International Diagnostic Interview (CIDI; World Health Organization 1990) sections B (tobacco use) and L (substance use). Current antipsychotic use was transferred into haloperidol dose equivalents (Kane et al., 2003). General IQ was estimated by means of the four-subtest short version of the Wechsler Adult Intelligence Scale (WAIS-III; Blyler et al., 2000).
Statistical analyses
Linear regression analysis was performed to determine whether level of parkinsonism (UPDRS score) predicted olfactory identification (Sniffin’ Sticks score) over and above other variables known to be associated with olfactory identification. In the first step, by means of Pearson’s correlations a range of potential confounders were tested separately for their association with Sniffin’ Sticks score. Age and gender were tested since older age and male gender are known to be associated with more OIDs (Hawkins and Pearlson, 2011; Malaspina et al., 2012). Estimated IQ score and highest level of education were tested since intellectual ability may have a positive influence on olfactory identification performance (Corcoran et al., 2005). PANSS positive, PANSS negative, PANSS general, GAF symptoms, GAF disabilities and illness duration in years were tested to exclude confounding by illness severity (Corcoran et al., 2005; Malaspina et al., 2012). The variable haloperidol dose equivalents was tested due to its association with parkinsonism (Seeman, 2010) and possibly OIDs. Past-year tobacco and cannabis use were tested since these may deteriorate peripheral odour sensitivity (Ishimaru and Fujii, 2007). In the second step, a multiple linear regression model was built using the stepwise procedure in SPSS 17.0 with UPDRS and significant covariates as predicting variables and Sniffin’ Sticks score as dependent variable. The significance level of α was set at <0.05.

3. RESULTS
Sample
The mean PANSS positive score was 11.2 (± 4.5), mean PANSS negative score was 12.4 (± 5.1), and mean PANSS general score was 24.5 (± 6.9). Mean age at psychosis onset was 22.2 years (± 6.2). Mean illness duration was 7.2 years (± 4.5). Daily nicotine use over the past year was present in 60.1% of patients and 25.0% had been using cannabis over the past year. Mean UPDRS score was 6.1 (± 7.4). The percentage of patients using antipsychotic medication at the time of testing was 79.7%, with a mean antipsychotic dosage in haloperidol dose equivalents of 4.1 (± 2.6).

Regression analysis
Pearson’s correlational analyses yielded significant associations between olfactory identification and PANSS negative (beta -0.32; p<0.001), UPDRS total (beta -0.30; p<0.001), WAIS IQ (beta 0.23; p<0.001), and haloperidol dose equivalents (beta -0.14; p<0.007). Hence, these variables were entered as predictor variables in the regression model by means of the stepwise procedure. Correlations with age, gender, highest educational level, PANSS positive and general score, GAF scores, illness duration, and past year tobacco and cannabis use were not significantly correlated with Sniffin’ Sticks score and therefore not entered into the model.

As presented in table 1, three variables in the final model significantly predicted olfactory identification performance: PANSS negative (R² change 0.10; p<0.001), UPDRS score (R² change 0.04; p<0.001) and WAIS estimated IQ (R² change 0.02; p<0.012). The variable haloperidol dose equivalents did not significantly predict olfactory identification over and above these three predictors and was excluded from the regression model.
4. DISCUSSION

The current study was the first to examine the association between OIDs and motor symptoms in a large sample of patients with non-affective psychosis. Two main findings arise from our cross-sectional study. First, we found that higher levels of parkinsonism were associated with lower olfactory identification scores. Second, higher level of negative—but not positive-symptomatology was also inversely associated with olfactory identification performance.

Our results are in line with a previous study that found a positive association between drug-induced parkinsonism and level of OIDs in patients diagnosed with depressive disorder (Kruger et al., 2008). In that study, patients were divided into three groups: one who had developed extrapyramidal symptoms (EPS) under antipsychotic treatment, one using antipsychotics without development of EPS, and one without use of antipsychotics. Patients in the EPS group exhibited significantly worse olfactory identification performance than those in the two other groups. The authors concluded that OIDs may be induced by antipsychotic treatment, but only in patients with a sensitivity toward developing EPS. In our study the association between parkinsonism and OIDs remained while correcting for antipsychotic dosage. It therefore appears that the sensitivity to develop parkinsonism and OIDs in patients with psychosis may be associated with an individual vulnerability of the dopaminergic system. This hypothesis is corroborated by a review and meta-analysis that did not find a relationship between OIDs and the use of antipsychotics per se (Rupp, 2010; Moberg et al., 1999).

In line with the literature, OIDs in our study were linked with more negative symptoms (Compton et al., 2006; Moberg et al., 1999; Rupp, 2010; Moberg et al., 2006). In a recent meta-analysis on the neuropsychology of deficit schizophrenia, which is characterized by idiopathic and enduring negative symptoms, olfactory functioning was mentioned as the task most affected in comparison to non-deficit patients with an effect size of 1.1 (Cohen et al., 2007). Moreover, both motor and negative symptoms have been linked to dopaminergic hypoactivity in specific brain regions. Parkinsonism, either drug-induced by blockade of the D2 receptor or spontaneous by a decrease in the production of dopamine, is believed to result from a relative shortage of dopaminergic signalling in the basal ganglia, especially the striatum (Caligiuri et al., 1993; Nord and Farde, 2011; Pappa and Dazzan, 2009). Negative symptoms on the other hand are known to correlate with lower dopaminergic activity in the frontal cortex (Hovington and Lepage, 2012; Semkovska et al., 2001).

Also with regard to OIDs there is evidence for an association with dopaminergic imbalance in subcortical and frontal brain regions. Dopaminergic involvement of the basal ganglia in OIDs...
was suggested in a recent SPECT study performed in psychiatric patients with drug-induced parkinsonism (Bovi et al., 2010). Worse olfactory performance was associated with lower dopamine uptake in the putamen. Moreover, evidence that the frontal cortex is involved in the development of OIDs was found already three decades ago in patients with orbitofrontal brain lesions that suffered from olfactory agnosia, i.e. inability to identify odours in the absence of olfactory sensitivity problems (Potter and Butters, 1980). Ever since, several imaging studies have shown a link between OIDs and hypoactivation of the frontal cortex in patients with schizophrenia (Schneider et al., 2007; Malaspina et al., 1998). Recent evidence furthermore indicates that the catechol-O-methyltransferase (COMT) val158met polymorphism, which is associated with dopamine levels mainly in the prefrontal cortex, may be linked with OIDs in patients with schizophrenia (Kamath et al., 2012).

Observations that OIDs are associated with parkinsonian and negative symptoms may be of clinical importance as the prodromal phase of psychosis is believed to be characterized by dopaminergic dysregulation that alters the appraisal of stimuli through a process of aberrant salience (Howes and Kapur, 2009). Motor and negative symptoms may be early markers of this dopaminergic imbalance, since they are experienced by individuals with an increased risk of developing psychosis, including genetic and clinical high risk individuals (Yung et al., 2012; Koning et al., 2011; Scala et al., 2012). OIDs may be another early dopaminergic marker that exhibits in medication-naive patients with first-episode psychosis (Nguyen et al., 2010), unaffected relatives (Turetsky et al., 2008; Roalf et al., 2006), schizotypy patients (Park and Schoppe, 1997), and individuals in the putative prodromal phase (Brewer et al., 2003).

In Parkinson’s disease, olfactory functioning is already considered to be a strong biomarker for pre-symptomatic disease detection. Prospective studies in first-degree relatives of Parkinson’s disease patients have established hyposmia as a pre-motor sign of Parkinson’s disease that can precede the onset of motor symptoms by as long as five years (Ponsen et al., 2010; Berendse et al., 2011; Haehner et al., 2011). Deeb and colleagues even found that a basic smell test is as sensitive as a dopamine transporter scan for the diagnosis of Parkinson’s disease (Deeb et al., 2010). In comparison to the body of research in Parkinson’s disease it is remarkable how little attention has been drawn to the predictive value of OIDs in psychosis. This is especially true since the need to improve psychosis prediction is high. Current ultra high risk (UHR) criteria only predict subsequent psychosis in 15-30% of cases, which restricts early intervention initiatives to delay, attenuate or even prevent development of psychosis (de Koning et al., 2009; Yung et al., 2007). To our knowledge, to date only two longitudinal studies have investigated the possible predictive value of OIDs for transition to psychosis (Brewer et al., 2003; Woodberry et al., 2010). Both studies found that olfactory identification performance was lower in UHR subjects that would subsequently develop schizophrenia. The use of OIDs as a possible predictor of psychosis in high-risk individuals therefore seems a promising topic of research that deserves further evaluation. In addition, OIDs as a marker of dopaminergic sensitivity may predict antipsychotic response in terms of both efficacy and side-effects. The prognostic validity of such procedures needs to be assessed.

Our findings should be viewed in the light of some limitations. The current study used only one behavioural measure of olfactory processing. Odour identification tasks, like the one used
here, are considered the most highly standardized and reliable measures of psychophysical olfactory processing in humans (Hummel et al., 2001). Nevertheless, studies have shown that dopaminergic agents such as methylphenidate may differentially affect different aspects of olfactory performance, including odour acuity, discrimination and identification (Schecklmann et al., 2011; Romanos et al., 2008). To test the role of dopamine in various olfactory processes a broader test battery would be required. Second, the variance in olfactory identification that could be explained by the UPDRS was small. Hence, it would be interesting to investigate whether a more elaborate assessment of motor symptoms, including e.g. an objective measure of motor symptoms (Mera et al., 2012), may explain larger proportions of variance in OIDs. Third, although we corrected the analyses for antipsychotic dosage, we did not take into account the affinity to the D2 receptor which is known to influence the development of extrapyramidal symptoms (Seeman, 2010) and possibly also OIDs. This would need to be addressed in a future study.

In conclusion, the current study in a large sample of patients with non-affective psychosis showed that the level of parkinsonian and negative symptoms significantly predicted OIDs. Results suggest that OIDs in patients may be influenced, in part, by functional dopaminergic hypoactivity. Future studies should evaluate the clinical value of this finding in order to see whether OIDs may be used as an early detection marker of psychotic disorders.

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COGNITIVE ALTERATIONS IN PATIENTS WITH NON-AFFECTIVE PSYCHOTIC DISORDER AND THEIR UNAFFECTED SIBLINGS AND PARENTS

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# GROUP investigators: René S. Kahn, Don H. Linszen, Jim van Os, Durk Wiersma, Richard Bruggeman, Wiepke Cahn, Lieuve de Haan, Lydia Krabbendam and Inez Myin-Germeys

ABSTRACT

Objective: The purpose of this study was to examine a range of cognitive measures as candidate phenotypic liability markers for psychosis in a uniquely large sample of patients with psychosis, their unaffected relatives and control subjects.

Method: Patients with non-affective psychosis (n=1093), their unaffected siblings (n=1044), parents (n=911), and controls (n=587) completed a comprehensive cognitive test battery. Cognitive functioning was compared using tests of verbal learning and memory, attention/vigilance, working memory, processing speed, reasoning and problem solving, acquired knowledge and social cognition. Age- and gender-adjusted z-scores were compared between groups using mixed-model analyses of covariance. Clinically relevant impairment (-1 and -2 SD from control mean) was compared between subject groups.

Results: Patients performed significantly worse than controls on all cognitive domains (z-range -0.26 to -1.34). Siblings and parents showed alterations for immediate verbal learning, processing speed, reasoning and problem solving, acquired knowledge and working memory (z-range -0.22 to -0.98). Parents showed additional alterations for social cognition. Prevalence of clinically relevant impairment in relatives ranged from 50% (-1 SD criterion) to 10% (-2 SD criterion).

Conclusion: Unaffected family members show mild alterations in specific cognitive domains that can be further tested as intermediate phenotypes in genetically sensitive analyses.

Significant outcomes:
» Patients with non-affective psychotic disorder are characterized by cognitive alterations across all cognitive domains with relatively small effect sizes compared to meta-analytic results.
» Verbal learning, processing speed, reasoning and problem solving, working memory, and acquired knowledge are the most promising cognitive intermediate phenotypes, demonstrating alterations in genetic high risk groups.
» The distribution of clinically relevant cognitive alterations in patients and their first-degree relatives is suggestive of a continuum of neuropsychological functioning, with approximately 30% of the patients and 50% of the relatives displaying no clinically manifest deficit.

Limitations:
» Effect sizes in parents might have been somewhat inflated due to differences in age-range between the parent and control group.
» Not all subjects had complete cognitive test scores, which may have impacted on the effect sizes.
» Group differences in educational achievement and IQ remain a potential explanation for group differences on other cognitive test scores and cannot be ruled out through statistical adjustment.
INTRODUCTION

Cognitive alteration is a stable, trait-related aspect of schizophrenia that has been associated with impaired quality of life and poorer functional outcome (1). Subtle cognitive deficits are present prior to psychosis onset and may help to predict conversion to psychosis in “clinical high risk” subjects who are in the putative prodromal phase of psychosis (2, 3). Attenuated cognitive alterations have also been reported in clinically unaffected relatives of schizophrenia patients who are referred to as being at “genetic high risk” for psychosis. Cognitive alterations may therefore reflect the expression of genetic vulnerability for schizophrenia (4-7). Identifying such cognitive intermediate phenotypes may be a productive approach in genetic linkage and association studies in schizophrenia as they are closer to the mechanism for gene action than the overall disease phenotype.

Although evidence on cognitive alterations as intermediate phenotypes in schizophrenia is promising, sample sizes have been limited (8). This is illustrated by the fact that the most recent review in young relatives of psychotic patients included 18 studies with a mean of 102 high-risk relatives (range 29-322) and 84 control subjects (range 26-201), while only 5 studies included a patient group (mean 76, range 27-207) (4). Thus, the most appealing evidence to date originates from meta-analyses and reviews. Summarizing evidence related to a specific hypothesis can be distorted however by the selective publication of studies with certain (especially positive) results (9). In addition, studies on cognition in genetic high risk samples have been limited by (i) the analysis of different biological relatives as one group (siblings, children and parents), (ii) the inappropriate screening for psychiatric disorders in the relatives, and (iii) limited assessment of cognitive functions (8). In combination with a high within- and between-subject variability of cognitive performance in genetic high risk samples (8), these methodological limitations have hampered the identification of cognitive intermediate phenotypes so far. There is also a lack of knowledge about the proportion of genetic high risk subjects that are cognitively indistinguishable from healthy controls and which proportion displays a clinically relevant cognitive impairment. While for patients with schizophrenia the proportion of cognitively spared patients lies around 15-30% (8, 10), little is known about this percentage in genetic high risk subjects.

AIMS OF THE STUDY

The aim of the present study was to test a broad range of cognitive measures as candidate intermediate phenotypes in a large population of patients with a non-affective psychotic disorder, their unaffected siblings and parents, and control subjects. Therefore, age- and gender-adjusted z-scores were compared between subject groups. Secondly, the proportions of clinically relevant cognitive impairment (no, mild, moderate, severe) were compared between subject groups, using both 1 and 2 SD below the control mean as impairment cut-off.
MATERIAL AND METHODS

The sample of the Genetic Risk and Outcome of Psychosis study (GROUP) was described previously (11). The baseline GROUP sample consists of 1120 patients with a non-affective psychotic disorder, 1057 unaffected siblings, 919 parents, and 590 unrelated control subjects. Within the patient group, 84% had a schizophrenia-related disorder (DSM-IV-TR code 295.x, 80.0% schizophrenia, 13.1% schizo-affective disorder, 6.9% schizophreniform disorder; n=945), 1% was diagnosed with psychotic illness in the context of substance abuse or somatic illness (DSM-IV-TR code 293.x/292.x, n=9), and 13% fulfilled criteria for other psychotic disorders (DSM-IV-TR code 297/298, n=149). Six patients had a missing diagnosis but fulfilled inclusion criteria, and 11 patients had a final diagnosis of affective psychosis after fulfilling diagnostic criteria of non-affective psychosis at study entry, which may have been the result of subtle diagnostic changes between the time of identification for inclusion and actual assessment.

The mean age at onset of psychosis was 22.6±6.7 years (range 10-54), and the mean illness duration was 4.4±4.1 years (range 0.1-41.1). At the time of testing 86.1% of the patients were on antipsychotic treatment with one or more antipsychotics, with olanzapine (27.8%), risperidon (23.7%), and clozapine (11.6%) being the antipsychotics most frequently used. The mean number of psychotic episodes was 1.7±1.1 (range 1-8) and the mean number of psychiatric hospitalizations was 1.9±2.3 (range 0-30). According to PANSS remission criteria (12, 13), 45.1% of the patients were in remission from psychosis at the time of testing. Patients had a mean PANSS positive score of 14.0±6.4 (range 7-41) and a mean PANSS negative score of 15.0±6.6 (range 7-39). In 12.1% of the siblings (n=152), 19.4% of the parents (n=178) and 10.0% of the controls (n=59) there was a lifetime history of a DSM-IV-TR mental disorder. Depressive disorders were by far most common, reported in 10.5% of siblings (n=111), in 17.7% of parents (n=163) and in 8.5% of controls (n=50).

Verbal learning and memory was assessed with a visually-presented Word Learning Task (WLT; 14). Outcome measures were: immediate recall (number of words recalled over the three 15-word trials), retention rate (delayed free recall after 20 minutes divided by the maximum score of immediate recall trials 1-3), and recognition (true positives – false positives). Attention/vigilance was assessed using a Continuous Performance Test (CPT-HQ) with working memory load, known in the literature as CPT-AX (15). Outcome measures were reaction time (reaction time for correct detections) and accuracy (proportion of correct detections). The WAIS-III subtest Arithmetic (16) was assessed to measure working memory. This subtest is a relatively complex measure of working memory capacity since it also addresses verbal comprehension and arithmetic skills, which are both associated with educational level (17). The Response Shifting Task (RST), a modified version of the Competing Programs Task (18, 19), was administered in order to assess set-shifting ability from an imitation response rule to a reversal response rule. Outcome variables were accuracy cost (proportion correct in the imitation condition – proportion correct in the reversal condition) and reaction time cost (reaction time in the reversal condition – reaction time in the imitation condition). The first response in each block and responses that were preceded by errors were excluded from analyses (20). In addition, only reaction times for correct responses were used and trials with a reaction time shorter than 150ms were eliminated from the analyses. The WAIS-III subtest Digit Symbol-Coding (16) was
used as a measure of speed of processing. Reasoning and problem solving was assessed using the subtest **Block Design** from the WAIS-III (16). The WAIS-III **Information** subtest (16) was used as a measure of acquired knowledge. Moreover, the cognitive assessment included two dimensions of social cognition. Outcome measures of the **Degraded Facial Affect Recognition** task (DFAR; 21) were the proportion correctly recognized neutral, happy, fearful and angry faces and the overall proportion correct. The short form of the **Benton Facial Recognition Test** (22) was assessed to be used as a covariate to adjust for non-emotional facial processing skills. Theory of mind was assessed using the **Hinting Task** that assesses mentalizing capacity required to comprehend real intentions behind indirect speech (23). Outcome measure was the sum of the ten separate item scores (range 0-20). It took approximately 90 to 120 minutes to complete the neuropsychological tests that were administrated in the following fixed order: WLT immediate recall, RST, CPT-HQ, Digit Symbol-Coding, WLT delayed recall, WLT recognition, DFAR, BFRT, Information, Arithmetic, Block Design, Hinting Task.

**Statistical analyses**

The data were analyzed using the SPSS 17.0 statistical package. To facilitate the comparison of cognitive functioning between patients, siblings, parents and control subjects, raw scores were converted into z-scores. Due to the fact that patients and siblings belong to different age categories than parents (Table 1), z-scores were adjusted for age and gender by dividing the control group into reference groups, setting a minimum of 50 subjects per stratum. This resulted in eight categories following methods described by Keefe et al. (24):

- Age ≤20: 71 males and 64 females
- Age 21-30: 85 males and 105 females
- Age 31-40: 59 males and 65 females
- Age ≥41: 55 males and 85 females

Adjusted z-scores were computed as follows. Let \( X_{jk} \) be the raw score \( X \) on subtest \( j \) (\( j=1 \) to 15) for subject \( k \). Assume that subject \( k \) has sex \( l \) (1 = male and 2 = female) and is in age category \( m \) (1≤20, 2=21-30, 3=31-40, 4≥41 years). The scaled score is then computed as follows: \( z_{\text{corrected}} = \frac{X_{jk} - M_{jm}}{SD_{jm}} \); where \( M_{jm} \) and \( SD_{jm} \) are the mean and standard deviation, respectively, for test \( j \) of the control population for sex \( l \) and age category \( m \). Resulting z-scores are identical to Glass’s delta estimator of effect size (25). Observations with more than three SDs from the mean were considered outliers and were replaced by the mean plus or minus 3 times the SD.

Subsequently, adjusted z-scores were compared between patients/siblings/parents and control subjects. In addition, adjusted z-scores were compared between siblings/parents and patients. To control for intra-family correlation mixed model analyses of covariance (ANCOVAs) were performed in which family was used as a random factor with a random intercept. Status (patient, sibling, parent, control) was the independent variable. Dependent variables were adjusted z-scores for 18 outcome measures derived from 10 cognitive tests. Although educational level of the subject and IQ may be associated with many of the putative intermediate phenotypes in question, they are also powerfully affected by schizophrenia (26). Therefore, the highest educational degree that had been obtained by one of the parents was entered into the model as a covariate instead. Since the Dutch educational system already
differentiates after primary school, we have chosen a coding system other than years of education. This ordinal 8-point scale indicates the level of education, and ranges from primary school to university. Mixed-model ANCOVAs for the DFAR variables incorporated the BFRT test scores as an additional covariate. Since mixed-model ANCOVAs were performed for multiple cognitive outcome parameters (n=18), a Bonferroni correction was adopted by setting the alpha level to $\alpha = 0.0028$.

Subsequently, between-group comparisons were performed only in those cognitive parameters for which the effect of Status in the ANCOVA was significant. Five post-hoc analyses were performed for each of those cognitive parameters, firstly to compare patients/siblings/parents with controls, and secondly to compare siblings/parents with patients. For these post-hoc analyses the alpha value was set to $\alpha = 0.05 / (5 \times \text{the number of cognitive parameters for which post-hoc comparisons were performed})$. In addition, the same correction for multiple analyses was also applied for the much more conservative alpha value of 0.001.

Normality of cognitive outcome measures was visually inspected and confirmed if the test-statistic W in the Shapiro Wilk test exceeded 0.90. All but three outcome measures were normally distributed. Ceiling effects were present for CPT accuracy, WLT recognition and the Hinting Task. Data transformation did not improve the normality of the distributions; therefore both parametric and non-parametric testing was conducted. Secondary to the mixed-model ANCOVAs, group-comparisons were performed using Kruskal-Wallis tests that were followed by post-hoc Mann-Whitney tests with Bonferroni correction. To minimize the risk of type-I errors, the analyses that yielded the most conservative results were chosen for further discussion.

Secondly, raw test scores were converted into dichotomous variables of ‘impaired’ or ‘not impaired’. A priori, both 1 SD (27-29) and 2 SD (30) below age- and gender-corrected control mean were selected as cut-off for clinical impairment. For cognitive tests with more than one outcome measure (e.g. RST reaction time and RST accuracy), an impairment was deemed present if the score of at least one measure was below the cut-off. Impairment scores were summed to generate total impairment scores (range 0-10). Based on the control mean of 1.8 tests with an impairment (based on 1 SD cutt-off), the criterion for ‘not impaired’ was defined as 0-2 tests with an impairment. For the width of the following categories, the control SD of 1.5 was used, resulting in the categories ‘mild impairment’ (impairment on 3-4 tests), ‘moderate impairment’ (impairment on 5-6 tests), or ‘severe impairment’ (impairment on 7 or more tests). Total impairment scores were calculated for subjects that had completed at least 9 out of 10 cognitive tests. Chi-square tests were used to detect statistically significant differences in total impairment scores between the subject groups. A Bonferroni correction was applied by setting the alpha value to $\alpha = 0.003$, since 4 dependent variables were compared between 4 subject groups. Analyses were performed using SPSS 17.0 for Windows. Release 2.0 of the GROUP database was used for the analyses.
RESULTS

Data inspection

Although WLT recognition was assessed for 89.3% of the subjects, for only 47.7% of all subjects reliable data were available for this task. This was mainly due to technical problems. These test scores were included into the mixed-model ANCOVAs, but not in the calculation of total impairment scores that allowed for a maximum of one missing value. Inspection of the missing values for the remaining nine cognitive tests showed that 2922 subjects (79.3%) had completed all tests, while 453 individuals (12.3%) had missing data for one test and 260 individuals (7.1%) had missing data for more than three tests. For 49 individuals (1.3%) no cognitive test results were obtained, so these subjects were excluded from the analyses. The mean proportion of missing tests was 6.0% (range 3.4%-11.4%). Test duration and test rank were not associated with proportion of missings, but tasks with computerized scoring had a higher mean proportion of missings (9.9%) than the paper-pencil scoring tasks (4.1%). One particularly interesting finding is the relatively low proportion of missing values (4.0%) for WLT immediate recall, for which stimuli were presented in a computerized fashion, but with paper-pencil scoring.

When comparing demographic variables of subjects categorized by the number of tests missing (no missings, 1-3 tests missing, >3 missings, not tested), no significant differences were found for gender, highest educational degree, or age. Patient status however was associated with the number of missing values. The proportion of missings between patients and the other three subject groups taken together (n=2565) was 12.5% vs. 12.2% (1-3 tests missing), 9.5% vs. 6.0% (>3 tests missing) and 2.4% vs. 0.9% (not tested), $\chi^2(3) = 28.27, P<0.001$.

Group comparisons

Patients were significantly more often male compared to siblings, parents, and controls. The mean age of patients and siblings was lower than the mean age in controls and in parents. Furthermore, there were statistical differences between the four subject groups in IQ, educational degree of the subject, and educational degree of the parent (table 1).

Observed means and standard deviations for cognitive test scores and results from mixed-model ANCOVAs are presented in table 2. Since mixed-model ANCOVAs were significant for 15 out of 18 cognitive outcome measures, post-hoc tests were denoted as significant at the 0.05 level if the $P$-value was smaller than 0.0007, resulting from 0.05/(5x15). Moreover, post-hoc tests were denoted as significant at the 0.001 level if the $P$-value was smaller than 0.00001, resulting from 0.001/(5x15). Age- and gender-adjusted z-scores in patients, siblings, and parents are displayed in figure 1. Because higher scores reflected worse performance for CPT-HQ reaction time, RST reaction time cost, and RST accuracy cost, z-scores for these measures were inverted.

For the three non-normally distributed tests, non-parametric testing yielded somewhat different results compared to results from mixed-model ANCOVAs. Mann-Whitney testing yielded significantly worse performance on the CPT accuracy in parents ($Mdn=583.65$) compared to control subjects ($Mdn=815.42$), $U=143156.50, Z=-10.71, P<.001, r=-0.29$. In addition, Mann-Whitney testing did not yield significant results on the WLT recognition for the comparison between patients ($Mdn=451.21$) and parents ($Mdn=499.78$), $U=99099.00, Z=-2.72,$
\( P = 0.450, r = -0.09 \), and for the comparison between siblings (\( Mdn = 386.20 \)) and control subjects (\( Mdn = 442.00 \)), \( U = 66659.50, Z = -3.28, P = 0.075, r = 0.12 \). For the Hinting Task, no differences emerged between parametric and non-parametric testing. For WLT recognition, the more conservative non-parametric results were chosen over results from mixed-model ANCOVAs. For the other two tasks, the parametric results were maintained.

Against the background of recent findings (31) the analyses were repeated with cannabis use (current, lifetime, or never) as an additional covariate. Co-varying for cannabis, however, did not change any of the group-comparisons from significant to non-significant or vice versa (results not shown).

**Total impairment scores**

Figure 2 shows that with a cut-off of 1 SD below control mean, 29.6% of patients are classified as having no cognitive impairment against 71.4% of controls, with in-between rates for parents and siblings (\( \chi^2(3) = 214.4, P < 0.05 \)). While the proportions of mild impairment did not differ between subject groups (\( \chi^2(3) = 10.4, P = 0.12 \)), both moderate (\( \chi^2(3) = 86.3, P < 0.05 \)) and severe impairment (\( \chi^2(3) = 127.6, P < 0.05 \)) showed significant differences between groups. Patients showed the highest proportion of moderate and severe impairment and control subjects the lowest, with in-between rates for parents and siblings. Figure 3 shows that with a cut-off score of 2 SD, the rate of subjects classified as having no impairment increased to 70.8% in patients and 98.2% in controls, with in-between rates for parents and siblings (\( \chi^2(3) = 225.3, P < 0.05 \)). Mild impairment rates decreased to 18.5% in patients and 1.3% in controls, \( \chi^2(3) = 114.3, P < 0.05 \). While 7.8% of patients displayed moderate impairment, this was very low in the other three subject groups (\( \chi^2(3) = 93.0, P < 0.05 \)). Severe impairment was rare in patients (2.9%), very rare in parents and siblings (0.2% and 0.3%, respectively) and absent in controls, \( \chi^2(3) = 46.8, P < 0.05 \).

**DISCUSSION**

In a uniquely large sample of patients with non-affective psychotic disorder, their unaffected relatives and control subjects, this study has replicated and extended meta-analytic results

| Table 1. Socio-demographic characteristics of patients, siblings, parents and controls |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                 | Patients n=1093 | Siblings n=1044 | Parents n=911 | Controls n=587 | \( \chi^2 \) | Test statistic | P value |
| % Male gender                  | 76.2%           | 45.8%           | 42.8%           | 45.5%           | 308.6          | 2354.1           | <0.001 |
| Age (years)                    | 27.7±8.1        | 27.8±8.3        | 54.8±6.9        | 30.4±10.6       | 33.7           | 34.2             | <0.001 |
| WAIS-III estimated IQ*         | 94.9±16.1       | 102.6±15.5      | 103.1±17.0      | 109.6±15.2      | 113.3          | 113.3            | <0.001 |
| Educational degree subject     | 4.1±2.0         | 5.1±2.1         | 5.1±2.3         | 5.4±1.8         | 74.4           | 74.4             | <0.001 |
| Educational degree parent      | 5.2±2.4         | 5.2±2.4         | 3.4±2.3         | 5.0±2.4         | 33.7           | 33.7             | <0.001 |

*Wechsler-Adult Intelligence Scale short form (55)
Figure 1. Age- and gender-corrected z-scores for patients, siblings, parents and controls. WLT = word learning task; Immed = immediate recall; Retent = retention rate; RST = response shifting task; RST RT = reaction time cost; RST Acc = accuracy cost; CPT = continuous performance test; CPT RT = CPT reaction time; CPT Acc = CPT accuracy; Digit symb = digit symbol coding; Inform = information; Arithm = arithmetic; Block Des = block design; DFAR = degraded facial affect recognition; Neutr = neutral; BFRT = Benton facial recognition test; Hint = Hinting Task.

Figure 2a and 2b. Proportions of 'no' (0-2 tests altered), 'mild' (3-4 tests altered), 'moderate' (5-6 tests altered) and 'severe' alteration (7 or more tests altered) for each subject group. Cut-off scores for alteration are ≤-1 SD (figure 2a) and ≤-2 SD (figure 2b) from the control mean.
Table 2. Observed means and standard deviations of cognitive test scores and \( P \)-values of between-subject comparisons following mixed-model ANCOVAs using z-standardized scores and adjusting for parental education level.

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Patients (n=1093) M (SD)</th>
<th>Siblings (n=1044) M (SD)</th>
<th>Parents (n=911) M (SD)</th>
<th>Controls (n=587) M (SD)</th>
<th>Test Statistic (df)</th>
<th>( P )-value Pat vs Co</th>
<th>( P )-value Sib vs Co</th>
<th>( P )-value Sib vs Pat</th>
<th>( P )-value Par vs Co</th>
<th>( P )-value Par vs Pat</th>
</tr>
</thead>
<tbody>
<tr>
<td>WLT Immediate Recall</td>
<td>22.93 (6.09)</td>
<td>26.89 (5.77)</td>
<td>23.26 (6.11)</td>
<td>28.43 (5.38)</td>
<td>132.17 (3, 3111)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>WLT Retention Rate</td>
<td>0.77 (0.21)</td>
<td>0.84 (0.17)</td>
<td>0.78 (0.20)</td>
<td>0.83 (0.16)</td>
<td>13.22 (3, 3105)</td>
<td>&lt;.001</td>
<td>NS</td>
<td>&lt;.001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>WLT Recognition(^1)</td>
<td>11.03 (3.48)</td>
<td>12.36 (2.99)</td>
<td>11.45 (3.33)</td>
<td>12.96 (2.13)</td>
<td>71.69 (3)</td>
<td>&lt;.001</td>
<td>NS</td>
<td>&lt;.001</td>
<td>NS</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>RST RT Cost</td>
<td>205.84 (221.40)</td>
<td>198.43 (208.91)</td>
<td>216.42 (240.00)</td>
<td>194.78 (176.21)</td>
<td>0.72 (3, 2610)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>RST Accuracy Cost</td>
<td>0.26 (0.27)</td>
<td>0.22 (0.25)</td>
<td>0.35 (0.33)</td>
<td>0.22 (0.25)</td>
<td>12.38 (3, 2841)</td>
<td>&lt;.001</td>
<td>NS</td>
<td>&lt;.001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>CPT Reaction Time</td>
<td>430.17 (84.43)</td>
<td>410.24 (78.39)</td>
<td>429.01 (81.90)</td>
<td>412.80 (82.67)</td>
<td>37.30 (3, 2856)</td>
<td>&lt;.001</td>
<td>NS</td>
<td>&lt;.001</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>CPT Accuracy</td>
<td>98.75 (2.27)</td>
<td>99.51 (1.50)</td>
<td>98.89 (2.18)</td>
<td>99.63 (1.01)</td>
<td>40.62 (3, 2831)</td>
<td>&lt;.001</td>
<td>NS</td>
<td>&lt;.001</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Digit-Symbol coding</td>
<td>65.43 (16.26)</td>
<td>79.23 (15.44)</td>
<td>67.97 (16.72)</td>
<td>83.89 (14.60)</td>
<td>223.40 (3, 3108)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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<tr>
<td>Information</td>
<td>16.78 (5.46)</td>
<td>16.83 (5.20)</td>
<td>17.61 (5.43)</td>
<td>18.82 (4.65)</td>
<td>33.69 (3, 3050)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
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<tr>
<td>Test</td>
<td>Average (SD)</td>
<td>Patient</td>
<td>Control</td>
<td><em>p</em></td>
<td><em>p</em></td>
<td><em>p</em></td>
<td><em>p</em></td>
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<tr>
<td>Arithmetic</td>
<td></td>
<td>12.28 (4.78)</td>
<td>13.84 (4.43)</td>
<td>13.70 (4.25)</td>
<td>15.30 (4.16)</td>
<td>122.57 (3, 3110)</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td>&lt; .001</td>
<td></td>
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<tr>
<td>Block Design</td>
<td></td>
<td>40.47 (17.00)</td>
<td>44.87 (15.08)</td>
<td>32.15 (14.52)</td>
<td>46.55 (14.17)</td>
<td>80.30 (3, 3098)</td>
<td>&lt; .001</td>
<td>&lt; .05</td>
<td>&lt; .01</td>
<td></td>
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<tr>
<td>DFAR Neutral</td>
<td></td>
<td>77.76 (17.75)</td>
<td>80.43 (15.03)</td>
<td>76.18 (16.95)</td>
<td>81.14 (15.17)</td>
<td>10.44 (3, 2981)</td>
<td>&lt; .001</td>
<td>&lt; .05</td>
<td>&lt; .01</td>
<td></td>
</tr>
<tr>
<td>DFAR Happy</td>
<td></td>
<td>86.48 (13.07)</td>
<td>88.20 (10.72)</td>
<td>82.59 (13.66)</td>
<td>87.33 (11.12)</td>
<td>5.51 (3, 2981)</td>
<td>&lt; .001</td>
<td>&lt; .05</td>
<td>&lt; .05</td>
<td></td>
</tr>
<tr>
<td>DFAR Fearful</td>
<td></td>
<td>47.23 (19.80)</td>
<td>52.54 (19.63)</td>
<td>48.35 (18.98)</td>
<td>53.75 (18.22)</td>
<td>23.39 (3, 2981)</td>
<td>&lt; .001</td>
<td>&lt; .01</td>
<td>NS</td>
<td></td>
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<tr>
<td>DFAR Angry</td>
<td></td>
<td>62.12 (20.88)</td>
<td>68.81 (19.22)</td>
<td>60.61 (20.46)</td>
<td>70.43 (18.60)</td>
<td>30.06 (3, 2981)</td>
<td>&lt; .001</td>
<td>&lt; .01</td>
<td>NS</td>
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<tr>
<td>DFAR total</td>
<td></td>
<td>68.40 (10.77)</td>
<td>72.50 (9.35)</td>
<td>66.93 (10.45)</td>
<td>73.16 (9.13)</td>
<td>40.78 (3, 2981)</td>
<td>&lt; .001</td>
<td>&lt; .01</td>
<td>NS</td>
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<td>BFRT</td>
<td></td>
<td>22.76 (2.31)</td>
<td>23.17 (2.16)</td>
<td>22.44 (2.44)</td>
<td>23.14 (2.05)</td>
<td>5.73 (3, 3178)</td>
<td>NS</td>
<td>&lt; .01</td>
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<td>Hinting Task</td>
<td></td>
<td>17.54 (2.78)</td>
<td>18.84 (1.66)</td>
<td>18.79 (1.62)</td>
<td>19.08 (1.31)</td>
<td>85.31 (3, 3101)</td>
<td>&lt; .001</td>
<td>&lt; .01</td>
<td>&lt; .05</td>
<td></td>
</tr>
</tbody>
</table>

WLT = word learning test; RST = response shifting task; RT Cost = reaction time cost; CPT = continuous performance test; DFAR = degraded facial affect recognition; BFRT = Benton facial recognition test

*p* values after Bonferroni correction

For WLT Recognition more conservative results from nonparametric analyses are presented
Unaffected siblings and parents performed intermediate between patients and control subjects on specific tasks. Alterations in verbal learning and memory, speed of processing, acquired knowledge, working memory, and reasoning and problem solving appear to be associated with a familial predisposition to psychotic disorder and may represent putative intermediate phenotypes with the potential of assisting in the genetic analyses of the psychosis phenotype. However, analyzing data in terms of cognitive alterations at the group level may obscure cognitive heterogeneity in the level of clinically relevant impairment. Especially given the relatively small effect sizes, it is important to explore how the mean cognitive alterations seen in patient and sibling groups translate into proportions of clinically relevant impairment (using the commonly used criteria of -1 SD and -2 SD from control mean). For both criteria, cognitive impairments in relatives were more common compared to controls, but less common compared to patients. Based on the 1SD cut-off around 50% of the unaffected relatives displayed some level of cognitive impairment; however this proportion diminished to around 10% by adapting the 2SD cut-off for impairment. Results illustrate that although half of the unaffected relatives may experience some degree of cognitive difficulty, severe cognitive impairments are restricted to a small minority.

Results in patients correspond to meta-analytic evidence that the majority of psychotic patients display a generalized cognitive alteration extending across most cognitive domains, with effect sizes ranging from small to large and clinically relevant (32-35). The magnitude of severity of alterations in patients ranged from -0.18 to -1.34 SD from the control mean, with an average cognitive alteration in patients of -0.61 SD (-0.70 for neurocognition and -0.45 for social cognition). This is mild compared to the approximate average cognitive deficit of -1 SD suggested by previous research in schizophrenia patients (33). One possible explanation for these conservative findings is that setting an extreme of three standard deviations below the mean may have artificially truncated the true range of some cognitive tasks. Another possibility is that the higher percentage of missing data in the patient group may have selected out those who were too impaired to complete cognitive testing. Alternatively, the inclusion of tests that have been previously associated with premorbid intellectual functioning and education (Information, Arithmetic) into a composite score may have produced a measure that is not optimally representative of current neurocognitive impairment (17). Moreover, even though the majority of patients were diagnosed with schizophrenia-related disorders, the decision to include patients with other non-affective psychotic disorders may have attenuated effect sizes. However, differentiating between non-affective psychotic disorders is sometimes difficult, and focusing exclusively on the inclusion of schizophrenia patients may inflate effect sizes through selection bias. Despite the fact that cognitive dysfunction is not a DSM criterion for schizophrenia, psychotic patients who are cognitively intact may be more likely to be diagnosed with e.g. psychotic disorder NOS or substance-induced psychosis. Finally, it cannot be excluded that the prerequisite for patients to have siblings and/or parents able and willing to participate in the study may have selected out the more socially isolated and impaired patients.

The relatively small effect sizes are especially noteworthy given that education or IQ were not pursued as covariates. It may be argued that not controlling for these potential confounders may have inflated effect sizes. However, psychotic disorders are neurodevelopmental in nature,
and subtle deficits on neurocognitive measures during childhood and adolescence have been associated with an increased risk of non-affective psychosis (36). Controlling for education or IQ would thus be inappropriate given that they are powerfully affected by psychosis (26) and genetic vulnerability for psychosis (37). Adjusting for education or IQ would successfully ‘remove’ the variance due to education or IQ, but would not successfully ‘control for’ the variance due to education and IQ, which are meaningful components of the psychotic disorder phenotype (38). The present study therefore pursued parental education as covariate in the analyses instead, since parental education is less likely to be substantially related to psychotic disorder (38).

Traditional neuropsychological criteria classify individuals scoring -1 SD or more from the control mean as cognitively impaired (27-29). While patients’ scores on most cognitive outcome measures were significantly below the healthy control mean, only WLT immediate recall, CPT accuracy, Digit Symbol-Coding, Arithmetic and Hinting Task performance would be classified as impaired according to these criteria. This is in line with previous studies that reported largest effect sizes in the domains of attention, speed of information processing, working memory, verbal learning and memory (15, 33, 34, 39). Impaired performance on the Hinting Task in patients is in accordance with meta-analytic results on theory of mind in schizophrenia (40).

The recognition of happy affect is known to be relatively preserved in patients with psychosis (41), which was illustrated by our results. The absence of significant alterations in RST conflict reaction time should be interpreted in combination with alterations in RST conflict accuracy. Results suggest that patients have more problems modifying their behaviour in response to negative feedback because they do not adapt adequately to the reversal condition by taking relatively more time. This could be explained by diminished cognitive flexibility in schizophrenia, conceptualized as “the ability to coordinate attention and response to two or more ongoing tasks and to adaptively switch response strategies in accord with contextual demands” (42).

Results in siblings and parents indicate that alterations in the domains of verbal learning, processing speed, reasoning, and problem solving, working memory and acquired knowledge, are amongst the most promising cognitive intermediate phenotypes for schizophrenia, which is supported by the literature (5, 8). Effect sizes for these domains were mild to moderate and between-group comparisons with control subjects survived conservative Bonferroni correction. The average effect size in siblings was, however, relatively low (-0.18 SD, range -0.01 to -0.43 SD) compared to the literature. Meta-analyses in unaffected relatives have reported effect sizes of -0.37 (range -0.28 to -0.54) and -0.41 (SD=0.38) (5, 6), which is more in line with the average effect size of -0.34 (range +0.13 to -1.17) that was found in the present parent sample.

Although several studies have reported that siblings perform worse on different versions of the CPT, including the CPT-AX (5, 6, 43), the present study did not find significant differences in siblings and parents. It may be that the CPT-HQ did not sufficiently burden early aspects of stimulus encoding and perceptual analysis, resulting in a processing load that was too low to be sensitive in relatives (43, 44).

While the social cognitive tasks yielded significant performance alterations in parents, differences between siblings and control subjects for DFAR Total (P<0.02), DFAR Fearful
(\(P<0.03\)), DFAR Angry (\(P<0.02\)) and the Hinting Task (\(P<0.04\)) did not survive Bonferroni correction. Worse performance in parents compared to siblings was unexpected because the parent group has passed the main age period of risk for developing a psychotic disorder (45). It is possible that the sibling group may have been relatively healthy, as perhaps they share less risk genes with their affected relatives than the parent group. However, it should be taken into consideration that age differences between the parent group and the oldest control group may have inflated the effect sizes in parents, although post-hoc analyses in the control group did not show an effect of age on the Hinting Task (\(B=0.00005, P=0.99\)) and the DFAR angry faces (\(B=-0.09, P=0.23\)). Although few studies have actually focussed specifically on parents of patients, worse theory of mind performance in parents of schizophrenia patients compared to parents of control subjects has been reported before (46). Compromised social cognitive functioning in parents but not in siblings supports prior evidence that mentalizing impairment in schizophrenia may reflect general cognitive deficits or residual symptom expression rather than representing a specific trait marker (47, 48). Previous research has suggested that neurocognition and social cognition are distinct, yet correlated, domains in psychosis (49, 50). Social cognition may serve as a mediator between neurocognition and community functioning, acting sequentially on the same pathway (51, 52). It can therefore be speculated that siblings with neurocognitive alterations but no social cognitive alterations may display no reduction in community functioning, whereas parents – displaying both neurocognitive and social cognitive alterations – might show diminished community functioning. The validity of this hypothesis should be tested in future studies.

Although comparing mean performance on individual cognitive domains between patients, relatives and controls provides indispensable information about putative intermediate phenotypes (figure 1), it does not show how the cognitive changes are distributed over the subject groups. For example, a mild alteration on a cognitive subtest in siblings could be caused by a majority of siblings displaying mild alterations or by a severe alteration in only a small subgroup while the majority displays no alterations. For this reason, total impairment scores were calculated for each of the subject groups. With the cut-off \(s\)-1 SD from the control mean, fairly equal proportions of patients demonstrated no, mild, moderate or severe impairments, which corresponds to the concept of a continuum of neurocognitive functioning in patients with schizophrenia (29). The proportion of patients with a neurocognitive profile within the normal range falls within the 15 to 30% that was reported in a recent review (10). Moving the cut-off from \(s\)-1 SD to \(s\)-2 SD dramatically increases the rate of patients without cognitive impairment, emphasizing the relevance of using more than one criterion for cognitive impairment (53).

The proportions of mild, moderate, and severe cognitive impairment in siblings and parents are intermediate between patients and control subjects, which may represent a dose-response relationship for genetic load. With the \(s\)-1 SD cut-off, approximately 50% of the relatives display no alterations against 70% of the control subjects. In a study by Egan et al (53), the proportions of subjects without cognitive impairments (\(s\)-1SD) were higher: 62-75% in siblings as compared with 77-91% in control subjects. Using \(s\)-2 SD as a cut-off, these rates rise substantially to around 90% in the relatives. This indicates that with a more conservative criterion of alteration, parents and siblings move away from their affected relatives to become almost indistinguishable from control subjects.

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Some limitations should be taken into consideration when interpreting the results. Not all subjects had complete cognitive test scores. This was predominantly due to problems in computerized assessment and data storage, which has been previously reported in a multi-centre study (54). Patient status however also affected the number of missing test results. Therefore, it cannot be excluded that patients with more cognitive alterations were more likely to have missing data, resulting in attenuated effect sizes. Secondly, the issue that control subjects are often matched to the patient group, resulting in control groups of younger age than the parent or mixed-relative group, is a common concern in this field of research (6). In a meta-analysis on cognitive functioning in unaffected relatives, an overall Cohen’s d=0.36 was reported for studies with age-matched groups versus d=0.48 for those with non-age-matched groups (6). Covarying for age in the analyses, although appealing, is an inappropriate way of dealing with group differences, because age represents a defining group characteristic of parents versus patients and siblings (38). Therefore, age-and gender corrected z-scores were calculated in this study to account for age differences. Although this resulted in the best possible fit, optimal age-correction could not be achieved, as parents in the highest age group had a mean age of 54 against a mean age of 46 in the oldest control group. Higher mean age in parents would be most likely to inflate performance differences in speeded tasks such as Digit Symbol-coding and CPT Accuracy. Instead, the tasks that showed more alterations in parents compared to siblings were unspeeded tasks assessing social cognition, making a confounding effect of age less likely.

In conclusion, this study suggests that familial predisposition to psychotic disorder is associated with immediate verbal learning, processing speed, reasoning and problem solving, acquired knowledge and working memory, with modest effect sizes. Tasks assessing set-shifting ability and vigilance with low processing load did not differentiate relatives from controls. While half of the unaffected relatives may experience some degree of cognitive impairment, severe cognitive impairment seems to be restricted to a minority.

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PREMORBID ADJUSTMENT PROFILES IN PATIENTS WITH PSYCHOTIC DISORDERS AND THEIR UNAFFECTED SIBLINGS: CLINICAL AND COGNITIVE CORRELATES

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ABSTRACT

Background: Distinct profiles of premorbid adjustment in psychotic disorders may be indicative for later disease heterogeneity. However, there is little consistency in how to evaluate these premorbid adjustment profiles in patients and less is known about their expression in unaffected relatives.

Methods: Six hundred sixty-six patients with psychotic disorder, 673 unaffected siblings, 575 unaffected parents and 585 unrelated controls were included in this study. Cluster analyses of the patients’ scores on the Premorbid Adjustment Scale (PAS) were performed. Resulting profiles were compared to clinical, functional and cognitive characteristics in patients and their unaffected relatives.

Results: Four clusters were identified in patients that were labelled ‘normal’, ‘poor social’, ‘academic decline’ and ‘poor overall’ adjustment. ‘Normal’ patients had better functional outcomes and more symptomatic remission while their siblings had better social adjustment levels. Both ‘normal’ and ‘poor social’ patients had a later age at psychosis onset, less clinical symptoms, better cognitive performance and higher parental education and IQ compared to the other patients. ‘Poor overall’ patients were more likely to have received special education in comparison to those with academic decline.

Discussion: Findings provide a powerful approach to the problem of clinical heterogeneity in psychotic disorders, with premorbid adjustment predicting cognitive and symptomatic functioning after psychosis onset.
1. INTRODUCTION

Schizophrenia is a complex psychiatric disorder, influenced by an interplay of genetic and environmental factors (van Os et al., 2008). Certain traits of the disorder, albeit in attenuated form (e.g. cognitive alterations, negative symptoms) have also been reported in unaffected first-degree relatives, suggesting familial aggregation (Chen et al., 2009). The understanding of the disorder has been complicated by the heterogeneity of the clinical picture, which is present at the level of disease onset, cognitive functioning, course and prognosis (Tandon et al., 2009). There are indications that this heterogeneity may be related to the level of functioning prior to the onset of the disease. A substantial number of patients display a decline in social and cognitive functioning during the years prior to psychosis, referred to as the “premorbid” phase (Gornick et al., 2005; Gold and Weinberger, 1995). So far, there has been little consistency as in how to evaluate premorbid adjustment patterns in patients with psychosis. Moreover, it remains unclear whether these patterns of premorbid course are also expressed in unaffected relatives, indicating familial aggregation.

Over the past decades, retrospective measures have been developed to assess the level and course of functioning prior to psychosis onset, of which the Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982) is the method most frequently used (MacBeth and Gumley, 2008). The PAS is a questionnaire that assesses academic and social functioning during different age epochs, from childhood to early adulthood. The relationship between the PAS and clinical symptoms, cognitive function and functional outcome after disease onset has been well established (Rund et al., 2004; Silverstein et al., 2002). At least three studies have investigated patterns of pre-onset course in relation to post-onset functioning by means of cluster analysis (Addington et al., 2003; Larsen et al., 2004) or latent class growth analysis (Cole et al., 2012). These analyses have been suggested to be the preferred method of use since they are free of prior hypotheses (Cole et al., 2012). Still, outcomes of these analyses depend on which parameters are included. For example, Cole and Addington performed their analyses based on PAS scores over the different age epochs without differentiating between social and academic performance. A distinction between these two domains is of importance however, since they seem to represent separate factors. While cognitive impairment has been related to academic premorbid adjustment, clinical symptoms have been linked to social premorbid adjustment in schizophrenia patients (Rund et al., 2007; Allen et al., 2001). Therefore, one may best conceptualize patterns of premorbid adjustment by including information on both developmental (age epochs) and domain (social/academic) aspects into one analysis. This conceptualization is currently underexploited (for a review: MacBeth and Gumley, 2008).

Next to the application of cluster analysis, a second approach that may enhance our understanding of the premorbid phase of psychotic disorders is the inclusion of unaffected relatives. Studies have found that childhood and adolescent adjustment in unaffected siblings deviates from healthy controls (Shapiro et al., 2009; de la Serna et al., 2011), although normal adjustment in siblings has also been reported (DeLisi et al., 1987). The development of adjustment problems prior to psychosis onset is likely to result from genotype-environment interplay. Since unaffected relatives of patients share a substantial amount of genetic and environmental factors, it would be interesting to investigate whether patients with distinct
patterns of pre-onset course also have relatives with comparable cognitive and subclinical expressions. To our knowledge, such a comparison has not been performed yet.

The current study investigated social and academic developmental profiles prior to disease onset in a sample of patients with psychotic disorders. By means of cluster analysis we examined whether different PAS profiles can be distinguished and whether these profiles show different associations with cognitive, clinical and functional measures after psychosis onset. As a second step of validation, we examined whether these premorbid adjustment profiles in patients showed different associations with cognitive functioning, clinical symptoms and level of functioning in their unaffected siblings and parents.

2. METHODS

2.1 Participants
There were 1120 patients, 1057 non-affected siblings, 919 parents and 590 unrelated healthy controls who participated in the Genetic Risk and Outcome of Psychosis (GROUP) study. The study objectives, sample characteristics, assessments and recruitment methods have been described elsewhere (Korver et al., 2012). Patients were included if they fulfilled criteria for non-affective psychotic disorder assessed with either the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Wing et al., 1990), or the Comprehensive Assessment for Symptoms and History (CASH; Andreasen et al., 1992). Their siblings and parents were included if they had no history of psychotic disorder. Control subjects were included if neither they, nor a first-degree relative, had a history of psychotic disorder. All participants had to be fluent in Dutch. Additional inclusion criteria for the current study were that participants had complete data on the PAS until late adolescence (19 years). Therefore, patients younger than 19 years old, as well as those who had experienced illness onset prior to that age, were excluded from the analyses together with their relatives.

2.2 Premorbid Adjustment Scale
The Premorbid Adjustment Scale (PAS; Cannon-Spoor et al., 1982) was designed to retrospectively evaluate the degree of achievement of developmental goals at each of several periods of a person’s life. Two distinctive factors have been found on the PAS: (i) social adjustment, referring to social behaviour, friendship and social sexual development, and (ii) school adjustment, referring to school performance and school adaptation (Allen et al., 2001). For the current study, adjustment scores were used on these two factors for the following age epochs: childhood (up to 11 years), early adolescence (12-15 years) and late adolescence (16-19 years).

2.3 Cognitive assessment
The following cognitive tasks were included: Continuous Performance Test – HQ (CPT), Response Set-shifting Task (RST), Wechsler Adult Intelligence Scale – III (WAIS-III) short form (Blyler et al., 2000), Word Learning Task immediate recall (Brand and Jolles, 1985), Degraded
Facial Affect Recognition task (DFAR), and the Hinting Task. The WAIS-III short form consisted of the subtests Block Design, Digit Symbol-Coding, Arithmetic, and Information. For the CPT, two parameters were created: CPT variance and CPT performance. CPT variance, or intra-individual variability (Hilti et al., 2010), was evaluated using the standard deviation score of the subject’s mean response time on the hit trials. For the RST, a measure of set-shifting ability and working memory, we evaluated an efficiency score on the reversal blocks, during which the subject had to find the alternated response rule. By calculating the mean of nine standardized cognitive scores a composite score was created for each participant to be used in the analyses. The cognitive battery used in the GROUP study has been described in more detail in an earlier study (Meijer et al. 2012).

2.4 Demographical, functional and clinical assessments
Past-week symptom severity in patients was measured with the 30-item Positive And Negative Syndrome Scale (PANSS; Kay et al., 1987), that scored each item on a scale ranging from 1 (absent) to 7 (extreme). For this study, positive, negative and disorganization scores from the 5-factor structure were utilized. (Lancen et al., 2000). Current remission was evaluated using the PANSS remission items (Andreasen et al., 2005). In siblings and parents, lifetime frequency of subclinical psychotic symptoms was measured by the Community Assessment of Psychic Experiences (CAPE; Brenner et al., 2007). Positive and negative symptoms of schizotypy were evaluated using the Structured Inventory for Schizotypy – Revised (SIS-R; Vollema et al., 2000).

The Social and Occupational Functioning Assessment Scale (SOFAS) was used to assess everyday functioning in patients during the previous week. Patients were also assessed for number of psychotic episodes, duration of untreated psychosis in weeks, age at illness onset, dosage of antipsychotic medication, independent living and financial responsibility. Educational degree was evaluated according to the methods of Verhage (Verhage, 1964). Also the proportion of subjects who had received special education was recorded.

2.5 Statistical Analyses
2.5.1 Descriptives
Controls, siblings, parents and patients satisfying the inclusion criteria were compared on demographic, clinical and cognitive variables. Numerical variables were compared using linear mixed models, with family representing the random effect. The method of maximum likelihood was used to estimate the model parameters. Categorical variables were compared by means of Pearson’s chi-square statistics or Generalized Estimating Equations (GEE) followed by Wald Chi-square statistics. In case of significance, contrast-statements were executed to test pairwise differences.

2.5.2 PAS profiles in patients
Prior to performing cluster analyses, inter-correlations between the six PAS scales were assessed by means of Spearman’s rho correlation coefficients. Subsequently, for families with multiple patients participating in the study one patient was randomly selected for analyses. Cluster analyses were performed as previously described (Everitt, 2011). Briefly, hierarchical cluster analysis was used to
evaluate the number of clusters and to select the initial starting values for the K-means clustering. The ‘stopping rule’ was set at the level of a normal percentile ($L(m) = 2.64$), which corresponds to a two-sided-significance level of $\alpha = .01$, resulting in a number of clusters. For the K-means clustering, the Ward method was used, based on pairwise and Euclidean distances. Instead of the means, the median scores from the hierarchical cluster analysis were used as centroids in the K-means cluster analysis. The profiles of patients that were obtained with the clustering strategy were evaluated by comparing demographical, clinical and cognitive characteristics by means of analysis of variance (ANOVA) and the Pearson chi-square statistic. Cognitive scores were normalized and transformed into z-scores as described in a previous study (Korver et al., 2012).

2.5.3 Comparisons in unaffected siblings and parents based on PAS profiles in patients

By means of ANOVA and chi-square tests we assessed group differences between unaffected siblings based on the PAS profile of their proband. Siblings were compared for demographical variables, PAS scores, the cognitive composite measure and clinical variables. In a similar way we analyzed group differences between parents, with the exception of the PAS comparisons. In case multiple unaffected siblings within a family participated in the study, mean scores were created based on scores of all the siblings within a particular family. Likewise, if both data from the father and the mother were available, a mean score was created for both parents. All tests were two-sided at a significance level of $\alpha = .05$. Statistical analyses were performed using SPSS 18.0.

3. RESULTS

3.1 Descriptives

A total of 666 patients, 673 siblings, 575 parents and 585 controls who fulfilled inclusion criteria were compared for demographic, clinical and cognitive variables (Table 1). Main effects were found to be significant for age, gender, education, estimated IQ and all PAS scales. Pairwise comparisons revealed significantly poorer PAS scores in patients compared to siblings and controls. PAS scores in siblings were not significantly different from controls.

3.2 PAS profiles in patients

After randomly selecting one patient per family and restricting the data to those without missing data on the PAS, 610 patients remained for the cluster analyses. Differences between PAS scores of this selected group and the original patient group were negligible (being <1% for the PAS overall score).

Four subtypes emerged from hierarchical cluster analysis in patients. The median values for each of these subtypes were used as starting points or centroids in the K-means analysis. Nine iterations were required for the K-means clustering to converge to a stable set of four clusters in the patients. Subtype 1 consisted of 178 patients (29%) and scores on the PAS were all in the normal range, with mean scores between 0.5 and 1.2. This subtype was labeled ‘normal’. Subtype 2 consisted of 163 patients (27%). Their scores were elevated for PAS social scales (mean scores 2.0-2.4), this subtype was therefore labeled ‘poor social’. Subtype 3 consisted
of 135 patients (22%) displaying academic problems that increased from childhood through adolescence (mean scores 1.5-3.5). This subtype was labeled ‘academic decline’. Subtype 4 consisted of 134 patients (22%). These patients displayed poor scores on academic and social scales over all age epochs (mean scores >2.4) and this subtype was labeled ‘poor overall’. The clusters showed significant mean differences on the six PAS scales (p<.001). In general, the patients within the normal cluster had the most favorable outcomes on all six subscales of the PAS. Differences between patients within the normal and poor social clusters were significant with respect to the social scales and non-significant with respect to the academic scales. On the contrary, patients within the normal and academic decline clusters differed significantly for academic but not for social scales. In addition, differences between patients within normal and poor overall clusters were significant on the social and academic domains.

Differences between patients in the four PAS clusters were also significant for education, estimated IQ, functional outcomes and clinical characteristics. Again, patients within the poor overall and academic decline clusters had poorer outcomes on these measures compared to the normal cluster. Patients within the poor social cluster reported more problems in social functioning during the previous week as assessed with the SOFAS compared to patients in the normal cluster. The data are presented in Table 2.

Patients within the different PAS clusters showed significant differences on cognitive performance (Figure 2). On the cognitive composite measure, patients within the normal and poor social clusters performed consistently better in comparison to their counterparts within

| Table 1. Group comparisons between controls, siblings, parents and patients |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|                              | Controls (N=585) | Siblings (N=673) | Parents (N=575) | Patients (N=666) | All groups |
| Age, M (SD)                  | 30 (7)           | 30 (8)           | 57 (7)          | 30 (7)          | 4773**  |
| Gender, % male               | 46               | 48               | 57              | 76              | 198*    |
| Education Highest, M (SD)   | 5.4 (1.8)        | 5.3 (2.0)        | 5.0 (2.3)       | 4.5 (2.1)       | 31**   |
| Special, %                   | 2                | 6                | -               | 13              | χ² =51**|
| IQ, M (SD)                   | 110 (15)         | 103 (17)         | 103 (15)        | 95 (16)         | 84*    |
| PAS School <12              | 1.0              | 1.2              | -               | 1.4             | 27*    |
| School 12-16                | 1.4              | 1.5              | -               | 2.0             | 57*    |
| School 16-19                | 1.3              | 1.4              | -               | 2.3             | 142*   |
| Social <12                  | 1.0              | 0.9              | -               | 1.4             | 38*    |
| Social 12-16                | 1.1              | 1.0              | -               | 1.7             | 79*    |
| Social 16-19                | 0.7              | 0.7              | -               | 1.7             | 183*   |
| Overall                     | 1.0              | 1.1              | -               | 1.9             | 256*   |

1 Main effect significant; Patient<Control, Sibling, Parent.
2 Main effect significant; Patient<Sibling<Control.
3 Main effect significant; Control, Sibling, Patient<Parent.
4 Main effect significant; Patient, Parent<Control, Sibling.
Table 2. Characteristics of patients in the four PAS profiles

<table>
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<tr>
<th></th>
<th>‘Normal’ (1)</th>
<th>‘Poor social’ (2)</th>
<th>‘Academic decline’ (3)</th>
<th>‘Poor overall’ (4)</th>
<th>Overall group differences</th>
<th>Pairwise comparisons</th>
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<td>N=135</td>
<td>N=134</td>
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<td>30 (6)</td>
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<tr>
<td>PANSS, M (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>12 (6)</td>
<td>13 (6)</td>
<td>14 (6)</td>
<td>14 (6)</td>
<td>F=4.1, p&lt;.006</td>
<td>1, 2, 4, 3; 3&lt;1</td>
</tr>
<tr>
<td>Negative</td>
<td>13 (6)</td>
<td>15 (6)</td>
<td>15 (7)</td>
<td>16 (7)</td>
<td>F=5.8, p&lt;.001</td>
<td>1, 3, 2, 4; 4&lt;4</td>
</tr>
<tr>
<td>Disorganization</td>
<td>15 (5)</td>
<td>15 (5)</td>
<td>17 (7)</td>
<td>18 (6)</td>
<td>F=8.5, p&lt;.001</td>
<td>1, 2, 3, 4; 3&lt;2</td>
</tr>
<tr>
<td>Remission, %</td>
<td>62</td>
<td>49</td>
<td>44</td>
<td>38</td>
<td>χ=19.5, p&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Cognition (M, SD)</td>
<td>-0.6 (0.8)</td>
<td>-0.6 (0.8)</td>
<td>-0.9 (0.9)</td>
<td>-0.9 (0.8)</td>
<td>F=9.8, p&lt;.001</td>
<td>1, 2, 4, 3; 4&lt;2</td>
</tr>
</tbody>
</table>
### Table 3. Main effects and pairwise comparisons in siblings, based on the PAS profile of patients

<table>
<thead>
<tr>
<th></th>
<th>Normal’ (1)</th>
<th>Poor social’ (2)</th>
<th>Academic decline’ (3)</th>
<th>Poor overall’ (4)</th>
<th>Overall group differences</th>
<th>Pairwise comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest education, M (SD)</td>
<td>N=139</td>
<td>N=134</td>
<td>N=97</td>
<td>N=107</td>
<td>F=3.5, p=.015</td>
<td>1, 2, 3, 4; 3&lt;1</td>
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<td>IQ, M (SD)</td>
<td>105 (17)</td>
<td>104 (15)</td>
<td>99 (13)</td>
<td>104 (15)</td>
<td>F=2.8, p=.041</td>
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<tr>
<td>PAS, M (SD)</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Social &lt;12</td>
<td>0.6 (0.8)</td>
<td>0.9 (0.9)</td>
<td>1.0 (1.0)</td>
<td>1.0 (1.1)</td>
<td>F=4.7, p&lt;.003</td>
<td>1, 2, 3, 4; 3&lt;1</td>
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<td>Social 12-16</td>
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<td>1.1 (0.9)</td>
<td>1.2 (1.0)</td>
<td>1.1 (0.9)</td>
<td>F=5.2, p&lt;.001</td>
<td>1, 4, 2, 3; 4&lt;1</td>
</tr>
<tr>
<td>Social 16-19</td>
<td>0.5 (0.7)</td>
<td>0.8 (0.8)</td>
<td>0.9 (1.1)</td>
<td>0.9 (0.9)</td>
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</tr>
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<td>School &lt;12</td>
<td>1.2 (0.9)</td>
<td>1.1 (0.7)</td>
<td>1.2 (1.0)</td>
<td>1.2 (1.0)</td>
<td>F=0.6, p=.628</td>
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</tr>
<tr>
<td>School 12-16</td>
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<td>1.3 (0.8)</td>
<td>1.6 (0.9)</td>
<td>1.6 (1.1)</td>
<td>F=2.3, p=.077</td>
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<tr>
<td>School 16-19</td>
<td>1.4 (1.1)</td>
<td>1.3 (0.8)</td>
<td>1.5 (0.9)</td>
<td>1.6 (1.1)</td>
<td>F=1.8, p=.146</td>
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<td>CAPE, M (SD)</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Positive</td>
<td>0.2 (0.2)</td>
<td>0.2 (0.2)</td>
<td>0.2 (0.2)</td>
<td>0.2 (0.2)</td>
<td>F=0.1, p=.971</td>
<td></td>
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<tr>
<td>Negative</td>
<td>0.5 (0.3)</td>
<td>0.5 (0.4)</td>
<td>0.6 (0.4)</td>
<td>0.5 (0.3)</td>
<td>F=2.5, p=.056</td>
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</tr>
<tr>
<td>Depression</td>
<td>0.6 (0.3)</td>
<td>0.6 (0.4)</td>
<td>0.6 (0.3)</td>
<td>0.6 (0.3)</td>
<td>F=0.7, p=.495</td>
<td></td>
</tr>
<tr>
<td>SIS-R, M (SD)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.3 (0.3)</td>
<td>0.3 (0.4)</td>
<td>0.4 (0.4)</td>
<td>0.4 (0.4)</td>
<td>F=1.5, p=.201</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0.2 (0.2)</td>
<td>0.3 (0.3)</td>
<td>0.3 (0.3)</td>
<td>0.3 (0.2)</td>
<td>F=3.1, p=.026</td>
<td></td>
</tr>
<tr>
<td>Cognition, M (SD)</td>
<td>-0.2 (0.8)</td>
<td>-0.2 (0.6)</td>
<td>-0.3 (0.6)</td>
<td>-0.2 (0.7)</td>
<td>F=0.8, p=.5</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Mean PAS scores for social and academic adjustment in the four patient clusters
Figure 2. Cognitive profiles in the four patient clusters

the academic-decline and poor overall clusters. With regard to the individual tasks, group differences were significant for Response Set-shifting, Block Design, Arithmetic and Information.

3.3 Comparisons in unaffected siblings and parents based on PAS profiles in patients

Pairwise comparisons revealed that siblings of patients within the normal cluster displayed the best social adjustment on the PAS (Table 3). For the parents, group differences were significant for education and estimated IQ, with poorer scores in parents of patients within academic decline and poor overall clusters (Table 4).

Table 4. Main effects and pairwise comparisons in parents, based on the PAS profile of patients

<table>
<thead>
<tr>
<th></th>
<th>'Normal' (1)</th>
<th>'Poor social' (2)</th>
<th>'Academic decline' (3)</th>
<th>'Poor overall' (4)</th>
<th>Overall group differences</th>
<th>Pairwise comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=99</td>
<td>N=84</td>
<td>N=69</td>
<td>N=76</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest education, M (SD)</td>
<td>5.5 (1.9)</td>
<td>5.0 (2.1)</td>
<td>4.4 (2.2)</td>
<td>4.8 (2.1)</td>
<td>F=4.0, p=.008</td>
<td>1, 2, 4, 3; 3&lt;1</td>
</tr>
<tr>
<td>IQ, M (SD)</td>
<td>105 (14)</td>
<td>104 (17)</td>
<td>99 (13)</td>
<td>100 (14)</td>
<td>F=3.9, p=.009</td>
<td>1, 2, 4, 3; 4&lt;1</td>
</tr>
<tr>
<td>CAPE, M (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.1 (0.2)</td>
<td>0.1 (0.1)</td>
<td>0.1 (0.1)</td>
<td>0.2 (0.1)</td>
<td>F=0.5, p=.667</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>0.3 (0.3)</td>
<td>0.5 (0.3)</td>
<td>0.6 (0.4)</td>
<td>0.6 (0.3)</td>
<td>F=2.3, p=.075</td>
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<tr>
<td>Depression</td>
<td>0.6 (0.3)</td>
<td>0.6 (0.4)</td>
<td>0.6 (0.3)</td>
<td>0.6 (0.3)</td>
<td>F=0.7, p=.532</td>
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<tr>
<td>Cognition, M (SD)</td>
<td>-0.4 (0.6)</td>
<td>-0.5 (0.7)</td>
<td>-0.6 (0.6)</td>
<td>-0.6 (0.6)</td>
<td>F=2.7, p=.045</td>
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</table>
4. DISCUSSION

The present study investigated premorbid adjustment trajectories in patients with psychotic disorders. We examined whether these clusters showed different profiles in terms of cognition, symptoms and functioning after psychosis onset in patients and in their unaffected siblings and parents. We found that patients displayed significant adjustment problems from childhood through adolescence in comparison to their unaffected siblings and controls. Moreover, using cluster analysis, four clusters in patients were identified: one cluster with normal premorbid adjustment, one with selective social maladjustment, one with selective decline in the academic domain and one with overall maladjustment starting during childhood. The clusters were roughly equal in sample size and were labelled ‘normal’, ‘poor social’, ‘academic decline’ and ‘poor overall’, respectively.

In general, our results corroborate findings of earlier studies that there is a gradual worsening of PAS scores towards the onset of psychosis (Larsen et al., 2004; MacBeth and Gumley, 2008) in both social and academic domains (Allen et al., 2001; Allen et al., 2005). When we look at the specific clusters however, these are difficult to compare to previous studies due to different methods that have been used. Larsen and colleagues for example performed two separate cluster analyses for social and academic adjustment in patients and concluded that these domains constituted “fairly independent dimensions of premorbid functioning” (Larsen et al., 2004). They found four social and four academic adjustment patterns (good stable, good deteriorating, intermediate stable, intermediate deteriorating). However, it remained unclear how these patterns of academic and social adjustment combine within patients. Alternatively, Cole (Cole et al., 2012) combined social and academic premorbid adjustment into one measure. Next to a ‘good-stable’ and a ‘poor-deteriorating’ group, what they called “a fuzzier intermediate group” was identified. This group consisted of 55.4% of the sample and displayed less clear associations with cognitive and symptom characteristics. When they set the number of clusters to four instead of three, this intermediate class was split in two, which may reflect our two intermediate clusters with isolated social and academic problems. These examples emphasize the additional value of entering scores for PAS social and PAS academic as separate domains into one cluster analysis as has been recommended in a recent review (MacBeth and Gumley, 2008). Moreover, it has been argued that an important evaluation in cluster analysis is an objective determination of the number of clusters (Everitt, 2011). Nevertheless, earlier studies investigating PAS clusters have predefined the number of clusters (Addington et al., 2003; Larsen et al., 2004). Therefore, the current study may provide a more complete picture of premorbid clusters in psychosis. After having identified patient clusters based on information on the PAS, we investigated differences in post-onset clinical and cognitive functioning.

Patients with academic decline and poor overall premorbid adjustment were characterized by significantly lower levels of education, higher rates of special education, lower IQ, younger age at psychosis onset, lower levels of financial responsibility and higher levels of positive and disorganized symptomatology in comparison to the other two clusters. Results are consistent with the literature that has linked poorer academic adjustment to lower educational level (Larsen et al., 2004; Allen et al., 2001; Allen et al., 2005; Monte et al., 2008), lower IQ (Allen et al., 2001), less meaningful activities including work (Larsen et al., 2004) and younger age at
onset (Larsen et al., 2004; Monte et al., 2008). The one variable that has not been associated with either social or academic premorbid adjustment is positive symptomatology (MacBeth and Gumley, 2008; Larsen et al., 2004). Patients within the poor overall cluster tended to have poorest functional and clinical outcomes, with the exception of educational level that was lowest in the academic decline group. We hypothesize that individuals with academic maladjustment starting in early childhood may be more likely to switch to special education, while those with maladjustment starting in adolescence may be more prone to experience a stay back or drop-out from school. Moreover, age at onset was lower in patients with academic decline compared to those with poor overall adjustment. This may reflect the fact that the onset of psychosis is normally preceded by a drop in functioning (Niendam et al., 2009), which explains why the group of individuals experiencing such a decline may be the first to develop psychosis. While the normal and poor social groups scored fairly equal on most variables, the latter scored lower on a social and functional occupational scale and displayed more negative symptoms after psychosis onset, which is in line with previous reports (Larsen et al., 2004; Allen et al., 2001; Monte et al., 2008; McClellan et al., 2003).

Regarding associations with cognitive functioning, the four PAS clusters roughly divided into two, based on the presence of premorbid academic problems (Figure 2). Patients classified in the academic-decline and poor overall clusters showed markedly impaired cognitive performance relative to the normal and social poor adjustment clusters, with a small to medium-sized effect. This is in line with the notion that poor premorbid school performers continue to perform poorly intellectually after illness onset (Rund et al., 2004). Contrary to studies that reported academic adjustment to be associated with a single distinctive cognitive deficit, such as verbal learning, processing speed, or working memory (Levitt et al., 1996; Rund et al., 2004; Larsen et al., 2004; Cole et al., 2012), our results indicate a decline on most cognitive domains compared to the normal and poor social clusters. Our findings therefore corroborate results from a previous study that poor premorbid adjustment is associated with a general -instead of a specific- cognitive deficit in patients with psychotic disorder (Bechard-Evans et al., 2010).

In the current study, premorbid adjustment in unaffected siblings was not significantly different from healthy controls for any of the age epochs, which is corroborated by some (DeLisi et al., 1987; Walshe et al., 2007) and contradicted by others (Shapiro et al., 2009; de la Serna et al., 2011). Nevertheless, the siblings of patients within the normal cluster did have better PAS scores for social adjustment when compared to siblings from the other clusters. Findings that patient PAS scores significantly predicted the scores of their own discordant siblings have been reported previously (Shapiro et al., 2009). Beyond this association there were no substantial differences in current cognitive and subclinical functioning in unaffected siblings based on the patients’ PAS profiles. Educational level and estimated IQ were significantly higher in parents of patients within the normal and poor social clusters, while no differences existed with regard to subclinical symptoms and the cognitive composite score. It can be speculated that particular stressors more prevalent in the rearing environment of patients with psychosis may concurrently influence social adjustment during childhood and adolescence in unaffected siblings. Such stressors may include urbanicity, ethnic minority
status, childhood adverse events and cannabis use (van Os et al., 2008). Siblings may in turn be more susceptible to these environmental adversities based on the shared genetic material with the proband (Tienari et al., 2004). This association may be explained by the fact that growing up with a patient developing schizophrenia is likely to influence the lives of siblings (Awad and Voruganti, 2008). Findings that PAS clusters in patients do not seem to influence current cognitive or symptomatic functioning in siblings suggest that the putative disadvantageous influence of growing up with a patient in the prodromal phase of psychosis does not extend into adulthood. Results that better premorbid adjustment in patients is associated with higher IQ and educational level in parents may reflect that parents who have had more education themselves may be more able to secure a certain level of adjustment in their offspring whose functioning may be at risk because of imminent psychosis. Another explanation may be that the higher IQ and educational level in parents reflect a cognitive reserve that is inherited by their children.

Our results should be viewed in the light of some limitations. First, since the assessment of premorbid adjustment was based on retrospective ratings, there remains some concern about accuracy of recollection which may have added a bias to PAS ratings (Shapiro et al., 2009). We did not use the recently developed Premorbid Adjustment Scale – Structured Interview (PAS-SI; Rabinowitz et al., 2007) which might have overcome this issue. The included sample however did have reasonably reliable informants with the prerequisite for patients that at least one parent could participate in the study. Moreover, the mean age of patients and siblings was still relatively young, which may have limited recall bias. Second, for the sake of cluster analysis, only patients were included with PAS data on the three age epochs which resulted in the exclusion of patients with an age at onset before the age of 19 years. This limits the generalizability of our findings to patients with adult onset psychosis and their families. Third, the current patient sample did not have severe problems in premorbid adjustment with a mean PAS overall score of 1.9, which is regarded as “mild impairment”. This may be explained by the prerequisite for patients to provide at least one sibling and parent willing to participate which may have excluded the more isolated and lower functioning patients. Alternatively, the inclusion of the wider range of non-affective psychotic disorders may have led to a lesser mean impairment in premorbid adjustment, as compared to pure schizophrenia samples. Finally, relatively favorable PAS scores may have been influenced by the exclusion of patients with an early age of onset, who are generally known to have a worse prognosis (Howard et al., 1993). On the other hand, the inclusion of patients with an earlier onset would have incorporated the risk of wrongly classifying initial psychotic symptoms as “premorbid”. In the current study it is unlikely that the deterioration in premorbid functioning displayed by a proportion of patients reflected the prodromal phase, because the PAS late adolescence period ends at 19 and the average age at psychosis onset was 25 years.

The aforementioned limitations notwithstanding, the current study has provided improvements on previous research, such as the largest sample size of patients with psychotic disorders to date, the inclusion of unaffected relatives and controls and the use of an elaborate cognitive test battery. An objective evaluation in the determination of clusters was used. Within patients, the four premorbid clusters proved to have convergent validity with regard
to clinical and cognitive correlates after disease onset. Our findings therefore illustrate a potentially powerful methodological approach to the problem of clinical heterogeneity in the research of psychotic disorders. In addition, analyses including unaffected relatives indicate that the role of familial factors in the development of premorbid adjustment problems appears to be modest.

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THE DUTCH TRANSLATION OF THE MATRICS: FIRST ASSESSMENT IN ULTRA HIGH RISK SUBJECTS AND SCHIZOPHRENIA PATIENTS COMPARED TO CONTROLS

Julia H. Meijer, Daniëlla S. van Dam, Carin J. Meijer, Mechteld H. Hoogendoorn, Sara Dragt, Peter M. Dingemans, Don H. Linszen, Lieuwe de Haan

Submitted for publication
ABSTRACT

Background: The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) was designed to assess cognitive treatment effects in clinical trials of patients with schizophrenia. This study addressed whether a first Dutch translation of the MCCB may differentiate between patients with first-episode schizophrenia (FES) and healthy controls. As an exploratory study, the MCCB was assessed in ultra high risk (UHR) individuals.

Methods: The MCCB was assessed in fifty-four FES patients, 23 UHR individuals and 23 healthy controls. To test whether cognitive profiles were significantly different in UHR and FES participants compared to controls, one-way multiple analysis of (co)variance (MAN(c)OVA) was performed with diagnostic group as fixed factor and cognitive scores as dependent variables.

Results: MANOVA revealed an overall effect of diagnostic group (UHR/FES/Control) on cognitive performance ($F(16)=2.34; P<0.004$). Post-hoc comparisons between FES versus control subjects were significant for all domains except visual learning. After co-varying for years of education, group differences for speed of processing, verbal learning and working memory remained significant. UHR individuals performed intermediate to FES and control subjects but differences were insignificant.

Conclusion: Preliminary findings add to the growing body of research on the presence of moderate cognitive alterations in the putative psychosis prodrome. Although results need replication in larger sample sizes, they suggest that the MCCB is sensitive to cognitive alterations in UHR individuals that are similar, albeit attenuated, compared to FES patients.
INTRODUCTION

Adolescents and young adults with an ultra high risk (UHR) for developing psychosis demonstrate cognitive alterations that are intermediate when compared to first-episode schizophrenia (FES) patients and healthy controls (Keefe et al., 2006; Eastvold, Heaton, & Cadenhead, 2007). UHR individuals with more cognitive alterations at baseline, as well as those experiencing further decline during the putative prodromal phase, may be more likely to develop psychosis at follow-up (Eastvold et al., 2007; Keefe et al., 2006; Becker et al., 2010; Lencz et al., 2006). There is however a lack of consensus on the time course and predictive value of specific cognitive alterations in the development of psychosis (Keefe et al., 2006).

Reliable assessment of the course of cognitive alterations during the UHR phase is important in understanding the pathogenesis of early psychosis and to enable the search for cognitive risk markers. The identification of such cognitive vulnerability markers may contribute to the development of a risk algorithm with greater predictive accuracy for psychosis than the clinical high risk criteria alone with an average 1-year transition rate of 36.7% (Ruhrmann et al., 2003). High rates of false-positives have raised both practical and ethical concerns about the development and implementation of interventions during the UHR phase (de Koning et al., 2009; McGorry et al., 2009).

The first intervention trials in UHR individuals mainly used pharmacological and psychological intervention strategies to reduce symptoms and to delay or prevent threshold psychotic symptoms (de Koning et al., 2009; McGorry et al., 2009). Although cognitive alterations in UHR individuals have been associated with lower levels of functioning independent of symptom severity (Niendam et al., 2006), there has been little focus on cognition as an outcome measure so far. It has been hypothesized that preventing or delaying the onset of frank psychosis may limit cognitive decline because alterations in the UHR phase are still mild (Simon et al., 2007). In addition, if cognitive skills, crucial for building adolescent relationships and academic performance, could be improved during the UHR phase, this might limit functional decline after psychosis onset (Hafner et al., 1995).

The current gold-standard for cognitive assessment in clinical trials for schizophrenia is the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery (MCCB; Kern et al., 2008; Nuechterlein et al., 2008). Although similar domains are affected in schizophrenia and the UHR phase (Keefe et al., 2006; Eastvold et al., 2007), the MCCB has to the best of our knowledge not yet been administered in an UHR sample. Implementation of a standard cognitive battery as outcome measure in UHR individuals may provide the comparability that is required in this difficult to recruit and heterogeneous population. It would also be in line with the current view that UHR research needs to progress to studies with substantially larger samples, which is most effectively achieved through multicenter studies (McGorry et al., 2009).

The purpose of this cross-sectional study was to compare cognitive functioning on the MCCB in a sample of UHR individuals, first-episode schizophrenia (FES) patients, and age- and gender-matched healthy controls. Based on previous findings, we hypothesized that UHR individuals show cognitive alterations when compared with controls and that these alterations are mild compared with FES patients (Eastvold et al., 2007; Keefe et al., 2006).
METHODS

Sample and measures
Through the early psychosis department of the Academic Medical Centre (AMC) in Amsterdam, the Netherlands, 23 UHR individuals and 54 patients with first-episode schizophrenia (FES) were recruited. Twenty-three age- and gender-matched non-psychiatric controls (Co) were recruited through advertisements in a local newspaper. Participants received cognitive assessment with the MCCB (Nuechterlein et al., 2008; Kern 2008). The MCCB contains 10 tests to measure cognitive performance in 7 domains: attention/vigilance, speed of processing, working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving and social cognition. The MCCB was translated by our research group according to guidelines for academic translations (Harvey et al., 2010) and assessed in all participants. A shortened version of the WAIS-III was assessed as an IQ-estimate (Blyler et al., 2000), consisting of the subtests information, digit symbol-coding, arithmetic and block design. UHR individuals were assessed with the Comprehensive Assessment for At-Risk Mental States (CAARMS; Yung et al., 2005). They were included if they fulfilled at least one of the following criteria: intermittent positive symptoms, attenuated positive symptoms, or a genetic risk/deterioration syndrome (Yung et al., 2005). FES patients were included if they fulfilled DSM-IV schizophrenia diagnosis after stabilization of the first psychotic episode, assessed with the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992). Substance use was assessed with the Composite International Diagnostic Interview (CIDI; World Health Organization, 1990), section L. The study was approved by the ethics committee of the AMC.

Statistical Procedures
Statistical analyses were performed with SPSS 17.0 for Windows. Socio-demographic data were compared between diagnostic groups (FES/UHR/Co) by means of one-way analysis of variance (ANOVA) for continuous variables and $\chi^2$ tests for categorical variables. Raw scores from each of the 10 tests were entered into the MCCB scoring program to produce age and gender corrected $T$ scores for the 7 cognitive domains (normative mean = 50; SD = 10). If the mean composite $T$ score of the controls fell within a 5% range of the American mean ($T$ scores 47.5 to 52.5), our control group was assumed to represent the much larger MCCB norm population (Kern et al., 2011). If not, analyses were performed with study-specific z-scores that were calculated using means and SDs of our control sample (Holmen et al., 2010).

To test whether cognitive profiles were significantly different in UHR and FES participants compared to controls, a one-way multiple analysis of (co)variance (MAN(C)OVA) was performed with diagnostic group as fixed factor and $T$ scores (or z-scores) as dependent variables, followed by Bonferroni post-hoc comparisons. Because lower educational achievement is likely to be an inherent part of the disorder, adjusting for education in psychotic samples may cause matching fallacy (Meehl, 1970). Therefore, the analyses were performed with and without years of education as a covariate. To correct for multiple testing, the alpha-level was set to $p<.01$. 
RESULTS

Diagnostic groups did not differ significantly in mean age (UHR 21.6; FES 22.7; Co 22.3; F(2,97)=0.84; p=NS) or gender (UHR 78.4%; FES 85.2%; Co 74.0% males; χ²(2)= 1.48; p=NS). None of the participants had used hard drugs over the past month and the groups did not differ in cannabis use over the past month (UHR 23.5%; FES 26.9%; Co 28.6%; χ²(2)= 9.15; p=NS). There were significant differences between the groups in years of education (UHR 14.8 years; FES 14.5 years; Co 16.4 years; F(2,97)= 8.53; p<.01), as well as estimated IQ (UHR 101.8; FES 92.6; Co 108.9; F(2,97)= 10.06; p<.01).

The MCCB cognitive profile of UHR and FES patients compared to controls is displayed in Figure 1. With the mean composite T score of 51.2 in controls (SD 10.5), analyses were performed using T scores. The MANOVA revealed an overall effect of diagnostic group (UHR/FES/Co) on cognitive performance (F(16) = 2.34; p<.004) (Table 1). Post-hoc comparisons between FES vs Co were significant for all domains except for visual learning. The comparisons between UHR vs Co did not yield significant results. After co-varying for years of education in a MANCOVA, group differences for speed of processing, verbal learning and working memory remained significant after correction for multiple comparisons (p<.01).

Figure 1. T scores for MCCB domains in patients, UHR subjects and controls. SOP: speed of processing; A/V: attention/vigilance; WM: working memory; VerbL: verbal learning; VisL: visual learning; Reas: reasoning and problem solving; Soc: social cognition

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>FES vs Co</th>
<th>UHR vs Co</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed Processing</td>
<td>12.02</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Attention/vigilance</td>
<td>5.95</td>
<td>&lt;.004</td>
</tr>
<tr>
<td>Working memory</td>
<td>8.39</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>10.95</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Visual learning</td>
<td>1.97</td>
<td>NS</td>
</tr>
<tr>
<td>Reasoning and problem solving</td>
<td>4.77</td>
<td>&lt;.010</td>
</tr>
<tr>
<td>Social cognition</td>
<td>7.80</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Table 1. Results from MAN(C)OVA with post-hoc comparisons
Discussion

Our results show that the MCCB is able to differentiate between FES patients and healthy controls. UHR individuals demonstrate intermediate performance on all domains which is in line with previous studies (Simon et al., 2007; Eastvold et al., 2007; Keefe et al., 2006; Niendam et al., 2006; Hawkins et al., 2008), although differences with the control group are not statistically significant. Moreover, FES patients show medium to large alterations that are significant in 6 out of 7 cognitive domains, with the exception of visual learning. After correction for years of education, the group differences between FES patients and controls remained significant for speed of processing, working memory and verbal learning.

Preliminary results indicate that the MCCB may be sensitive to detect cognitive alterations in the UHR phase, but findings need to be replicated in a larger population. The power to detect two-tailed group differences with an alpha value of .01 was only 64% for UHR individuals compared to 99% for FES patients (nQuery Advisor 7.0 power calculator). The mean composite T score in UHR individuals (Figure 1) is however similar to the mean difference of -0.81 SD that was reported in 67 UHR individuals that had completed a cognitive assessment covering 5 out of 7 MCCB domains (Simon et al., 2007). In that study, UHR individuals performed significantly worse than controls on almost every domain; however analyses were not corrected for multiple comparisons.

### Table 1. Results from MAN(C)OVA with post-hoc comparisons

<table>
<thead>
<tr>
<th>Cognitive Domains</th>
<th>MANOVA (MANCOVA*)</th>
<th>Post hoc</th>
<th>FES-CO</th>
<th>UHR-Co</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speed of processing</td>
<td>12.02 (&lt;.001*)</td>
<td>F &lt;.001*</td>
<td>&lt;.001*</td>
<td>NS</td>
</tr>
<tr>
<td>Attention/vigilance</td>
<td>5.95 (&lt;.004*)</td>
<td>F &lt;.001*</td>
<td>&lt;.003*</td>
<td>NS</td>
</tr>
<tr>
<td>Working memory</td>
<td>8.39 (&lt;.007*)</td>
<td>F &lt;.001*</td>
<td>&lt;.001*</td>
<td>NS</td>
</tr>
<tr>
<td>Verbal learning</td>
<td>10.95 (&lt;.001*)</td>
<td>F &lt;.001*</td>
<td>&lt;.001*</td>
<td>NS</td>
</tr>
<tr>
<td>Visual learning</td>
<td>1.97 (NS)</td>
<td>F NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Reasoning and problem solving</td>
<td>4.77 (NS)</td>
<td>F &lt;.010*</td>
<td>&lt;.008*</td>
<td>NS</td>
</tr>
<tr>
<td>Social cognition</td>
<td>7.80 (&lt;.026)</td>
<td>F &lt;.001*</td>
<td>&lt;.001*</td>
<td>NS</td>
</tr>
<tr>
<td>Composite MATRICS</td>
<td>14.59 (&lt;.001*)</td>
<td>F &lt;.001*</td>
<td>&lt;.001*</td>
<td>&lt;.030</td>
</tr>
</tbody>
</table>

* years of education as covariate

* significant MAN(C)OVA after correction for multiple comparisons
The FES group displayed medium to large cognitive alterations compared to the control group on almost all domains, which is consistent with the view of a generalized cognitive deficit in schizophrenia (Chapman and Chapman 1973; Keefe et al., 2006). Absent group differences on visual learning illustrates that FES patients may experience relatively little problems with the recall of visual compared to verbal information (Kalkstein et al., 2010). This is further supported by our finding that out of 10 MCCB subtests, FES patients obtained highest scores on the Wechsler Memory Spatial Span that assesses visual working memory ($T = 46.15, SD = 11.12$) (data not shown).

In chronic, clinically stable schizophrenia outpatients, the MCCB composite $T$ score was 37.0, comparable to the mean composite score in our patients (Kern et al., 2010). Moreover, a Norwegian study that assessed the MCCB in patients with early onset schizophrenia spectrum disorders reported that impairment in patients ranged from -0.8 to -1.8 SD on all of the MCCB domains except for social cognition (Holmen et al., 2010). Authors reasoned that the subtest of use may not be appropriate to assess social cognition in adolescents, since the vignettes describing social situations were developed for an adult population. In our adolescent sample this task was however sensitive for group differences, which may be due to the fact that our FES patients were almost 7 years older than the Norwegian sample.

Alterations in verbal learning, working memory and speed of processing were present in FES patients after correction for years of education. It may be argued that these are the domains least affected by educational achievement in schizophrenia. This is not in line with the literature however, reporting that verbal memory is the MCCB domain correlating strongest with educational achievement in schizophrenia (Liu et al., 2006). A more plausible explanation might be that performance on all cognitive domains correlates with years of education in schizophrenia and that the statistical significance of only the top three MCCB domains is robust enough to withstand correction for it (Table 1). The group difference for social cognition however was equally statistically significant, but this domain did not survive correction for years of education. This is in line with the presumption that Theory of Mind, which is the subtype of social cognition assessed in the MCCB, might be more reflecting general intelligence rather than a “genuine compromised mental state” (Brune, 2003).

There are some limitations to the study. First, the power was too low to ‘prove’ cognitive alterations with small to moderate effect sizes in UHR individuals to be significant. Second, our study reports cross-sectional data and hence we do not know which of our UHR individuals will progress to develop a diagnosable psychotic disorder. Therefore we cannot draw conclusions about the course of cognitive alterations during the UHR phase and whether the MCCB may be useful to assess cognitive risk markers as has been suggested previously (Keefe et al., 2006).

In conclusion, these preliminary findings add to the growing body of research on the presence of moderate cognitive alterations in the putative psychosis prodrome. Although results need replication in larger sample sizes, they suggest that the MCCB is sensitive to cognitive alterations in UHR individuals that are similar, albeit attenuated, compared to FES patients. We therefore recommend further research on the use of the MCCB as a standardized cognitive outcome measure in both observational and intervention studies during the UHR phase.
REFERENCE LIST


SEMANTIC FLUENCY DEFICITS AND REDUCED GREY MATTER BEFORE TRANSITION TO PSYCHOSIS: A VOXELWISE CORRELATIONAL ANALYSIS

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ABSTRACT

Background: Early identification of subjects with an increased risk of psychosis is necessary to develop interventions to delay or prevent disease onset. We recently reported that decreased semantic verbal fluency performance in ultra high risk (UHR) subjects predicts the development of psychosis (Becker et al., 2010). The present study investigated whether semantic and phonological verbal fluency scores correlate with grey matter density in UHR subjects.

Methods: Thirty-seven UHR subjects underwent structural MRI scanning and verbal fluency assessment after which they were followed up for 2 years. Using voxel-based morphometry, we investigated whether grey matter density correlated with verbal fluency scores in 10 UHR subjects who developed psychosis during follow-up and 27 UHR subjects who did not develop psychosis.

Results: In UHR subjects developing psychosis, lower semantic fluency scores correlated significantly with reduced grey matter density in the right superior and middle temporal gyrus, the right insula, and the left anterior cingulate cortex.

Conclusion: This study shows that a correlation between semantic fluency performance and grey matter density in task-related areas may differentiate between UHR subjects who subsequently will develop psychosis and those who will not. Combining these two measures could improve psychosis prediction in UHR subjects.
1. INTRODUCTION

Prospective identification and treatment of subjects in the putative prodromal phase of schizophrenia could ameliorate or delay psychosis onset, improve disease outcome or even prevent psychotic disorder (Falloon et al., 1996; Yung et al., 1996). Since ‘prodromal phase’ is a retrospective concept, sets of criteria have been developed to prospectively identify subjects at clinically increased risk of psychosis, also referred to as “ultra high risk” (UHR) subjects. A review of prospective investigations in UHR samples found that between 9% and 54% of UHR subjects develop psychosis within 1 year (Olsen and Rosenbaum, 2006). However, the high rate of false-positives lowers the benefit/risk ratio of possible prodromal interventions (de Koning et al., 2009) and increases the need for additional criteria to predict future transition to psychosis more accurately.

In schizophrenia cognitive impairment is a core feature of the disease. Because selected cognitive domains are already impaired before the development of psychosis (Fusar-Poli et al., 2007; Simon et al., 2007), cognitive deficits may index genetic liability for schizophrenia and could be candidate endophenotypes for the illness (Snitz et al., 2006). Verbal fluency is one of the most impaired cognitive domains in schizophrenia with a recent meta-analysis reporting large effect sizes (Mesholam-Gately et al., 2009). Typically, subjects are asked to generate as many words as possible from a category in a given time. This category can be semantic (e.g. words designating ‘animals’ or ‘objects’) or phonological (e.g. words beginning with the phoneme ‘F’ or ‘S’). These measures are intended to make comparable demands on executive functioning, because both imply efficient organisation of verbal retrieval and recall, self-monitoring, effortful self-initiation and inhibition of inappropriate responses (Ruff et al., 1997). Conversely, while phonological verbal fluency (PVF) implies search strategies based mainly on lexical representations, semantic verbal fluency (SVF) depends intrinsically upon the integrity of semantic associations within the lexicon (Ojeda et al., 2010).

Two meta-analyses, including studies in which patients with schizophrenia and healthy controls completed both PVF and SVF tasks, concluded that patients with schizophrenia showed a larger deficit for SVF relative to PVF (Bokat and Goldberg, 2003; Henry and Crawford, 2004). The disproportionate SVF deficit in schizophrenia patients points towards a problem in semantic storage or retrieval, on top of general executive search and retrieval problems. The same pattern of disproportionate impairment in SVF over PVF is seen in UHR subjects (Magaud et al., 2010). Moreover, Szoke et al. (2008) suggested that SVF may be the best candidate cognitive endophenotype for schizophrenia because it is impaired in schizophrenia patients independent of disease or treatment state and in unaffected first-degree relatives of schizophrenia patients (Snitz et al., 2006).

We recently reported that SVF deficits in UHR subjects can predict development of psychosis (Becker et al., 2010). Becker et al. assessed SVF and PVF in 47 UHR subjects who were followed up for 2 years to assess transition to psychosis. Results showed that SVF scores were significantly lower in those UHR subjects who developed psychosis during follow-up (UHR-P) compared with UHR subjects who did not develop psychosis (UHR-NP) and healthy controls. The aetiology of these deficits in UHR subjects is however unclear. In schizophrenia patients neuroimaging studies have linked SVF and PVF deficits to abnormalities in the frontal
and temporal areas (Spence et al., 2000; Boksman et al., 2005; Kircher et al., 2008; Ragland et al., 2008). UHR subjects also show grey matter reductions in areas similar to those affected in schizophrenia (Pantelis et al., 2003; Borgwardt et al., 2007). Although other cognitive functions such as verbal learning have been successfully linked to grey matter reductions in subjects with a clinical high risk for psychosis (Hurlemann et al., 2008), for verbal fluency this association has not yet been investigated.

The aim of this study was to answer the following questions: 1) Is lower SVF and PVF performance correlated with reduced grey matter density (GMD) in UHR subjects? and 2) Is this correlation significantly different between UHR-P and UHR-NP subjects? Based on previous findings, we hypothesised that SVF and PVF scores would be correlated with GMD in frontotemporal areas in all UHR subjects. Secondly, we hypothesised that this correlation would be more prominent in UHR subjects that developed psychosis subsequent to scanning.

## 2. MATERIAL AND METHODS

### 2.1. Study design

Between August 2002 and July 2009, UHR subjects were consecutively recruited at the Adolescent Clinic of the Academic Medical Center (AMC) in Amsterdam, the Netherlands. Recruitment took place within a naturalistic, longitudinal study programme (European Prediction of Psychosis Study (EPOS); Klosterkotter et al., 2005). Subjects were help-seeking individuals that had been referred by mental health services under suspicion of an increased risk for developing psychosis. Subjects were interviewed by a psychiatrist and a psychologist, while parents or caretakers were interviewed by a psychologist or a psychiatric nurse. The Semi-structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2002) and the Bonn Scale for the Assessment of Basic Symptoms - Prediction List (BSABS-P; Klosterkotter et al., 2005) were used to assess whether or not subjects fulfilled the UHR criteria that were required for study participation. This study was carried out in accordance with the latest version of the Declaration of Helsinki. The study design was approved by the Medical Ethical Committee of the AMC. Written informed consent of the participants was obtained after the nature of the procedures had been fully explained.

### 2.2. Subjects

Thirty-seven UHR subjects were recruited, of whom 10 developed a psychotic illness during a 2-year follow-up (UHR-P) against 27 who did not (UHR-NP). Subjects were considered to be at UHR if they met the criteria for one or more of the following groups: 1) Attenuated symptoms: psychotic-like symptoms that have not proceeded to frank psychosis, 2) Brief Limited Psychotic Symptoms (BLIPS): a frank psychotic period that subsided spontaneously in less than 1 week, 3) A decline in functioning over the past year (30% reduction in the Global Assessment of Functioning scale) plus a genetic risk (first-degree family member with a psychotic disorder or a schizotypal personality disorder in the identified patient) and/or 4) At least two "basic symptoms" which are cognitive, perceptual, emotional and social disturbances (Klosterkotter...
et al., 2005). Exclusion criteria were as follows: age < 12 or >35 years, estimated premorbid verbal IQ < 85 as assessed with the Dutch Adult Reading Test (Schmand et al., 1991), neurological or endocrine disease that may affect brain structure, use of illicit drugs other than cannabis during 3 months prior to the assessment as assessed with the Comprehensive International Diagnostic Interview sections J and L (CIDI; Andrews and Peters, 1998) and a previous psychotic episode for more than 1 week as assessed with the Structured Clinical Interview for Diagnosis Axis I (SCID-I; Spitzer et al., 1992).

2.3. Timeline
After inclusion into the study, subjects were assessed with two verbal fluency tests and structural magnetic resonance imaging (MRI) of the brain. Subsequently, subjects were followed up for 2 years to monitor their clinical development by assessment of the SIPS. After 9, 18 and 24 months, the SIPS was repeated to assess potential transition to psychosis during a face-to-face contact. If during follow-up it appeared that a subject had experienced a transition to psychosis, the SCID-I was used to establish a formal diagnosis.

2.4. Assessment of verbal fluency
To measure verbal fluency, subjects were asked to name as many words as possible within 1 minute belonging to the semantic category “animals”, or words beginning with the phoneme “F”. The outcome variable for this task was the number of acceptable words produced in each condition.

2.5. Statistical analyses
Group differences in demographical and neuropsychological data were examined using SPSS 16.0 for Windows. Group differences in age, premorbid IQ estimates and verbal fluency scores were analysed using Mann Whitney U tests due to the small sample size of the UHR-P group. Group differences in gender, handedness, psychiatric medication use and lifetime/past month cannabis use were analysed with chi-square tests. Level of statistical significance was defined as p < 0.05 (two-tailed).

2.6. Image acquisition and analyses
Whole brain images of the UHR subjects were acquired at baseline on a Philips Intera 3 Tesla whole-body MRI scanner (Philips Intera, Philips Medical Systems, Best, the Netherlands). We used optimised voxel-based morphometry (VBM) (Good et al., 2001) implemented in SPM2 (Institute of Neurology, Queen’s Square, London, UK, www.ion.fil.ac.uk) to identify regional GMD in all UHR subjects. Optimised VBM techniques were employed, including customised template creation, spatial normalisation, tissue segmentation and smoothing (Ashburner and Friston, 2000). A participant-based template was created, using all original 3D TI-weighted images of the complete sample. Next to the customised template, prior images of grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) were generated, based on the existing [Montreal Neurological Institute (MNI)] TI-weighted template in SPM2, and smoothed with a Gaussian kernel of 8-mm full width at half-maximum (FWHM).
Thereafter, automated optimisations (Department of Psychiatry, University of Jena, Germany) in SPM2 were used to spatially normalise and segment all T1-weighted images, based on the customised T1-weighted template. The prior images of GM, WM, and CSF were used for segmentation and stripping. All standard presets in SPM2 were maintained. For statistical comparison, GM segments were smoothed with a 10-mm FWHM isotropic Gaussian kernel, which rendered the data normally distributed to achieve optimal outcome in parametric statistical comparisons. In SPM2 the PVF and SVF scores were correlated with GMD. This analysis was performed in UHR-P and UHR-NP subjects separately. Results were localized using the Talairach and Tournoux atlas (Talairach and Tournoux, 1988).

3. RESULTS

In the 10 subjects that developed psychosis during follow-up, the median transition time to psychosis was 14 months. After transition to psychosis, the subjects received the following diagnoses: schizophrenia (n = 8), schizophriform disorder (n = 1) and schizoaffective disorder (n = 1). As shown in Table 1, groups did not statistically differ with respect to age, premorbid IQ, gender, handedness, psychiatric medication or cannabis use. In the SVF test, UHR-P subjects generated 2.32 animal names less than UHR-NP subjects, a difference that was not significant (p = 0.38). In the PVF test UHR-P subjects generated 0.38 words more than UHR-NP subjects, a difference that was not significant (p = 0.76).

<table>
<thead>
<tr>
<th></th>
<th>UHR-P (n = 10)</th>
<th>UHR-NP (n = 27)</th>
<th>UHR-P vs. UHR-NP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Mean ± S.D.)</td>
<td>20.7 ±4.3</td>
<td>18.9 ±4.0</td>
<td>p = 0.35</td>
</tr>
<tr>
<td>IQ (Mean ± S.D.)</td>
<td>105.8 ±5.2</td>
<td>100.2 ±10.5</td>
<td>p = 0.10</td>
</tr>
<tr>
<td>Male/Female</td>
<td>8/2</td>
<td>18/9</td>
<td>p = 0.43</td>
</tr>
<tr>
<td>Handedness (right/left/both/unknown)</td>
<td>10/0/0/0</td>
<td>22/3/1/1</td>
<td>p = 0.42</td>
</tr>
<tr>
<td>N of subjects using antipsychotics in the past 3 months</td>
<td>4</td>
<td>6</td>
<td>p = 0.28</td>
</tr>
<tr>
<td>Antipsychotic dose (chlorpromazine equivalents*, mean ± S.D.)</td>
<td>187 ±233</td>
<td>295 ±213</td>
<td>p = 0.50</td>
</tr>
<tr>
<td>N of subjects using antidepressants in the past 3 months</td>
<td>4</td>
<td>4</td>
<td>p = 0.17</td>
</tr>
<tr>
<td>N of subjects using benzodiazepines in the past 3 months</td>
<td>2</td>
<td>6</td>
<td>p = 0.29</td>
</tr>
<tr>
<td>N of subjects using cannabis lifetime/in the past month</td>
<td>3/2</td>
<td>17/10</td>
<td>p = 0.07/0.33</td>
</tr>
<tr>
<td>SVF score (Mean ± S.D.)</td>
<td>19.60 ± 4.77</td>
<td>21.92 ±6.92</td>
<td>p = 0.38</td>
</tr>
<tr>
<td>PVF score (Mean ± S.D.)</td>
<td>11.50 ±5.36</td>
<td>11.12±5.48</td>
<td>p = 0.79</td>
</tr>
</tbody>
</table>

UHR-P; Ultra High Risk subjects who developed psychosis, UHR-NP; Ultra High Risk subjects who did not develop psychosis. * Chlorpromazine equivalents for the subjects that have been using antipsychotics were calculated according to Woods (2003).
As shown in Figure 1 and Table 2, in the UHR-P group lower SVF scores correlated significantly with reduced GMD in an area encompassing the right superior temporal gyrus (STG) and middle temporal gyrus (MTG) (Brodmann area (BA) 21) (p<0.001), the right posterior insula (BA 13) (p<0.001), and the left anterior cingulate cortex (ACC) (BA 32) (p< 0.036). In the UHR-NP subjects SVF scores did not correlate significantly with GMD. Also, PVF scores did not correlate significantly with areas of GMD in UHR-P or UHR-NP subjects. Table 2 also reports the results for three brain regions in the right ACC, the left cingulate gyrus and the right middle frontal gyrus that did not survive correction for multiple analyses.

Figure 1. Grey matter density of the left anterior cingulate cortex and right posterior insula correlating with semantic verbal fluency scores in UHR subjects that subsequently developed psychosis (n = 10).

Table 2. SPM Correlations between semantic verbal fluency scores and grey matter density in UHR subjects that subsequently developed psychosis.

<table>
<thead>
<tr>
<th>$p$ value</th>
<th>Cl Cluster size</th>
<th>Brain region</th>
<th>BA</th>
<th>$T$ &amp; $T^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$x$</td>
</tr>
<tr>
<td>0.036</td>
<td>1433</td>
<td>Left anterior cingulate</td>
<td>32</td>
<td>-10</td>
</tr>
<tr>
<td>0.001</td>
<td>2908</td>
<td>Right middle temporal gyrus</td>
<td>21</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right insula</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>0.001</td>
<td>1261</td>
<td>Right anterior cingulate</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>0.001</td>
<td>1097</td>
<td>Left cingulate gyrus</td>
<td>31</td>
<td>-14</td>
</tr>
<tr>
<td>0.001</td>
<td>1053</td>
<td>Right middle frontal gyrus</td>
<td>6</td>
<td>39</td>
</tr>
</tbody>
</table>

4. DISCUSSION

To our knowledge, this is the first study to examine UHR-P and UHR-NP subjects for GMD correlates with verbal fluency scores using optimised VBM. Our first prediction that verbal fluency scores would correlate with GMD in frontotemporal areas was true for semantic but not for phonological fluency. Moreover, in line with our second hypothesis, this correlation was only present in UHR subjects that developed psychosis subsequent to scanning. In UHR-P subjects, SVF performance was correlated with GMD reductions in the right STG and MTG (BA 21), right posterior insula (BA 13) and the left ACC (BA 32), areas that have been related to verbal fluency performance in previous functional and structural imaging studies in schizophrenia and healthy controls as discussed here. Findings indicate that the correlation between SVF, but not PVF, and GMD in frontotemporal and insular areas may be an additional risk marker for psychosis.

The MTG was one of the regions associated with semantic processing in a large-scale review of 120 functional neuroimaging studies of semantic memory (Binder et al., 2009). The STG has a role in the semantic representation of words (Frith et al., 1995). Access to, and decisions about, lexical-semantic information engage the STG and MTG in both hemispheres in healthy controls (Pugh et al., 1996). In schizophrenia patients performing a SVF task, activations in the STG and MTG have been reported to be stronger than in healthy controls, which may be reflecting an inefficient hemodynamic response (Ragland et al., 2008). Our finding that SVF correlated with GMD reductions in the right temporal region is surprising since linguistic functions of speech are normally primarily controlled by the left hemisphere (Gauthier et al., 2009). In schizophrenia however, a decreased or reversed language lateralization in the temporal lobes has been described (Weiss et al., 2006; Bleich-Cohen et al., 2009). Furthermore, a decreased lateralization is also present in non-psychotic monozygotic co-twins of schizophrenia patients (Sommer et al., 2004), which implies that decreased language lateralization may reflect a genetic risk factor for psychosis rather than a state-related trait.

The ACC is the structure typically known to be activated in word production tasks with increased demands like SVF compared to control tasks such as free verbal association (Whitney et al., 2009) or overlearned sequences (Gourovitch et al., 2000). Additionally, BA 32 of the ACC was activated in healthy controls during SVF performance compared to reading as a control task, while activation in schizophrenia patients was absent (Kircher et al., 2008). Kircher et al. suggested that the decreased performance on SVF in patients could have resulted from deficient control processes mediated by the ACC. On the contrary, an over-activation of the right ACC during SVF in schizophrenia patients compared to healthy controls has also been reported (Ragland et al., 2008), leading the researchers to suggest that an inefficient hemodynamic response in this area is associated with SVF deficits. In functional MRI (fMRI) studies assessing PVF, which is comparable to SVF in terms of the frontally controlled executive demands of the task (Whitney et al., 2009), first episode schizophrenia patients showed reduced activation of the right (Schaufelberger et al., 2005) and left (Boksman et al., 2005) ACC compared to control subjects. Similarly, in a study using positron emission tomography (PET), clinically stable schizophrenia patients were found to exhibit a functional disconnectivity between the ACC...
and other prefrontal regions during PVF performance compared to healthy controls and first
degree relatives (Spence et al., 2000).

Although involvement of the insular cortex is a common finding in neuroanatomical studies
of schizophrenia, the correlation with SVF performance was less expected. While the anterior
insula in humans is best known for the awareness of oneself, others and the environment, and
thus a potential neural correlate of consciousness (Craig, 2009), the posterior insula is known
to be involved in the subjective experience of body-ownership (Tsakiris, 2010). In schizophrenia
patients, abnormalities in both activity and anatomy of the insula have been associated with
experiencing hallucinations (Shergill et al., 2000). Failure of the insula in schizophrenia may
lead to internally generated sensory information being attributed to an external source,
contributing to hallucinations (Wylie and Tregellas, 2010). However, more in line with our
findings, involvement of the insula in linguistic tasks such as phonological processing and the
coordination of speech articulation has also been described (Ackermann and Riecker, 2010;
Price, 2010). In schizophrenia, GM reduction and dysfunction of the insular cortex has been
implicated in cognitive impairments (Curtis et al., 1998; Crespo-Facorro et al., 2000). Finally, in
support of our findings, schizophrenia patients have been found to display stronger activation
in the bilateral insula during SVF tasks compared with healthy controls (Ragland et al., 2008).

Our results suggest that worse SVF performance in UHR-P subjects is at least partly
reflected in GMD reductions that are present well before the development of frank psychosis.
Previous VBM studies have demonstrated that GM reductions in the right STG and right insular
cortex predate the onset of frank symptoms and are more pronounced in UHR-P compared to
UHR-NP subjects, making them potential markers of future transition to psychosis (Pantelis et
al., 2003; Borgwardt et al., 2007). Moreover, Koutsouleris et al. (2009) found that subjects in a
late UHR state showed more pronounced volume losses in the ACC, insula and MTG compared
to subjects in an early UHR state, showing that GM loss in the same areas that we found is
progressive towards transition to psychosis.

To our knowledge, SVF in UHR subjects has not been studied with structural or functional
neuroimaging, but PVF has been assessed in an fMRI study (Broome et al., 2009). During PVF
performance, UHR subjects showed activation in the ACC that was statistically intermediate
compared with controls and psychotic patients. Also, in the left insula, UHR subjects showed
intermediate patterns of activation during PVF that was highest in the psychosis group and
weakest in the control group. The relatively greater engagement of the insula was hypothesised
to reflect a compensatory response to compromised processing and attenuated activation of
the inferior frontal gyrus. The absence of temporal involvement in the study by Broome et
al. (2009) is in line with the view of PVF as a predominantly frontally based task (Henry and
Crawford, 2004).

Our findings are further corroborated by recent evidence integrating genetic and
neuroimaging techniques. Studies in healthy controls investigating the link between brain
activation during SVF and three susceptibility genes for schizophrenia (neuregulin 1, dysbindin
1, D-amino acid oxidase activator G 72) found alterations of brain activation in the right MTG
and ACC that correlated with the number of risk alleles (Kicher et al., 2009; Markov et al.,
2009; Krug et al., 2010). In addition, schizophrenia susceptibility genes have been successfully
linked to SVF, but not to PVF. Kebir et al. (2009) found that SVF, as opposed to PVF, was associated with a polymorphism on the brain derived neurotrophic factor (BDNF) gene in schizophrenia patients. Patients homozygous for the VAL allele produced significantly more words on SVF with a medium effect size. Similar results were found in the study by Kircher et al. (2009), demonstrating a linear effect of Neuregulin 1 status on SVF but not PVF, with an inverse correlation between test performance and the number of risk alleles.

The following limitations should be acknowledged. Because we used a conservative analysis that was corrected for multiple comparisons in a limited study population, we might have missed structure-function correlations with smaller effect sizes. In addition, although the UHR-NP group was the most appropriate to control for potential influence of trait or state factors shared by the two cohorts (Sun et al., 2009), a healthy control group would have enabled us to draw conclusions regarding the specificity of the correlations found here. Furthermore, the assessment of just one semantic and phonological category may have limited the strength of the results due to potential bias of subjects for the specific category and adding one semantic (“objects”) and one phonemic category (“s”) would have increased generalisability. Finally, the correlation that we found does not allow us to make causal inferences, and future studies are needed to investigate the time sequence of GMD reductions and SVF deficits in UHR subjects.

In summary, this study demonstrates that frontotemporal and insular GMD reductions correlate with SVF performance in UHR individuals that subsequently develop psychosis. These regions have previously been related to SVF performance and to the neuroanatomy of schizophrenia. The correlation with GMD reductions was found in the absence of SVF performance differences between UHR-P and UHR-NP subjects, suggesting that combining structural and behavioural measures could be a more sensitive marker to identify future transition to psychosis than each of these measures separately.

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SUMMARY AND GENERAL DISCUSSION
1. SUMMARY

In Chapter 1 a background was provided on the nature, course and clinical correlates of cognitive alterations in patients with psychotic disorder and individuals with an increased genetic risk for psychosis. The outline of this thesis was presented including the research questions.

Chapter 2 focused on the association between current and lifetime cannabis use and cognitive functioning in patients with psychotic disorder, their unaffected siblings and controls. Two main findings resulted from this study that seemed contradictory at first sight. Although current cannabis use was associated with worse processing speed and working memory, lifetime use was associated with better acquired knowledge and social cognition. Associations between cannabis use and cognition did not differ between patients, siblings and controls. Results in patients corroborate the existing hypothesis that different pathways to psychosis exist, depending on level of genetic risk in combination with early and late environmental risk factors.

In Chapter 3 it was investigated whether the use of stimulants (cocaine, ecstasy, amphetamine) was associated with different cognitive performance in patients with psychosis, their unaffected siblings and controls. We found that current and lifetime frequent stimulant use was associated with more deficits in verbal learning, working memory and acquired knowledge in comparison to never users. Lifetime infrequent use was associated with a general pattern of better cognitive functioning in comparison to never users, however these results did not reach significance. As with cannabis, the relation between stimulant use and cognition did not differ between patients, siblings and controls. Findings suggest that cognitive deficits in lifetime stimulant users depend on the frequency of use.

Chapter 4 examined the existing premise that schizophrenia patients with and without obsessive-compulsive symptoms (OCS) may be distinguished based on cognitive performance. In the largest study to date we found that patients and unaffected first-degree relatives with and without OCS did not perform different on a range of cognitive domains. Cross-trait cross-relative analyses neither yielded a clear association between OCS and cognitive performance in patients and their unaffected relatives. Therefore, results do not support the existence of a “schizo-obssesive subtype” associated with cognitive impairment. Although OCS was associated with a moderately worse clinical state, results may be explained by a continuum of symptom severity instead of a categorization.

In Chapter 5 we assessed whether the identification of odours, a higher-order olfactory process, is associated with symptoms of parkinsonism in patients with non-affective psychosis. We found that olfactory identification deficits were associated with more parkinsonian and negative symptoms. These preliminary results suggest that dopaminergic disbalance may contribute to the pathophysiology of olfactory identification deficits in patients with psychosis. Olfactory identification deficits may be used as an early risk marker of increased sensitivity of the dopaminergic system, as it already is in patients with Parkinson’s disease. This may be of use for early identification of ultra high risk (UHR) individuals in the true prodromal phase as well as for prediction of antipsychotic response and adverse effects.

Chapter 6 focused on the identification of cognitive endophenotypes in patients with psychotic disorder and their unaffected siblings and parents. We found that the familial predisposition to psychotic disorder is associated with alterations in immediate verbal learning,
processing speed, reasoning and problem solving, acquired knowledge and working memory. The distribution of cognitive alterations in patients and their first-degree relatives suggests a continuum of neuropsychological functioning, with 30% of the patients and 50% of the relatives displaying no clinically manifest (-1 SD) deficit. Severe cognitive impairments (-2 SD) seem to be restricted to a minority of patients (30%) and unaffected relatives (10%).

In chapter 7 we identified four profiles of social and academic adjustment in patients prior to psychosis onset: normal adjustment, isolated social problems, academic decline from childhood through late adolescence and poor overall adjustment. These clusters of premorbid adjustment proved to have convergent validity with regard to clinical correlates after disease onset. Moreover, patients in the academic decline and poor overall clusters showed a generalized decline in cognitive performance on domains of attention, problem solving, processing speed, working memory, acquired knowledge and social cognition. Findings illustrate a valuable approach to improve our understanding of the cognitive and clinical heterogeneity in psychotic disorders. The premorbid clusters in patients could not be validated by different associations with cognitive and subclinical functioning in their unaffected relatives.

In chapter 8 we described the first assessment of the Measurement And Treatment Response Initiative to Improve Cognition in Schizophrenia (MATRICS) test battery in a Dutch sample of first episode psychosis patients. Also we included a group of individuals at ultra high risk (UHR) of developing psychosis. With the current Dutch translation of the MATRICS test battery we were able to differentiate patients with first episode psychosis from control subjects on six out of seven domains, with the exception of visual learning. Second, a preliminary finding was that the MATRICS seems sensitive to assess cognitive alterations in UHR individuals, who performed intermediate to patients and controls. The size of the UHR sample in this study was too small to obtain significant results however.

Chapter 9 focused on the question whether lower semantic and phonological verbal fluency performance correlate with grey matter density (GMD) in UHR subjects with and without subsequent transition to psychosis. Using voxel-based morphometry we found that lower semantic fluency scores correlated significantly with reduced GMD in the right superior and middle temporal gyrus, the right insula and the left anterior cingulate cortex. This correlations were only present in UHR patients that developed psychosis during follow-up. This study suggests that the association between semantic fluency performance and GMD in task-related areas may be of use to improve psychosis prediction in UHR subjects.

2. CONCLUSIONS

The central objective of this thesis was to increase our knowledge on what explains the cognitive heterogeneity in patients with psychosis, their unaffected relatives and individuals who are in the putatively prodromal phase of psychosis. In the following paragraphs I will summarize and reflect on our main results and finish with a discussion and recommendations for future research.

1. Although sub-acute effects of cannabis impair processing speed and working memory, lifetime cannabis using patients with psychosis seem to have a higher cognitive potential compared to non-users.
2. Cognitive deficits associated with lifetime stimulant use are dependent on the frequency of use in patients with psychosis, their unaffected siblings and controls.

3. While 50% of genetic high risk individuals may experience some degree of cognitive impairment relative to controls (-1 SD), severe cognitive impairment (-2 SD) seems to be restricted to a minority (10%).

4. Olfactory identification deficits may reflect dopaminergic imbalance and therefore could be a valuable risk marker in psychosis prediction.

5. Cognitive functioning seems a promising candidate endophenotype with first-degree relatives performing intermediate to patients and controls. The specificity of the cognitive deficit is however under debate.

6. The MATRICS cognitive consensus battery is a valuable initiative to standardize cognitive assessment in patients with psychosis and possibly in UHR individuals, although the inclusion of tasks with less cognitive density would promote clinical utility.

7. Poor premorbid academic functioning before the age of nineteen is predictive for a broad-based cognitive impairment after psychosis onset.

8. Combining cognitive measures such as verbal fluency with structural brain imaging techniques may improve psychosis prediction in UHR individuals.

3. DISCUSSION

The search for aetiological factors in schizophrenia has been hampered by phenotypic variability and genetic heterogeneity ever since the diagnostic category was introduced. There has been a longstanding debate as to whether schizophrenia is a single process with pleiotropic manifestations at the level of cerebral organization, or a collection of aetiologically unrelated but dynamically interacting processes (Jablensky, 2006). The objective of the Genetic Risk and Outcome of Psychosis (GROUP) study, that provided data for most of the studies in this thesis, underlines the broader definition of the psychosis definition (Korver et al., 2012; van Os and Linscott, 2012). This was reflected in the inclusion of patients with a range of psychotic disorders, e.g. schizophrenia, schizo-affective disorder, schizophreniform disorder, psychosis not otherwise specified and substance-induced psychosis.

Although agreeing that schizophrenia does not seem to demarcate a homogeneous disease entity may be one step forward, the need to arrive at a better understanding of the heterogeneity of this broader psychosis phenotype remains vital. The current DSM-IV-TR criteria distinguish between different psychotic disorders on the base of duration, dysfunction, associated substance use, bizarreness of delusions and presence of depression or mania (APA, 2000; van Os and Kapur, 2009). Beside the limited stability of the different psychosis diagnoses within patients over time (Schwartz et al., 2000), the current classification of schizophrenia and other psychotic disorders is not associated with robust aetiological, prognostic, or therapeutic validity (Korver-Nieberg et al., 2011; Laursen et al., 2009).

This thesis focused on cognitive impairment in an attempt to unravel the diverse clinical picture in patients with psychotic disorders and in people at increased risk for psychosis. In order to do so, we examined whether cognitive dysfunction was associated with several clinical
Two studies associating cognition with substance use (chapter 2 and 3) revealed that especially recency of cannabis use and frequency of stimulant use was associated with worse cognitive functioning in domains of verbal learning and working memory. The small effect sizes suggested that, despite clear psychotomimetic effects of both cannabis and stimulants (Fiorentini et al., 2011), the cognitive effects may be limited. Moreover, findings that substance using patients display better cognitive functioning than never users is in line with recent findings (Leeson et al., 2011; Schnell et al., 2009; Jockers-Scherubl et al., 2007). In contrast to previous studies (Löberg and Hugdahl, 2009; Jockers-Scherubl et al., 2007) our results do not support the hypothesis that substance use may have a stimulating or neuroprotective effect in patients, since superior intellectual ability was only associated with lifetime (instead of current) use, and with infrequent (instead of frequent) use.

Alternatively, our results may indicate different pathways to psychosis in substance using patients. People who develop schizophrenia in the absence of cannabis use may have prevailing early (genetic or environmental) risk factors, which may be reflected in poorer premorbid adjustment. Contrarily, patients who develop psychosis in response to a late environmental factor such as substance use may have less impaired early development due to more cognitive reserve capacity. Findings by Leeson and colleagues supported this proposition as they found that superior cognitive functioning in patients with a history of cannabis use was probably the result of higher premorbid IQ (Leeson et al., 2011). Since cross-sectional studies like ours can not infer about causality, hypotheses on cognitive reserve and substance use should be confirmed by longitudinal studies.

In chapter 6 and 8 we investigated cognitive profiles of patients with non-affective psychosis in comparison to individuals at increased genetic and clinical risk. Both studies found a broad-based deficit in patients. Cognitive alterations in high risk samples were smaller, while the pattern was similar to that in patients. These findings add to the long-term discussion whether the cognitive heterogeneity in patients with schizophrenia-related psychosis is better accounted for by a generalized deficit of varying degree, or by specific cognitive impairments (Joyce and Roiser, 2007). The magnitude of particular cognitive deficits such as declarative memory and processing speed has led researchers to characterize them as specific to schizophrenia (Ragland et al., 2009; Dickinson et al., 2007). Others however argued that schizophrenia is represented by a generalized cognitive deficit (Blanchard and Neale, 1994; Heinrichs and Zakzanis, 1998). Two different explanations may account for these findings. The first explanation is that there is indeed no cognitive deficit specific for schizophrenia. A second explanation is that we are currently unable to reliably identify a specific deficit due to methodological difficulties that we will discuss here.

If the first explanation proves to be true, this would correspond with findings from neuroimaging studies that the neurobiological substrate of cognitive impairment affects almost all brain regions (Joyce and Roiser, 2007). Further support for a non-specific impairment can be derived from findings from recent cross-diagnostic studies on cognitive impairment in various psychiatric populations. Comparisons of patients with schizophrenia, schizoaffective disorder, bipolar disorder and major depressive disorder demonstrated a similar pattern of neurocognitive performance across groups, including deficits in memory, attention...
and processing speed. Schizophrenia patients were however the most impaired, suggesting that cognitive differences between patients with schizophrenia and other major psychiatric disorders may be more quantitative than qualitative (Reichenberg et al., 2009; Weiser et al., 2008). If however the second possibility is true that we have been unable to detect a specific impairment that is actually there, we should identify and address methodological pitfalls that may have accounted for this type of error. First, there is a problem of task heterogeneity common in the research field. In this thesis, task heterogeneity is illustrated by the fact that the test batteries of the GROUP study (chapter 6) and the MATRICS (chapter 8), both designed to assess domains typically affected in schizophrenia, did not have one cognitive task in common. Correspondingly, when we look at a meta-analysis on a specific cognitive deficit in schizophrenia, e.g. “working memory”, this single domain was assessed by 36 different cognitive measures (Forbes et al., 2009).

A second methodological difficulty is the cognitive density of neuropsychological tests that are currently being used. The majority of conventional neuropsychological tests in schizophrenia, including those in our studies, probably tap many basic processes simultaneously (Carter and Barch, 2007). For example, the “verbal fluency” task like the one used in chapter 8 and 9 may reflect multiple cognitive sub-processes. Different studies using this particular task have referred to its content as “executive functions and attention”, as “executive functions and working memory”, as “processing speed”, or as a cognitive domain on its own (Pukrop and Klosterkotter, 2010). These various assignments to cognitive functions imply inconsistencies in the communication of results leading to scientific ambiguity. Moreover, when cognitive performance tasks rely on diverse cognitive processes this may confound results on the specificity of the cognitive deficit. For example, processing speed is one of the two domains frequently mentioned as the most impaired in schizophrenia (Dickinson et al., 2007). Nevertheless, the MATRICS assesses domains of visual learning, attention/vigilance and reasoning/problem solving by means of speeded tasks. The fact that even a standardized and very well-considered measure like the MATRICS consensus battery has incorporated several cognitively dense tasks may illustrate that basic neuropsychological assessments are still sparsely used. Likewise, with the GROUP test battery, performance on tasks of reasoning/problem solving, working memory and set shifting ability may have also been confounded by lower processing speed in patients compared to controls. These observations emphasize the need for an update of the current testing material, for example by computerized tasks that parse sub processes more clearly (Brewer et al., 2006).

4. IMPLICATIONS AND FUTURE DIRECTIONS

Our results provide promising leads to increase our understanding of cognitive diversity in non-affective psychosis and high risk samples. For this purpose we investigated associations with clinical variables (e.g. substance use, obsessive-compulsive symptoms and motor symptoms), trajectories of premorbid functioning, and structural brain imaging. However, in order to proceed from here, the development of psychometric tools to operationalize cognitive constructs with more comparability and reliability is warranted. Doing so may aid
the cognitive endophenotype approach to improve understanding of the genetic base of the disorder (Gur et al., 2007). From a therapeutic perspective, the use of homologous cognitive models is required for the development of drugs that may enhance cognitive functioning (Carter and Barch, 2007). Beside the poor comparability of current cognitive assessments, face validity is also limited. This may hamper the understanding of how cognitive functioning may be influenced by clinical symptomatology and vice versa. Promising approaches include the development of paradigms that link relevant cognitive processes with specific symptoms of psychosis. Such studies have investigated associations between reality or source-monitoring deficits and auditory hallucinations (Ditman and Kuperberg, 2005), or between abnormalities in emotional perception of stimuli and delusions (Holt et al., 2006).

Future studies should focus on a dimensional approach to psychotic disorders and psychiatric disorders in general. There has been a long tradition of efforts to categorize patients based on clinical variables. For example several studies described in chapter 4 of this thesis refer to an aetiologically different subtype based on the presence of one clinical symptom (OCS). However, these were all small studies with a high risk of sampling bias and results were not confirmed in the present study. Currently, there is a paradigm shift toward a more continuous approach of non-affective psychosis that may also stimulate the understanding of cognitive heterogeneity in this population. Categorization of patients may lead to artificial distinctions that actually exist on a severity continuum (Goldberg and Weinberger, 1995). Rather than trying to establish the deficits of a non-existent ‘average’ patient, it may be more fruitful to consider the factors which do or do not co-aggregate with different patterns of cognitive impairment (Palmer et al., 2009).

Finally, the results of the studies described in this thesis raise new questions that highlight the importance of longitudinal studies. The GROUP study is such a longitudinal cohort study. While our analyses were based on the baseline assessment, the second and the third wave of this longitudinal study will allow to further investigate hypotheses that we have proposed. For example: will current users who stop using cannabis during the three and six-year follow-up period demonstrate an increase in cognitive ability as suggested by the cognitive reserve hypothesis? And: will patients with poor premorbid adjustment also show a worse disease course during follow up, which would support the hypothesis that these are the developmentally most impaired patients?

5. LIMITATIONS

The following limitations should be taken into account. Although our studies on cognitive functioning and substance use (chapter 2 and 3) yielded consistent results, analyses might have benefited from a more detailed assessment of the frequency of substance use. The current subdivision of the Composite International Diagnostic Interview (CIDI) into daily, weekly and less than weekly could have precluded a dose-response relationship between frequency of cannabis use and cognition that may be actually present. Therefore, we would recommend the use of a continuous scale of substance use to be incorporated into future studies (e.g. number of cigarettes or amount of money spent). Moreover, the prerequisite for patients to have
family members able and willing to participate in the GROUP study may have excluded the more isolated and impaired patients. Together with the wider inclusion criterion of all non-affective psychotic disorders, this may explain why the cognitive impairment in patients was lower (ES -0.7) than the average cognitive deficit normally reported (ES -1.0) (chapter 3). Another limitation is that the size of the UHR samples that we included was limited. In chapter 8, insufficient power may account for the fact that the difference in semantic fluency between converters and non-converters did not reach statistical significance. In addition, findings that the MATRICS may be sensitive to the cognitive alterations in UHR individuals should be regarded as preliminary for this reason (chapter 9).

6. STRENGTHS

Due to the multicenter nature of the GROUP-study, we were able to test our hypotheses in a substantial sample of patients, unaffected relatives and controls. This provided the analyses with sufficient power to solve contradicting findings from previous studies. For example, we did not find evidence for a schizo-obsessive subtype associated with cognitive performance (chapter 4) or for abnormal childhood and adolescent adjustment in unaffected siblings (chapter 7).

In addition, the inclusion of unaffected relatives of patients enabled us to investigate associations between cognitive functioning and clinical variables without disease-related confounding. Another strength of the studies in this thesis is the extensive cognitive test battery that was assessed in the GROUP study and in the MATRICS study. The thesis also includes exploratory studies that address some new and relevant topics for the field of psychosis and UHR research. For example, the association between parkinsonism and olfactory identification deficits in patients with psychosis has not been assessed previously. Moreover, it was for the first time that a Dutch translation of the MATRICS was assessed in patients with first episode psychosis and UHR individuals.

In conclusion, results of this thesis underline the value of examining cognitive functioning as a core symptom of psychosis that may offer a window into brain development and functioning. Future studies concerning cognition and psychosis should focus on longitudinal aspects of cognitive functioning and on improving domain-specificity and face validity of cognitive measures.

REFERENCE LIST


ADDENDUM

Nederlandse samenvatting
List of publications
Curriculum Vitae
Dankwoord
De Nederlandse titel van dit proefschrift luidt: “Inzicht in cognitieve heterogeniteit bij mensen met psychose en een verhoogd risico op psychose”. Een psychose kan ontstaan in het kader van schizofrenie. Schizofrenie is een ernstige psychiatrische aandoening die voorkomt bij ongeveer 1% van de wereldbevolking en gekenmerkt wordt door vier soorten symptomen: (i) positieve symptomen, zoals wanen en hallucinaties, (ii) negatieve symptomen, zoals verlies van motivatie en sociale interesse, (iii) affectieve symptomen, zoals een sombere stemming en (iv) cognitieve problemen. Dit laatste symptoomcluster staat centraal in de studies die in dit proefschrift worden beschreven.

Cognitie betekent “denken” en cognitieve processen refereren naar de wijze waarop informatie wordt verworven, verwerkt en opgeslagen. Deze cognitieve processen zijn nodig voor het volbrengen van taken die te maken hebben met aandacht en concentratie, geheugen, verbaal leren, verwerkings- en problemenoplossend vermogen. Mensen met schizofrenie ervaren vaak een achteruitgang in cognitief functioneren met een begin gedurende de jaren voorafgaand aan de ziekte en een verdere verslechtering rondom de eerste psychose. Deze cognitieve achteruitgang blijkt meer bepalend te zijn voor belangrijke levensaspecten zoals het hebben van werk en een zelfstandige woning dan bijvoorbeeld positieve symptomen. Ook blijven de cognitieve problemen veelal voortbestaan nadat de positieve symptomen zijn verdwenen.

Meer inzicht in de cognitieve problemen bij patiënten met een psychose is een voorwaarde voor het ontwikkelen van adequate behandelingen, waaronder medicamenteuze en gedragsmatige interventies. Patiënten verschillen onderling sterk in de mate waarin zij cognitieve problemen ervaren en deze variatie is tot op heden niet goed begrepen. Terwijl ongeveer een kwart van de patiënten cognitief zeer slecht functioneert, presteert een zelfde deel van de patiënten op een vergelijkbaar niveau als controlpersonen.

Het doel van dit proefschrift was om de kennis over cognitief functioneren en psychose te vergroten. Dit hebben wij gedaan door te kijken naar de samenhang tussen cognitief functioneren en verschillende factoren die geassocieerd zijn met psychose. Zo hebben we associaties onderzocht met cannabis- en stimulantia gebruik, met obsessief-compulsieve klachten, met bewegingsstoornissen en met het niveau van functioneren voorafgaand aan de eerste psychose. Dergelijke verbanden kunnen echter vertroebeld worden door ziektegerelateerde factoren, bijvoorbeeld of patiënten ten tijde van het onderzoek al dan niet medicatie kregen of langdurig opgenomen waren in een psychiatrische instelling. Daarom is het zinvol om dezelfde verbanden ook te onderzoeken bij mensen die een verhoogd risico hebben om een psychose te ontwikkelen. Eerstegraads familieleden vormen de zogeheten “genetisch hoog risico groep” omdat zij qua erfelijk materiaal en omgevingsfactoren een overlap vertonen met patiënten. De tweede groep met een verhoogd risico op psychose wordt de “ultra hoog risico” (UHR) groep genoemd. Dit zijn adolescenten en jongvolwassenen met affectieve, cognitieve, psychosociale en/of milde psychotische klachten zoals die ook voor kunnen komen tijdens het prodromale stadium van psychose. Voor de studies in dit proefschrift hebben we cognitief functioneren onderzocht bij patiënten met een psychotische stoornis (voornamelijk}
schizofrenie), hun eerstegraads familieleden (ouders en broers/zussen), UHR patiënten en gezonde controles.

In hoofdstuk 2 is gekeken naar het verband tussen huidig en vroeger cannabisgebruik en cognitief functioneren bij patiënten met een psychose, hun niet-psychotische broers en zussen en gezonde controles. De twee hoofdbevindingen van deze studie leken op het eerste gezicht tegenstrijdig. Terwijl huidig cannabisgebruik geassocieerd was met slechtere prestaties op verwerkingssnelheid en werkgeheugen was cannabisgebruik in het verleden juist geassocieerd met betere prestaties op verworven kennis en sociale cognitie. Deze associaties verschillen niet tussen patiënten, hun broers en zussen en controles. Resultaten in patiënten ondersteunen de hypothese dat er verschillende routes naar psychose bestaan, afhankelijk van de hoeveelheid genetische belasting in combinatie met vroege en late omgevingsfactoren. In hoofdstuk 3 onderzochten we of het gebruik van stimulantia (cocaïne, ecstasy, amfetaminen) geassocieerd was met het niveau van cognitief functioneren bij patiënten met een psychose, hun niet-psychotische broers en zussen en gezonde controles. We vonden dat zowel huidig stimulantiagebruik als frequent gebruik in het verleden geassocieerd was met meer problemen in verbaal leren, werkgeheugen en verworven kennis in vergelijking tot nooit-gebruikers. Laagfrequent stimulantiagebruik in het verleden was geassocieerd met een algemeen patroon van beter cognitief functioneren vergeleken met nooit-gebruikers, maar deze verschillen waren klein en niet significant. De associatie tussen stimulantiagebruik en cognitief functioneren was niet verschillend tussen patiënten, hun broers en zussen en gezonde controles. Hoofdstuk 4 gaat over de bestaande opvatting dat psychotische patiënten met en zonder obsessief-compulsieve symptomen (OCS) onderscheiden kunnen worden op basis van hun cognitief functioneren. In de grootste studiepopulatie tot op heden vonden we dat patiënten en eerstegraads familieleden met en zonder OCS geen verschillen vertoonden op een uitgebreide cognitieve testbatterij. Zogeheten “cross-trait cross-relative analyses” lieten evenmin een verband zien tussen OCS en cognitief functioneren. Onze resultaten ondersteunen daarom niet het bestaan van een “schizo-obssessief subtype” van schizofrenie. Hoewel OCS in patiënten wel samenging met een slechter klinisch beeld kunnen deze resultaten verklaard worden door een continuüm in ernst in plaats van een onderverdeling in categorieën. In hoofdstuk 5 hebben we gekeken of het identificeren van geuren, een reukfunctie van de hogere orde, geassocieerd is met symptomen van parkinsonisme bij patiënten met psychotische stoornissen. We vonden dat problemen in de geuridentificatie geassocieerd waren met meer symptomen van parkinsonisme en negatieve symptomen. Deze twee symptoomclusters zijn geassocieerd met een disbalans in het dopaminesysteem in de hersenen. Voorlopige resultaten van deze studie wijzen er dan ook op dat een dopaminerge disbalans zou kunnen bijdragen aan een vermindere geuridentificatie bij patiënten met psychose. Geuridentificatie zou in de toekomst gebruikt kunnen worden als een risicomarker van dopaminerge gevoeligheid zoals dit reeds bij patiënten met de ziekte van Parkinson gebeurt. Hoofdstuk 6 richt zich op het identificeren van cognitieve endofenotypen bij patiënten met een psychose en hun niet-psychotische familieleden. We vonden dat familiale kwetsbaarheid voor psychose geassocieerd is met problemen in verbaal leren, verwerkingssnelheid, redeneren en probleemoplossen, verworven kennis en werkgeheugen. De spreiding van deze cognitieve problemen suggereert een continuüm, met 30% van
de patiënten en 50% van de familieleden zonder klinisch relevante cognitieve problemen (d.w.z. één standaarddeviatie onder het controlegemiddelde). Het voorkomen van zwaardere cognitieve problemen (twee standaarddeviaties onder het controlegemiddelde) blijkt zich te beperken tot een minderheid van de patiënten (30%) en familieleden (10%). In hoofdstuk 7 hebben we door middel van clusteranalyse vier profielen onderscheiden in het beloop van sociaal en academisch functioneren in de periode voorafgaand aan de eerste psychose, ook wel de “premorbide fase” genoemd. Deze premorbide profielen bleken samen te hangen met klinische variabelen na het begin van de eerste psychose. Daarnaast presteerden psychotische patiënten met premorbide academische problemen slechter op domeinen van aandacht, probleemoplossen, verwerkingsnelheid, werkgeheugen, verworven kennis en sociale cognitie. Onze bevindingen illustreren hoe het bestuderen van premorbide functioneren het inzicht in cognitieve heterogeniteit bij psychose kan vergroten. Hoofdstuk 8 beschrijft de eerste afname van de Measurement And Treatment Response Initiative to Improve Cognition in Schizophrenia (MATRICS) test batterij bij een groep Nederlandse patiënten met een eerste psychose. Daarnaast werd de batterij ook afgenomen bij een groep UHR patiënten. Met de Nederlandse vertaling van de MATRICS konden patiënten met een psychose onderscheiden worden van gezonde controles op zes van de zeven cognitieve domeinen, met de uitzondering van visueel leren. Daarnaast, was er een voorlopig resultaat dat de MATRICS mogelijk sensitief is om cognitieve problemen te identificeren bij UHR patiënten, die tussen patiënten met een psychose en controles in scoorden, de grootte van de UHR populatie was echter beperkt en de verschillen met controles waren niet significant. In hoofdstuk 9 is gekeken of lagere verbale vlotheid correleerde met afwijkingen in de grijze stof van de hersenen bij UHR patiënten die wel en niet de transitie naar psychose doormaakten tijdens follow-up. Met behulp van magnetic resonance imaging (MRI) en voxel-based morphometry vonden we dat slechter presteren op semantische vlotheid significante correleerde met een verlaagde dichtheid van de grijze stof in de rechter gyrus temporalis superior en medius, de rechter insula en de linker cortex cingularis anterior. Deze correlaties waren enkel aanwezig in UHR patiënten die vervolgens de transitie naar psychose doormaakten. Deze studie laat zien dat het combineren van structurele MRI met cognitieve taken mogelijk kan bijdragen aan een betere voorspelling van psychose in UHR patiënten.
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<td>Meijer JH, van Dam DS, Meijer CJ, Hoogendoorn MH, Dragt S, Dingemans PM, Linszen DH, de Haan L.</td>
<td>The Dutch translation of the MATRICS: First assessment in ultra high risk subjects and schizophrenia patients compared to controls. <em>Submitted for publication</em>.</td>
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* joint first authors
CURRICULUM VITAE

Julia Helene Meijer was born on August 27, 1980 in Amsterdam, the Netherlands. She graduated from high school in 1998 at the Vossius Gymnasium in Amsterdam. In the same year, she started her medical studies at the University of Amsterdam. During her education she worked as a student teaching-assistant at the Department of Anatomy. In 2002 she spent six months in Brazil where she did a scientific internship at the Universidade Federal de Sergipe. Here she interviewed three hundred mothers at local health centers in order to understand their motivation to initiate and abandon the breastfeeding process. Her experiences as a nurse-assistant in Surinam (1999) and her rotations in tropical medicine in Kenya (2006) increased her interest in different cultural perceptions of health. After graduating as a medical doctor in 2006 she worked one year in child psychiatry. In 2007 she started her PhD project under supervision of prof. dr. Don Linszen who was succeeded by prof. dr. Lieuwe de Haan. In 2011 she started her psychiatric training which she hopes to finish in 2016.
DANKWOORD

“You never know what motivates you”. Net als een marathon is een promotie een ogenschijnlijk solistische onderneming. De eenzame lange afstandsrenner lijkt het ook vooral op eigen kracht te doen, maar is dat zo? Zijn het niet vooral de mede-renners die hem inspireren om tot het uiterste te gaan? Is het de stem van zijn coach die scandert in zijn hoofd als er niemand in de buurt is? Is het die ene held aan de muur van zijn jongenskamer? Of zijn het de lieve dames op de spons- en verzorgingsposten die hem flesjes drinken toewerpen met een knipoog? De uitzinnige toeschouwers aan de zijlijn wier aanwezigheid hem vleugels geeft? Of is het dat thuisfront dat hem, ongeacht winst of verlies, altijd met hetzelfde enthousiasme zal onthalen?

Ten eerste wil ik iedereen bedanken die heeft deelgenomen aan de studies beschreven in dit proefschrift: patiënten, hun broers, zussen, ouders en controlepersonen. Niet zelden kwamen jullie na een lange werkdag ‘s avonds naar het AMC voor drie uur lang testen en vragenlijsten. Jullie inzet was voor ons van onmetelijk belang.

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Dr. Carin Meijer, mijn co-promotor, of toch… een zus? Een mooie combinatie van Groningse nuchterheid, Oosterse mindfulness en Mokumse gekte. Jij hebt al die jaren als één blok achter me gestaan. Bedankt dat ik altijd jouw kamer mocht binnenvallen met een dilemma van statistische, persoonlijke of politieke aard. Jij wist me dan af te remmen door te vragen: “maar wat is belangrijk voor jou?”. Verder ben je de beste in het bijsturen van een artikel (“less is more”), in het wegduiken voor de camera, en in het verleiden van anderen tot het (mee)eten van familiezakken chocolade bevattend snoep.

De overige leden van de promotiecommissie, Prof. dr. A.H. Schene, Prof. dr. M. van der Gaag, Dr. M.W.J. Koeter, Prof. dr. H.E. Hulshoff Pol en Prof. dr. R.W.H.J. Wiers, wil ik bedanken voor het beoordelen van mijn proefschrift. Alle co-auteurs (in het bijzonder steun en toever laten Piotr en Claudia) en collega’s van het GROUP project: bedankt voor de vruchtbare samenwerking. Jullie hebben deze onderneming tot een feestje gemaakt! En Nicole, voor jouw vertrek naar
Londen was jij degene die mij als werkbegeleider wegwijze maakte in de diepste spelonken van de onderzoekswereld. Wat was het heerlijk om onder het genot van een berg croissantjes alle frustratie over niet functionerende MRI databases te reduceren tot de vergelijking “Publishing is all like being a used car salesman”.

Lieve collega’s van de zorglijn Vroege Psychose. Een afdeling om trots op te zijn! Stuk voor stuk kleurrijke figuren met een missie! Met bevoegdheid en kunde, aangelengd met de nodige dosis humor en relativeringsvermogen, vormen jullie de perfecte cocktail voor deze bijzondere doelgroep. Altijd het best vertegenwoordigd (en uitgedost) op het decemberfeest, de enige rechtsmatige winnaars van d’Vaas van het volleybaltoernooi en het ultieme gezelschap voor een avondje nachtbraken op de wallen of in een Gentse pianobar. Op het klinische vlak heb ik me bij jullie kunnen ontplooien. Roland, jij hebt me geleerd psychose te benaderen vanuit de belevingswereld van een patiënt. Willemijn, je bent en blijft mijn werknemer van het jaar!

En dan natuurlijk mijn geliefde bewoners van de AMC zolder... wat waren we (en zijn jullie nog steeds) een dreamteam! Ook nu mijn hok ergens anders is, op de derde arriveren voelt nog altijd als thuiskomen. Het is alsof er een soort sonarsysteem heerst: zodra één iemand een kamer binnenglipt om een intrigé, roddel, mee- of tegenvaller te bespreken staan er binnen no-time tien mensen. Sardientje! En alle clichés zijn waar. Geen bergtop zo hoog of wij hebben hem bedwongen: op de barricade tegen de gevreesde kantooruit, een kroegcrash organiseren in een onderwereldcafé, overnachten in een Londense versie van het moordhotel uit “the Shining”, creatief omspringen met teruglopende inclusie- en transitiecijfers, ons leven in de waagschaal leggen bij Florentijnse taximaffiosi, de AMC koffie, cameravrees overwinnen voor de Vroege Psychose Tube, kamperen tijdens een wolkbreuk in Lieuwe’s tuin… het was allemaal één grote uitdaging.

In den beginne was er Oswald, de man die de piano bespeelt totdat er stoom uit alle kieren slaat. In andere opzichten ben je misschien niet het prototype “kraker”, maar wat heb jij die driepersoons sauna goed geconfisqueerd toen wij nog als kamerlozen ronddopten! Met Sara de Opperpluis waren we de pioniers van het Untzettend Handige Rekruteer-genootschap dat standaard bij de nieuwjaarsborrel als laatst naar buiten werd geveegd. Kort daarna kwam Bouke alias strijkboukje. Met verbijstering heb ik toegezien hoe jij in je (D)UPpie een megalomaan project op de kaart hebt gezet, tot de filmcatering aan toe. Marise, wat cool dat we een saaie onderzoekspresentatie hebben omgeturnd tot een slapstick. Albertine, bij jou wordt zelfs een babybezoek een borrel. Eva, jij kleine tornado, je ziet er misschien lichter uit dan bent. Maar mag ik je nog één keer over de schouder gooien? Nikie, wat hebben wij veel tijd doorgebracht al worstelend met het GROUP databeest zonder ooit uitgepraat te raken. Zonder jou lag ik nu niet op de sofa (en ja, dat is een compliment!). Renate, of was het An Hedonie? Je eigen Laura Zepam wil nog altijd met jou de hitlijsten bestormen. Lindy, over verhoogd associatief gesproken. Ik heb het afgelopen jaar niet zo hard gelachen als aan die kroegtafel in Florence tijdens onze brainstormsessie over proefschrifttitels. Daniëlla en Soleil, jullie waren de leukste en best georganiseerde stagiaires die een chaotische onderzoeker zich wensen kan. Nienke, I am ever so gobsmacked by your prodigious punctuality and tremendous tidiness, combined with dazzling devotion and cuddlesome craziness. Maarten, op elke foto die ik van je heb sta jij met dezelfde quasi nonchalante blik te midden van hordes vrouwen die minstens een kop
groter zijn, hoe doe je dat toch? Floor (you’re so fluffy!): wij zijn geen ideale combi voor een quick & dirty artikel. Wel denk ik dat als “De Fotoshoot” uitkomt we meteen gescout worden voor een horrorfilm. Laura, ik zou een moord doen voor één van je krullen. Jet, mooi mens, wat een rust kun jij uitstralen in hectische tijden. Leuk jurkje trouwens, nieuw? Erik, ik heb nooit begrepen hoe jij met één onderzoeksdag per week eerder gepromoveerd bent dan ik. Dorien, wat was het leuk om door jou als therapeut bij het EDIE onderzoek betrokken te worden. En Marijen. Congreshotel, Vancouver, Buitenjacuzzi. Need I say more?

Fabiana, paranimf querida. Você era minha surpresa tropical quando cheguei no AMC. Que delicia de poder compartilhar tudo com você, incluindo estáticas aborrecidas, fofocas cremosas, bolos irresistíveis, lágrimas salgadas e o sabor doce de felicidade. Sua alegria é contagante e seu coração é imensurável. Como nos rimos quando você descobriu seus “resultados mais significativos do mundo”, e quando ganhamos o prêmio como Glenda Litter e Gery Lamour. Obrigada para sempre ser minha amiga.

Berna en Marjon, dank voor jullie devotie, die zo ver gaat als het trotseren van een watersnoodramp om het archief te redden en het op,- en afbouwen van de meest onmogelijke feestlocaties. Henny, jij bent als scan-koningin de stabiele factor geweest achter de schermen van GROUP Amsterdam. En Annick, zonder jouw all-round capaciteiten was het nooit gelukt om deze datum te halen. Je bent een topper!

En dan de mensen die nog steeds vragen “waar gaat je onderzoek ook alweer precies over?” maar vanaf de zijlijn o zo betrokken zijn geweest bij het hele proces. En met het leven ernaast, want dat was er gelukkig ook nog.

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Os, mijn stoere teddybroer met keihard zakeninzicht en een hart van goud. Dat je voor mij door de shit gaat heb je op mijn dertigste verjaardag laten zien tijdens jouw Rembo & Rembo act. De gebeurtenissen van het afgelopen jaar, zowel de mooie (welkom lieve Duuk!) als de spannende hebben onze band verder versterkt. Hoe kan ik je ooit weggenest hebben vroeger? Je bent de liefste grote broer die een meisje kan hebben!

En dan mijn pips en mips. Toen de afronding van dit proefschrift naast het klinische werk zijn tof begon te eisen werden mij kortdurende opnames in kuuroord Ton & Tinus aangeboden. In mijn eigen hokje waar de paperassen tot aan het plafond reikten zat ik dan te typen. Pap, jij was de ideale kelner: liefst nog met een theedoek over de arm kwam je mij op gezette tijden het ene “plateau” na het andere uitserveren waarop een Braziliaans sapje, een trosje “van de fijnste druiven”, en een selectie aan noten en zuidvruchten minutieus gerangschikt lagen (“Dame, staat u mij toe”).
Mam, met jouw bemoedigende woorden (“cada dia pouca”), rotsvast vertrouwen en doorzetters-DNA kan ik zo nog drie proefschriften schrijven. Wat kunnen we lekker grappen & grollen (met ’n zachte g), rock ’n rollen in de keuken en arm in arm “tippelen” door de Schuyt bij wijze van studie-break. Beginnen die mensen die zeggen dat we op elkaar lijken dan nu toch gelijk te krijgen?

Lieve Niels. Wij zeggen dat je met iemand de oorlog moet aankunnen. Ik kan je midden in de nacht wakker maken wegens een ICT-storing in combinatie met presentatiestress en jij staat meteen naast je bed in kong-fu houding en een blik van “where is the enemy?”. Jij bent er altijd en onvoorwaardelijk met je engelengeduld, jij bent aarde waar ik water en vuur tegelijk ben, jij weet van alles wat ik kwijt ben waar het ligt (“middelste laatje achterin”) en jij stimuleert mij om soms even helemaal niets te moeten. Ik kijk uit naar het avontuur met onze kleine jongen erbij. En die spartelaar wil ik bedanken voor precies dat laatste zetje (of schopje) dat ik nodig had. Het was nogal een eindspurt, maar alles ter wille van wat rust en reinheid als jij er bent én…. dat ene voorleesboek.