Evaluation of candidate endophenotypes for schizophrenia

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Evaluation of Candidate Endophenotypes for Schizophrenia

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Evaluation of Candidate Endophenotypes for Schizophrenia

PROEFSCHRIFT

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Promotores:

Prof. dr. J. van Os

Prof. dr. J. Peuskens (Katholieke Universiteit Leuven, België)

Copromotor:

Dr. I. Myin-Germeys

Beoordelingscommissie:

Prof. dr. M. De Vries (voorzitter)

Prof. dr. J. Bobes (Universiteit Oviedo, Spanje)

Em. prof. dr. H.M. van Praag

Prof. dr. B. Sabbe (Universiteit Antwerpen, België)

Prof. dr. C. Stehouwer

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*Two roads diverged in a yellow wood,
And sorry I could not travel both
And be one traveler, long I stood
And looked down one as far as I could
To where it bent in the undergrowth;*

*Then took the other, as just as fair,
And having perhaps the better claim,
Because it was grassy and wanted wear;
Though as for that the passing there
Had worn them really about the same,*

*And both that morning equally lay
In leaves no step had trodden black.
Oh, I kept the first for another day!
Yet knowing how way leads on to way,
I doubted if I should ever come back.*

*I shall be telling this with a sigh
Somewhere ages and ages hence:
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.*

Robert Frost, The road not taken.

Paranimfen

Mark van Winkel

Cécile Henquet

CONTENTS

Chapter 1 **9**

Introduction.

COGNITIVE IMPAIRMENT AS CANDIDATE ENDOPHENOTYPE

Chapter 2 **23**

Premorbid IQ as a predictor for the course of IQ in first onset patients with schizophrenia: a ten year follow-up study.

Chapter 3 **41**

The association between cognition and functional outcome in first-episode patients with schizophrenia: mystery resolved?

STRESS-SENSITIVITY AS CANDIDATE ENDOPHENOTYPE

Chapter 4 **57**

Evidence that the COMT Val158Met polymorphism moderates sensitivity to stress in psychosis: an experience-sampling study.

Chapter 5 **79**

Evidence that the COMT Val158Met polymorphism moderates subclinical psychotic and affective symptoms in first-degree relatives of patients with schizophrenia.

METABOLIC DISTURBANCES AS CANDIDATE ENDOPHENOTYPE

Chapter 6 **93**

Screening for diabetes and other metabolic abnormalities in patients with schizophrenia and schizoaffective disorder: evaluation of incidence and screening methods.

Chapter 7 **111**

Major changes in glucose metabolism, including new-onset diabetes, within 3 months after initiation of or switch to atypical antipsychotic medication in patients with schizophrenia and schizoaffective disorder.

Chapter 8 **127**

Prevalence of diabetes and the metabolic syndrome in a sample of patients with bipolar disorder.

Chapter 9 **143**

Discussion.

Summary **155**

Samenvatting **161**

Dankwoord **167**

Curriculum vitae **169**

Publications **171**

CHAPTER 1

INTRODUCTION

Phenomenology of schizophrenia

Schizophrenia is one of the most severe mental illnesses affecting about one percent of the population worldwide (Jablensky et al., 1992). The DSM-IV diagnostic criteria include psychotic and negative symptomatology severe enough to cause social and occupational dysfunction over a period of at least 6 months (American Psychiatric Association, 1994). Although psychotic (hallucinations, delusions, disorganized speech and behavior) and negative symptoms (eg flattened affect, avolition, social withdrawal) are widely recognized as core symptoms of schizophrenia, there also is consensus on the marked heterogeneity in clinical presentation of patients diagnosed with schizophrenia (McCormick and Flaum, 2005). In psychiatric literature, the clinical manifestations of schizophrenia were usefully divided into two main forms first suggested by Robins and Guze (Robins and Guze, 1970), which were variably modified in later efforts at subtyping (Carpenter et al., 1999; Crow, 1980; DeQuardo et al., 1994; Murray et al., 1992; Sham et al., 1996). These two main forms represent the extremes of the 'schizophrenia spectrum' encountered in clinical settings: an episodic, reactive, non-progressive good outcome form with mainly positive symptoms and a chronic, neurodevelopmental form characterized by high levels of negative symptoms and cognitive impairments.

Whereas increased sensitivity to stress is hypothesized to be at the core of the clinical manifestation of the first subtype, cognitive impairments represent a major part of the clinical manifestation of the latter. Evidence confirmed that sensitivity to stress and cognitive impairments are not correlated in patients with psychosis and may even be mutually exclusive (Myin-Germeys et al., 2002; Morrens et al., 2007). In line with these findings, a recent Experience Sampling study found significant associations between negative symptoms and cognitive impairments and between psychotic symptoms and increased stress-sensitivity (Lataster et al., submitted).

The hunt for schizophrenia genes

Although the heritability of schizophrenia is high (Gottesman, 1991), and promising candidate genes involved in neurodevelopment (eg DISC-1, neuregulin, BDNF) and the dopamine system (eg COMT) have been identified, genetic association studies have yet to produce consistent results. Reasons for these inconsistent results may be found in the heterogeneity of the disorder and in the importance of environmental factors in the development of a psychotic disorder in at-risk persons.

The failure to identify schizophrenia genes through genetic association studies have lead to alternative approaches such as studies taking into account gene-environment interaction (Caspi et al., 2005; Henquet et al., 2006) and replacement of the dichotomous disorder-outcome with continuous, 'endophenotypic' outcomes. Endophenotypes are quantifiable intermediate factors in the genes-to-

behaviors pathways which make genetic and biological studies for disease categories more manageable (Gottesman and Gould, 2003; Gould and Gottesman, 2005). Five criteria distinguish endophenotypes from biological markers: 1. they are associated with the illness in the population, 2. they are heritable, 3. they are state independent, 4. they cosegregate with the illness within families and 5. an endophenotype identified in probands is found in their unaffected relatives at a higher rate than in the general population. Markers that have been put forward as endophenotypes for schizophrenia include cognitive impairments, deficits in sensory motor gating, glial cell abnormalities, eye-tracking dysfunctions, metabolic disturbances, stress-sensitivity, and others (Gottesman and Gould, 2003; Lataster et al., 2007; Thakore, 2007; Turetsky et al., 2007). Possible areas of endophenotypic research are 1. the identification of possible endophenotypic markers, 2. the characterization and phenomenology of identified endophenotypic markers and 3. the genetic underpinning of identified endophenotypic markers. Some of the candidate endophenotypes are already fairly well established (ie cognitive impairments, deficits in sensory motor gating, eye-tracking dysfunctions), whereas others have been put forward more recently (ie metabolic disturbances, stress-sensitivity). This thesis will focus on cognitive impairments, stress-sensitivity and metabolic disturbances, and more specifically their characterization, phenomenology and genetic underpinning, as these are endophenotypic markers with large and direct impact on treatment and outcome compared to other, more subtle endophenotypic markers such as deficits in sensory motor gating and eye-tracking dysfunctions.

Cognitive impairment as an endophenotype and its relation to functional outcome

Cognitive impairments are widely recognized as core features of schizophrenia. A meta-analysis of 204 studies found relatively large cognitive impairments in memory, attention and executive functioning and moderate impairments in vocabulary and visual perceptual skills in 7420 patients with schizophrenia compared to 5865 controls (Heinrichs and Zakzanis, 1998). These cognitive impairments were also found, to a lesser degree, in first-degree relatives of patients with schizophrenia (Finkelstein et al., 1997; Gold, 2004). Given these findings, there is a general consensus that cognitive impairment is a useful endophenotype for studying schizophrenia (Gottesman and Gould, 2003; Gould and Gottesman, 2005).

The presence of cognitive impairments in schizophrenia is also reflected in the global intelligence measure IQ (Intelligence Quotient), with patients with schizophrenia functioning at a lower intellectual level than matched controls (Rabinowitz et al., 2000; Caspi et al., 2003).

It is accepted that intellectual decline is present long before disease onset (Amminger et al., 2000; Caspi et al., 2003; Fuller et al., 2002; Gunnell et al., 2002) and may further progress nearer to disease onset (Rabinowitz et al., 2000). However, next to further research into the genetic underpinning of cognitive impairments, perhaps the most important area of research currently is whether in schizophrenia these impairments further decline or remain relatively stable after disease onset. This

discussion was fueled by recent reports showing progressive brain tissue loss (van Haren et al., 2007; Cahn et al., 2006), suggesting further decline in intellectual capacities after disease onset. These findings seem in line with earlier, cross-sectional studies that found evidence for a progressive decline in intellectual abilities (Bilder et al., 1992; Zampera, 1999), but in contrast with recent longitudinal studies that showed no further decline (Heaton et al., 2001; Russell et al., 1997) or even a modest improvement of (performance) IQ (Gold et al., 1999) or other cognitive measures (Bryson et al., 2002). Other studies reported a decline in cognitive measures in older schizophrenia patients (Friedman et al., 2001; Friedman et al., 2002) whereas cognitive measures in younger patients remained stable (Friedman et al., 2001; Hoff et al., 1999; Hoff et al., 2005).

Part of the explanation for these apparently contrasting findings may be found in the heterogeneity of the disorder, with evidence for functional deterioration in some patients, but stability or improvement in others (Rabinowitz et al., 2007). These findings are also relevant for the course of cognition in schizophrenia, as cognitive impairments were found to strongly correlate with different domains of functional outcome and to predict future functional outcomes in a review of studies with a minimum follow-up period of 6 months (Green et al., 2004). Remarkably, first episode studies have found little evidence for such a prospective association (Bilder et al., 2000; Stirling et al., 2003; Verdoux et al., 2002).

Stress-sensitivity as an endophenotype for schizophrenia

A hallmark of studies have provided evidence for the role of stressors such as life events (Bebbington et al., 1993; Bebbington et al., 1996; Carr et al., 2000), critical family environments (Bebbington and Kuipers, 1994; Butzlaff and Hooley, 1998; Brown et al., 1972), urbanicity (Krabbendam and van Os, 2005b; van Os et al., 2003) and victimization and childhood trauma (Read et al., 2005; Bebbington et al., 2004; Janssen et al., 2004) in the formation of psychotic symptoms.

Despite highlighting the role of stress in the formation of psychosis, these studies were unable to assess stress-sensitivity as a possible endophenotype, as they did not provide quantifiable data on individuals' capacities to cope with stressors, or on the stressors-individual interplay. An interesting approach that did allow to quantify moment-to-moment interactions between daily life stressors and the individual is the Experience Sampling Method (ESM), which is a structured self-assessment diary technique that is used to assess current context, thoughts, mood and symptoms in the flow of daily life (Myin-Germeys et al., 2002; Myin-Germeys et al., 2005a; Myin-Germeys et al., 2005b; Myin-Germeys et al., 2001; Delespaul, 1995). Based on these ESM studies, 'stress-sensitivity' was defined as the symptomatic response to self-reported daily life stressors, in terms of affective as well as psychotic symptoms. As this approach allowed to quantify stressors-individual interplay, it paved the way to study stress-sensitivity as a possible endophenotype for schizophrenia.

These studies have shown that stress-sensitivity is higher in patients with psychosis than in controls, with first-degree relatives scoring intermediate (Myin-Germeys et al., 2001; Myin-Germeys et al.,

2005a). These studies also found evidence for state-independency, as they investigated stress-sensitivity in remitted patients. Furthermore, evidence was found for cosegregation within families (Lataster et al., submitted). Based on these findings, stress-sensitivity has recently been suggested as an endophenotype for schizophrenia (Lataster et al., 2007).

Stress-sensitivity, dopamine and COMT

Whereas there is fairly good evidence that stress-sensitivity is a useful endophenotype for schizophrenia, research into the genetic underpinning is lacking. Interestingly, in an ESM study in first-degree relatives, increased stress-sensitivity was associated with greater dopaminergic responsivity, defined as elevations in plasma homovanillic acid following metabolic perturbation by 2-deoxy-D-glucose administration, which leads to mild glucoprivation (Myin-Germeys et al., 2005b). As these results suggest that increased stress-sensitivity is related to dopaminergic reactivity, an obvious candidate gene to investigate the genetic underpinning of stress-sensitivity is the Catechol-O-Methyltransferase (COMT) gene, since it encodes an enzyme that is critical in the breakdown of dopamine, especially in the prefrontal cortex. COMT contains a functional polymorphism that results in a change from Valine (*Val*) to Methionine (*Met*) (COMT^{Val158Met}) which directly affects enzyme function: individuals with the *Val/Val* genotype have a 40% higher brain COMT enzyme activity than individuals with the *Met/Met* genotype (Chen et al., 2004).

Evidence suggesting a possible role of COMT^{Val158Met} in increased stress-sensitivity comes from a number of general population studies, suggesting that carriers of the *Met* allele may react stronger to stress, by showing that *Met/Met* subjects display greater stress hormone response to a physical stressor (Oswald et al., 2004); greater brain activation in the limbic region to unpleasant (but not pleasant) stimuli (Smolka et al., 2005) and greater limbic, hippocampal and prefrontal cortex reactivity to an emotional face processing task (Drabant et al., 2006), which suggests that *Met* carriers may have greater reactivity to situations that provoke negative affective states (Drabant et al., 2006). This is in keeping with findings from the general population that the *Met* allele is associated with propensity to anxiety (Enoch et al., 2003; Olsson et al., 2005; Stein et al., 2005; Mathew et al., 1980), reduced extraversion (Reuter and Hennig, 2005; Stein et al., 2005) and reduced novelty seeking (Reuter and Hennig, 2005; Tsai et al., 2004; Benjamin et al., 2000). These findings provide a rationale to study the possible role of COMT^{Val158Met} in stress-sensitivity in schizophrenia, especially given its genomic localization in the 22q11 region. This region has been identified as one of three loci that had the highest likelihood of harbouring schizophrenia-risk genes in a meta-analysis of genome-wide linkage scans (Badner and Gershon, 2002) and is deleted in the velo-cardial-facial syndrome, of which the psychiatric presentation resembles the clinical syndrome of schizophrenia (Shprintzen et al., 1992; Bassett et al., 2003).

Metabolic disturbances in schizophrenia: another endophenotype?

Next to cognitive impairments and stress-sensitivity, the increased vulnerability to develop metabolic disturbances such as diabetes and the metabolic syndrome, which comprises abnormalities in glucose metabolism, lipid metabolism, obesity and blood pressure, is a third domain of major clinical importance in patients with schizophrenia (Newcomer, 2006). Increased central obesity (Thakore et al., 2002), decreased insulin sensitivity (Cohn et al., 2006), impaired fasting glucose (Ryan et al., 2003) and impaired glucose tolerance (Spelman et al., 2007) were shown at increased rates in unmedicated first-episode subjects compared to matched controls. Furthermore, high prevalences of diabetes and cardiovascular morbidity were reported in unaffected first-degree relatives (Mukherjee et al., 1989; De Hert et al., 2006a; Lamberti et al., 2004). A recent study in unmedicated first-episode patients, their first-degree relatives and patient-matched controls found impaired glucose tolerance in 10.5 and 18.2 % in patients and first-degree relatives respectively, compared to 0.0% in controls (Spelman et al., 2007). These findings have led to the identification of the vulnerability for metabolic disturbances as another possible endophenotype for schizophrenia (Thakore, 2007), as it is unlikely that shared familial environmental factors solely explain the increased rate of metabolic disturbances in patients and first-degree relatives.

Despite these promising findings, it is currently still unclear whether metabolic abnormalities indeed are a useful endophenotype for schizophrenia, as the identification as an endophenotype has been troubled by the large influence of environmental risk factors. Especially evidence linking the new-generation, ‘atypical’ antipsychotics with an increased liability to induce diabetes and the metabolic syndrome when compared to older, ‘typical’ antipsychotics (Newcomer and Haupt, 2006) has been a limiting factor. Furthermore, differences in general risk factors for metabolic disturbances such as age and weight have troubled a clear identification of metabolic abnormalities as an endophenotype for schizophrenia.

Much of the research has focused on mapping metabolic disturbances in terms of prevalence and incidence and differential effects of antipsychotics and other risk factors, with olanzapine and clozapine commonly implicated as most deleterious (Newcomer et al., 2002; Newcomer and Haupt, 2006). Researchers were prompted to focus on these topics because of the major importance of metabolic abnormalities for treatment and outcome, with evidence suggesting a large impact on medication adherence (Weiden et al., 2004), quality of life (Dixon et al., 1999; De Hert et al., 2006b) and physical health, with a cardiovascular mortality rate twice as high as in the general population (Osby et al., 2000), and a ten-fold higher incidence of diabetic ketoacidosis (Henderson et al., 2007) in patients with schizophrenia.

Despite studies showing the large clinical impact of these abnormalities, the increased scientific interest may have led to increased awareness among caregivers, but not yet to major changes in treatment, with high rates of non-treatment for hypertension, hyperlipidemia and diabetes (Frayne et al., 2005; Nasrallah et al., 2006). Furthermore, several guidelines for screening and monitoring

metabolic abnormalities were published in recent years, but they have yet to make their way to clinical psychiatrists (Wampers et al., 2004; Hanssens et al., 2006). These findings suggest that mapping the influence of medications and other risk factors, and investigation and publication of guidelines (ie characterization and phenomenology of the candidate endophenotype) can be seen as the most urgent topics for research in this area, because of their great clinical relevance. Furthermore, knowledge of the influence of medications and other risk factors is also mandatory for the identification, or rejection, of metabolic abnormalities as another endophenotype for schizophrenia. For example, within-person assessment of the influence of symptomatology on the prevalence of metabolic disturbances (ie assessment of ‘state-independency’) is difficult, if not impossible, without knowledge about the influence of treatment itself.

Aims of the thesis

The overall aim of this thesis was to assess the usefulness of 3 candidate endophenotypes for schizophrenia: cognitive impairments, stress-sensitivity and metabolic disturbances. This was done by evaluating the criteria put forward by Gottesman and Gould (Gottesman and Gould, 2003) and subsequently delineating areas of research for each candidate endophenotype with insufficient current knowledge in order to evaluate a specific criterion. This led to the following specific research questions:

For cognitive impairments, the aim was to evaluate the course of the global cognitive measure IQ in patients who presented with a first episode of psychosis. As the existing data on the course of IQ in these patients did not show a clear picture and in part even appeared contradictory as a possible result of underlying heterogeneity, a second aim was to investigate possible differences in course of IQ resulting from this underlying heterogeneity, with premorbid IQ differentiating between cognitively impaired patients and cognitively preserved patients. A third aim was to investigate the relationship between IQ measures and functional outcome in this sample of first-episode patients, and especially whether underlying heterogeneity, reflected in a differential course of IQ, could also explain the intriguing finding in the literature that no clear association was found between cognition at the first episode and functional outcome years later, whereas cognition and functional outcome are consistently associated in chronic patients.

For stress-sensitivity, the aim was to evaluate whether COMT^{Val158Met} would moderate the psychotic and affective reaction to daily life stressors in a sample of patients with psychosis and controls, with the anticipation that the *Met* allele would moderate the effects of stress on negative affect in controls, and on negative affect and psychosis in patients with a psychotic disorder. A second aim was to evaluate if this possible COMT^{Val158Met} moderation could also be a causal mechanism in the development of psychosis, by evaluating whether unaffected first-degree relatives of patients with

schizophrenia who share a *Met* allele have greater concordance of subclinical symptomatology than relatives not sharing a *Met* allele.

For metabolic abnormalities, aims were to assess the comparative adequacy of the widely used American Psychiatric Association/American Diabetes Association (APA/ADA) screening guidelines for detecting diabetes versus a screening guideline derived from the guidelines of the World Health Organization (WHO) in a sample of patients with schizophrenia who were on stable medication for more than three months and who were not known with diabetes prior to study entry. By doing so, the incidence of new-onset diabetes in this sample could also be evaluated. In a second study, 3-month incidence rates of new-onset diabetes and early changes in glucose metabolism were evaluated, including differential effects of individual antipsychotics, in a sample of patients who were newly initiated on antipsychotic medication. Furthermore, given the genetic overlap between schizophrenia and bipolar disorder and the analogous use of atypical antipsychotics as antimanic and mood-stabilizing medication, the prevalence of diabetes and metabolic syndrome was also assessed in a sample of patients diagnosed with bipolar disorder.

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COGNITIVE IMPAIRMENT AS CANDIDATE ENDOPHENOTYPE
CHAPTER 2

PREMORBID IQ AS A PREDICTOR FOR THE COURSE OF IQ IN FIRST ONSET PATIENTS WITH SCHIZOPHRENIA: A TEN YEAR FOLLOW-UP STUDY.

Ruud van Winkel^{a,b}, Inez Myin-Germeys^b, Philippe Delespaul^b, Joseph Peuskens^a, Marc De Hert^a, Jim van Os^{b,c}

^a University Psychiatric Center Katholieke Universiteit Leuven, Leuvensesteenweg 517, 3070 Kortenberg, Belgium.

^b Department of Psychiatry and Neuropsychology, EURON, South Limburg Mental Health Research and Teaching Network, Maastricht University; PO box 616, 6200 MD Maastricht, The Netherlands.

^c Division of Psychological Medicine, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK.

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Abstract

The aim of the present study was to examine the longitudinal course of IQ and its heterogeneity in patients with schizophrenia, from the perspective of the two main “subtypes” of schizophrenia described in the literature: progressive cognitive deficit versus cognitive stabilisation or recovery. Premorbid IQ scores and WAIS IQ scores of 100 first onset patients were obtained at first hospitalization (T1) and after ten years (T2). Significant changes in IQ over time were found, representing i) at T1, a deterioration compared to premorbid intelligence ($B = -6.3$, 95% CI -9.5 - -3.0 , $p < 0.0001$), followed by ii) a recovery at T2 where IQ matched premorbid intelligence again ($B = 0.5$, 95% CI -3.1 - 4.0 , $p = 0.79$). In addition, a significant interaction was found between course of IQ over time and estimated premorbid IQ, demonstrating that subjects with lower premorbid IQ levels remained stable over time whereas in individuals with higher premorbid IQ levels a pattern of deterioration was evident at T1, followed by a recovery up to premorbid level at T2. The data confirm the importance of estimated premorbid IQ as an indicator of the longitudinal course of cognitive functioning in patients with schizophrenia and add evidence to the hypothesis of heterogeneity or “subtypes” of schizophrenia. The data, however, do not confirm the existence of progressive deterioration of cognitive functioning. Rather, catching up of cognitive function later in the course of the illness may take place in those whose deficits become apparent in the early phases of illness, whereas those with the most severe premorbid impairments remain stable.

Keywords: Schizophrenia, Subtypes, Intelligence, Premorbid

Introduction

Cognitive symptoms have been recognized as core symptoms of schizophrenia since the times of Kraepelin (Kraepelin, 1919) and Bleuler (Bleuler, 1950). There is a general consensus that patients diagnosed with schizophrenia function at a lower intellectual level than matched control persons (Caspi et al., 2003; David, 1998; Rabinowitz et al., 2000). Several longitudinal studies have shown that intellectual decline is present long before disease onset (Amminger et al., 2000; Caspi et al., 2003; Fuller et al., 2002; Gunnell et al., 2002). Moreover, this intellectual impairment may further decline nearer to disease onset (Rabinowitz et al., 2000). The course after disease onset, however, is much debated. Earlier, cross-sectional studies suggested a progressive decline in intellectual abilities (Bilder et al., 1992; Zampera, 1999), but this view was not supported in recent longitudinal studies on the course of IQ in schizophrenia, showing no further decline in IQ after onset (Heaton et al., 2001; Russell et al., 1997) or even a modest improvement of (performance) IQ (Gold et al., 1999) or other cognitive measures (Bryson et al., 2002). In addition, some studies reported a decline in cognitive measures in older schizophrenia patients (Friedman et al., 2001; Friedman et al., 2002) whereas cognitive measures in younger patients remained stable (Friedman et al., 2001; Hoff et al., 1999; Hoff et al., 2005). Apart from methodological issues, diagnostic issues may underlie the controversy regarding course of IQ in patients diagnosed with schizophrenia. Although the clinical utility of the concept of schizophrenia is generally considered satisfactory, there is a broad consensus that there is underlying heterogeneity in etiology and pathophysiology in patients diagnosed with schizophrenia, complicating data collection and interpretation of IQ scores and other measures (McCormick and Flaum, 2005). As first suggested by Robins and Guze (Robins and Guze, 1970), and later variably modified in later efforts at subtyping (Carpenter et al., 1999; Crow, 1980; DeQuardo et al., 1994; Murray et al., 1992; Sham et al., 1996), the clinical manifestations of schizophrenia can be usefully divided into two main forms, that represent the extremes of the 'schizophrenia spectrum' encountered in clinical settings: an episodic, reactive, non-progressive good outcome form with mainly positive symptoms and a chronic, neurodevelopmental form characterized by high levels of negative symptoms, cognitive impairments and progression. Because intellectual functioning is hypothesized to be (progressively) impaired in the poor outcome group but not necessarily in the other, the analytical strategy of using the two subtypes as a starting point in the investigation of the course of IQ may be productive. The validity for this approach is suggested by recent research providing evidence that in clinical psychotic syndromes, different underlying mechanisms may result in different clinical manifestations (Myin-Germeys et al., 2002; Myin-Germeys et al., 2003; Myin-Germeys et al., 2004). For example, the episodic subtype may be characterized by hyperdopaminergic reactivity reflected in good responses to antipsychotics (Garver et al., 2000) and increased stress-sensitivity (Myin-Germeys et al., 2005). Interestingly, excessive mesocortical dopaminergic stimulation has been associated with increased long-term potentiation (LTP) of hippocampal-prefrontal synapses, a classic measure of neuroplasticity (Jay et al., 2004). Therefore, it is attractive to hypothesize that there is a possibility for

recovery or change of IQ, as a consequence of increased neuroplasticity in this group. The underlying pathology of the neurodevelopmental subtype, on the other hand, is thought to be represented in particular in structural brain abnormalities (Garver et al., 2000; Lieberman et al., 1996) secondary to alterations already present in early life (Murray et al., 1992). According to this view, neurocognitive impairments are present long before the clinical characteristics of the disorder become apparent, and show a stable or deteriorating course of IQ over time.

Classifying patient in subtypes early in the course of the illness is a challenging task. A classification based on symptomatology is problematic, because of the interrelationship of positive and negative symptoms in the acute phase of the illness (Lieberman et al., 1996). Premorbid IQ, on the other hand, can be reliably determined and there is strong evidence that low premorbid IQ is associated with structural brain abnormalities, cognitive impairments and negative symptoms, all features of the neurodevelopmental type (Antonova et al., 2004; Antonova et al., 2005; Tamminga et al., 1998). The current study investigated the course of IQ in a 10-year follow-up study in a sample of 100 first episode patients with a psychotic disorder. In addition, given the evidence for two different subtypes representing the extremes of the spectrum seen in clinical settings, it was hypothesized that estimated premorbid IQ would moderate the course of IQ in patients with schizophrenia.

Methods

Subjects

One hundred consecutive first episode patients admitted with a psychotic disorder, recruited at the university psychiatric hospital St. Jozef in Kortenberg (Belgium), which serves a catchment area of approximately 250 000, were followed for an average period of 10.7 years (range 6-14 years; SD=1.6). Of these 100 patients, 70 were male and 30 were female. They were informed about the purpose of the study and provided written informed consent according to local ethical directives.

Assessment of premorbid intellectual functioning (T0)

Several methods to estimate premorbid IQ are available, and are typically based on 1) demographic characteristics (such as educational achievement) or on 2) current reading ability. Both perspectives have proven their value in the general population (Russell et al., 2000). For the population of patients diagnosed with schizophrenia, however, demographic characteristics such as educational achievement are likely to be influenced by the developmental impairments and prodromal phase of the illness, resulting in an underestimation of premorbid IQ. Evidence suggests that an assessment of premorbid IQ in patients with schizophrenia using a method that uses reading ability is less sensitive to such underestimation, as reading ability is usually well maintained in schizophrenia (Nelson et al., 1990) and is not affected by the acute phase of the illness (O'Carroll et al., 1992). Therefore, the 'Vragenlijst voor Intellectuele Status' (VIS), an algorithm to assess premorbid IQ based on reading ability, was chosen as the indicator for premorbid IQ (Mas, 1979).

Premorbid IQ based on Highest Attained Educational Level (HAEL IQ) was also assessed, as a significant difference between VIS IQ, based on reading ability, and the HAEI IQ estimate of premorbid IQ, based on educational achievement, may serve as evidence for a deterioration in intellectual functioning during adolescence (Stinissen, 1987).

Because VIS IQ was considered to be the most reliable assessment of premorbid IQ, it was chosen as the indicator for premorbid level in all analyses. Since VIS IQ is a single value, it was used as the premorbid value of both Total, Verbal and Performat IQ. HAEI IQ was only computed for the comparison with VIS IQ, in order to assess the possibility of deterioration of intellectual functioning during adolescence.

Assessment of intellectual functioning at first hospitalisation (T1) and follow-up (T2)

Intellectual functioning of the patients was assessed during their first hospitalization (T1) for psychosis, as soon as patients had achieved clinical stability. After a mean follow-up period of 10.7 years (range 6-14 years; SD=1.6), patients were invited again for a new assessment of intellectual functioning (T2). The Flemish translation and norms of the Wechsler Adult Intelligence Scale (WAIS) were used to assess Total IQ, Verbal IQ and Performance IQ (Stinissen et al., 1970a). None of the patients had a WAIS IQ testing between T1 and T2.

Study time line and assessment of diagnosis

At T1, WAIS IQ was assessed. After a mean follow-up period of 10.7 years (T2; range 6-14 years), patients were invited to be interviewed for a formal assessment of diagnosis according to DSM-IV criteria, a WAIS IQ assessment, a VIS premorbid IQ assessment and a PANSS rating. All assessments were conducted by a trained psychologist.

The patients who were interviewed at T2 (n=53) had diagnoses of schizophrenia (n=43), schizoaffective disorder (n=8) and schizophreniform disorder (n=2). For the remainder of the patients, diagnoses were assessed by contacting their psychiatrist (n=15), their family (n=14) or by chart review (n=18). These patients had clinical diagnoses of schizophrenia (n=36), schizoaffective (n=6) or schizophreniform (n=4) disorder and unspecified psychosis (n=1). As the present study focussed on etiological specificity, patients with a T2 diagnosis of schizophreniform disorder or psychosis not otherwise specified were excluded from the analyses.

Analysis

The IQ data are hierarchically structured: multiple assessments of IQ (level 1) are nested within subjects (level 2). Since observations from the same subject are more similar than observations from different subjects, conventional regression techniques are not suited for analyzing these data.

Therefore, multilevel linear random regression analyses were conducted, taking into account the variance components at two levels (time-point level and subject level)(Goldstein, 1987). Data were analyzed with the XTREG module in Stata.

In order to investigate statistically significant changes in IQ over time, regression analyses were conducted with a categorical variable time (with T0 as reference category) as independent variable and IQ as dependent variable. Separate analyses were conducted for Total IQ, Verbal IQ and Performance IQ.

Secondly, IQ was regressed on the interaction “time*VIS IQ” in order to investigate whether premorbid IQ moderated the IQ changes over time.

Finally, the association between VIS IQ and HAEL IQ was estimated using multilevel regression analysis.

Main effects and interactions were assessed with Wald test (Clayton and Hills, 1993).

Results

Subjects

The mean age of the patients was 23.2 years (SD=4.0) at the start of their first hospitalization and 33.8 years (SD=4.9) at follow-up. At T1 some (n=20) patients could not be tested with a WAIS IQ assessment because they remained floridly psychotic or left the hospital unplanned. No large or significant differences in gender or premorbid IQ were found between these patients and those who could be tested at T1. For age, a suggestive difference was found (table 1).

At T2, 52 patients could not be retested with a WAIS IQ assessment. Of this group, 11 patients had committed suicide. The remaining patients (n=41) could not be reached at the time of follow-up or did not consent to be tested again. No large or significant differences in gender, age or premorbid IQ were found between the patients who could be retested at T2 and those lost to follow-up (table 2).

Fifty-three patients were interviewed at T2. They had a mean total PANSS score of 71.5 (SD=17.3), a mean positive PANSS score of 17.5 (SD=6.1) and a mean negative PANSS score of 17.4 (SD=5.9). Of these 53, 48 also consented to do a WAIS IQ testing, which could be completed in 45 patients. In 5 of the 45 patients with a formal diagnostic assessment and a complete T2 WAIS testing, no VIS data could be obtained, yielding a sample of 40 patients with a VIS IQ and a T2 WAIS assessment.

Another 19 patients were willing to fill in questionnaires on demographic variables and do a VIS testing, but refused a formal interview with a diagnostic assessment, a PANSS rating and WAIS IQ testing, so that for 59 patients a VIS IQ assessment was obtained. Of the 40 patients with complete VIS and T2 WAIS IQ data, there were no T1 WAIS IQ data for 10 patients, yielding a sample of 30 patients with complete T0, T1, T2 IQ data and a formal diagnostic assessment. An overview of the characteristics of the available IQ measures is presented in table 3.

Course of IQ

The multilevel regression analysis revealed significant differences over time for Total IQ. At T1, there was a significant deterioration compared to T0 ($B = -6.3$, 95% CI -9.5 - -3.0 , $p < 0.0001$), which was no longer present at T2 ($B = 0.5$, 95% CI -3.1 - 4.0 , $p = 0.79$). A similar pattern was found for Verbal IQ (T0-T1: $B = -3.7$, 95% CI -6.9 - -0.6 , $p = 0.02$; T0-T2: $B = -0.03$, 95% CI -3.4 - 3.3 , $p = 0.99$), and for Performance IQ (T0-T1: $B = -9.1$, 95% CI -12.9 - -5.2 , $p < 0.0001$; T0-T2: $B = -1.2$, 95% CI -5.4 - 3.0 , $p = 0.57$).

Furthermore, a significant interaction was found between course of Total IQ and VIS IQ ($\chi^2 = 7.6$, $p = 0.02$). To clarify the nature of the interaction between course of IQ and VIS IQ, stratified analyses were conducted with a low and high VIS IQ subgroup (dichotomized at the 50th percentile). Patients in the low IQ group (VIS IQ < 108) were considered to be more likely neurodevelopmentally compromised (compatible with the 'neurodevelopmental subtype'), whereas the patients in the high IQ group (VIS IQ ≥ 108) were considered to have a preserved premorbid IQ (compatible with the 'episodic subtype').

In the low IQ subgroup (mean = 98, SD = 2.2), no significant differences over time were found in Total IQ (T0-T1: $B = -2.2$, 95% CI -7.2 - 2.8 , $p = 0.39$; T0-T2: $B = 3.1$, 95% CI -2.5 - 8.7 , $p = 0.28$), Verbal IQ (T0-T1: $B = -0.7$, 95% CI -5.6 - 4.1 , $p = 0.77$; T0-T2: $B = 3.0$, 95% CI -2.3 - 8.4 , $p = 0.27$), and Performance IQ (T0-T1: $B = -3.3$, 95% CI -8.9 - 2.2 , $p = 0.23$; T0-T2: $B = 2.4$, 95% CI -3.6 - 8.4 , $p = 0.44$).

In the high IQ subgroup (mean = 119, SD = 1.8), multilevel regression revealed significant differences over time, consisting of a deterioration from premorbid level followed by a restoration of IQ up to premorbid level for Total IQ (T0-T1: $B = -10.3$, 95% CI -14.3 - -6.2 , $p < 0.0001$; T0-T2: $B = -1.1$, 95% CI -5.2 - 3.0 , $p = 0.61$), Verbal IQ (T0-T1: $B = -7.2$, 95% CI -11.0 - -3.3 , $p < 0.0001$; T0-T2: $B = -1.1$, 95% CI -4.9 - 2.8 , $p = 0.59$) and Performance IQ (T0-T1: $B = -14.5$, 95% CI -19.9 - -9.1 , $p < 0.0001$; T0-T2: $B = -4.2$, 95% CI -9.6 - 1.3 , $p = 0.14$). An overview of mean IQ scores for the low and high IQ subgroups at T0, T1 and T2 is given in table 4.

Assessments of premorbid IQ

For the whole patient group, HAEL IQ scores were significantly lower than VIS IQ scores ($B = -4.8$, 95% CI -7.1 - 2.4 , $p < 0.0001$). This finding was confirmed in the high IQ group ($B = -9.8$, 95% CI -12.1 - -7.5 , $p < 0.0001$), but not in the low IQ group ($B = 1.2$, 95% CI -2.0 - 4.4 , $p = 0.48$).

Discussion

This paper described the longitudinal course of IQ in first episode patients diagnosed with schizophrenia. After ten years follow-up, there was no evidence for a deterioration of IQ. The hypothesis that estimated premorbid IQ would moderate the course of IQ was confirmed. Dichotomization revealed that in the high IQ group, which was hypothesized to reflect the 'episodic

subtype', IQ measures did not remain stable over the follow-up period. A significant deterioration at the first hospitalization was seen, followed by an improvement up to premorbid level. In the low IQ group, which was hypothesized to reflect the 'neurodevelopmental subtype' a stable course of IQ was found.

Findings

To our knowledge, this paper is the first study to include both measures of premorbid IQ, IQ at first hospitalization and at ten years follow-up. The deterioration preceding the first hospitalization is in line with previous research (Amminger et al., 2000; Caspi et al., 2003; Fuller et al., 2002; Gunnell et al., 2002; Rabinowitz et al., 2000; Reichenberg et al., 2005), as is the global stability of cognitive measures over the course of the illness (Rund, 1998; Kurtz, 2005). The possibility of improvement following the first episode, however, has not received much attention so far. Several studies reported a modest improvement in cognitive measures, typically in first episode patients (Addington et al., 2005; Gold et al., 1999; Hoff et al., 1999). Likewise, in the study of Heaton et al (Heaton et al., 2001), patients with a long duration of illness (mean, 24 years at baseline) showed an improvement of neurocognition that was as large as controls, possibly due to learning effects. Patients with a short duration of illness (mean, 2 years at baseline), however, showed a significantly larger improvement. These findings support the notion that there is an actual improvement of cognition after the first episode, that is not just due to learning effects. In the present study, an improvement was only seen in the high IQ group. These findings suggest that patients with higher premorbid IQ levels are likely to display higher levels of neuroplasticity than patients with lower premorbid IQ levels. There was no significant improvement in the low IQ group after the first hospitalization, as there was also no deterioration from premorbid level. The absence of significant differences in VIS IQ, HAEL IQ and WAIS IQ scores at the first hospitalization and at follow-up suggest that in this group, cognitive deficits are present long before illness onset and remain stable in the years preceding the first psychotic episode, and afterwards. This indeed suggests a 'neurodevelopmental' type of illness, although there was no suggestion of progression over the first ten years of the illness.

Moderation of course of IQ by VIS IQ: evidence for 'subtypes'?

The finding that the course of IQ was moderated by VIS IQ, with a stable course in the low VIS IQ group and a typical pattern of deterioration and subsequent recovery in the high VIS IQ group is interesting, and could be compatible with a more neurodevelopmental type of illness in the low VIS IQ group and a more episodic type of illness in the high VIS IQ group. Nevertheless, some remarks concerning this interpretation can be made.

First, it could be argued that the lack of intellectual deterioration of the low IQ group is the consequence of an error in the operationalization of the 'neurodevelopmental subtype', and that when conceptualized differently, there would have been a progressive intellectual deterioration. However,

neither in the overall sample, nor in the low or high IQ subsamples was there any suggestion of intellectual deterioration, which argues against this explanation.

Second, the reliability of the classification in ‘subtypes’ largely depends on the reliability of the VIS estimate of premorbid IQ. The VIS IQ score, taken at T2, did not differ significantly from the T2 WAIS Verbal IQ score. Furthermore, the VIS IQ score, although statistically significantly different, was only moderately higher than the T1 WAIS Verbal IQ score (3.7 IQ points), in contrast to the T1 WAIS Total (6.3 IQ points) and Performance IQ (9.1 IQ points) scores. This underscores the reliability of verbal IQ measures such as the VIS to estimate premorbid IQ, which is supported by the findings of Russell and colleagues (Russell et al., 2000), who showed that in schizophrenia the Vocabulary subscale of the WAIS was even a more reliable estimate of premorbid IQ than the NART. Third, one could argue that the obtained VIS IQ scores are relatively high and that subjects scoring well below the 50th percentile may have intellectual capacities that are too high to be considered neurodevelopmentally comprised. However, the standardization of the WAIS for Belgium was done in 1970. Since then, no restandardization was done until 1997, with the introduction of WAIS-III (Wechsler, 1997), meaning that for the WAIS IQ scores of the current sample, the Flynn-effect was not taken into account. This phenomenon consists of a mean estimated rise in IQ scores of 15 IQ points per generation (30 years) (Flynn, 1987). This effect was present in every country for which IQ follow-up data were available, including Belgium. Therefore, at the time this cohort had their first-episode WAIS IQ assessment (1985-1989), the average IQ in the general population in Belgium can be estimated at around 108 (15 to 19 years since standardization in 1970, times 0.5 IQ points gained per year), suggesting that the VIS IQ score of 108 actually represents an average score that can be used to differentiate between low and high IQ subjects. It is important to notice that the Flynn effect concerns a rise in average IQ when comparing generations, but does not apply to within-subject test-retest reliability.

Regression to the mean and bottom effect

Alternative explanations for the distinct courses of IQ in subgroups can be postulated. It could be argued that the decrease in the high IQ group results from a regression to the mean. However, the recovery at T2 in the high IQ group cannot be explained by this mechanism. In addition, the significant difference between VIS IQ and HAEL IQ in the high IQ group provides evidence that a functional and intellectual deterioration takes place in the years preceding the first hospitalization in the high IQ group. These findings, together with the possibility of increased neuroplasticity in this group, strengthen the hypothesis that the difference in rate of deterioration between the high and the low VIS IQ subgroups is not solely due to the statistical effect of a regression to the mean in the high IQ group. An alternative explanation could be that the low IQ group showed no deterioration of IQ at T1 due to a bottom effect. This, however, seems unlikely since the mean VIS IQ in the low IQ group was still 98, leaving enough range to measure a possible deterioration in this group.

The differential improvement of Total and Performance IQ scores depending on estimated premorbid IQ could also reflect differences in learning potential. Patients with a higher premorbid IQ may gain more from practice, resulting in a larger improvement in IQ from T1 to T2. However, the relative stability of verbal IQ measures over the course of the follow-up period (VIS IQ, WAIS Verbal IQ at T1 and T2) argue against the simple attribution of the improvement of Total and Performance IQ at T2 to practice effects. This is strengthened by the finding that the VIS IQ scores did not differ significantly from the T2 WAIS IQ scores. As the VIS was taken only once, at T2, this equivalence argues against the presence of differential learning effects. Furthermore, WAIS IQ scores have been shown to have a good test-retest stability (Shatz, 1981).

Methodological issues

The present study has some limitations. First, not all patients could be tested at their first hospitalization (T1) because they left the hospital unplanned or were too psychotic for an IQ test. Furthermore, a substantial group were lost to follow-up after ten years (T2). However, no large or significant differences in gender, age or premorbid IQ were found between the study patients and the patients who could not be tested, both at T1 and at T2. Second, the mean premorbid and follow-up IQ scores of 109 suggest that the current sample of first onset patients with schizophrenia may not be representative for patients with schizophrenia in general, since patients diagnosed with schizophrenia were reported to function at a below-average intellectual level in several studies (Caspi et al., 2003; David, 1998; Rabinowitz et al., 2000). However, the high premorbid IQ scores can probably be explained by the Flynn effect. In addition, the high premorbid IQ scores probably also reflect the particular demographic characteristics of the catchment area, as this catchment area mainly serves the area around the city of Leuven. This is a small city with approximately 90 000 inhabitants, that harbours the largest university of Belgium with around 30 000 students. As a result, 47 of the 100 first-episode patients were students, thus considerably raising the mean IQ of our cohort. In line with this explanation is the observation that the VIS IQ score was equivalent to the T2 WAIS IQ scores. This argues against the explanation that the VIS IQ score is high because it is a single test, since it was equivalent to the WAIS estimate of IQ that is based on a wider variety of subtests. Fourth, premorbid IQ scores were estimated using VIS IQ scores. The use of VIS IQ to estimate premorbid IQ could be less reliable than actually measured WAIS IQ scores. However, as the collection of actually measured premorbid WAIS IQ scores would require extremely large cohorts because of the low incidence of schizophrenia, the current approach provides an attractive alternative to gather insight into the course of cognition in this very important phase. Furthermore, the WAIS IQ scores after ten years follow-up add to the credibility of the VIS premorbid IQ estimate; no large or significant differences were found between premorbid IQ scores and assessments of IQ at ten year follow-up, both for the low and the high premorbid IQ group. Fifth, the current study only included IQ measures, but did not assess measures of executive functioning and episodic memory.

Conclusion

In conclusion, the distinct trajectories of IQ in our patient sample could be compatible with the general notion of an episodic and a neurodevelopmental subtype in schizophrenia patients, as first proposed by Robins and Guze (Robins and Guze, 1970). Our data highlight the importance and clinical relevance of estimated premorbid IQ as an indicator for the subsequent course of IQ and thus, the distinction between ‘subtypes’. The possibility of improvement of cognitive measures after the first episode, and the factors determining this recovery, certainly need further investigation.

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Table 1. Characteristics of patients tested and not tested at first hospitalisation (T1).

	Patients tested	Patients not tested	Comparison
Gender (M/F)	57/23	13/7	p=0.59
Age	22.8 (0.4) N=80	24.7 (1.1) N=20	p=0.06
Premorbid IQ	108.2 (1.8) N=49	111.7 (3.9) N=10	p=0.41

Table 2. Characteristics of patients tested and not tested at follow-up (T2).

	Patients tested	Patients not tested	Comparison
Gender (M/F)	30/15	40/15	p=0.51
Age	23.6 (0.6) N=45	22.9 (0.5) N=55	p=0.35
Premorbid IQ	110.2 (1.9) N=40	105.7 (2.8) N=19	p=0.19

Table 3. Overview of premorbid intelligence and WAIS Total, Verbal and Performance IQ at first hospitalization and at follow up.

Variable	N	Mean	SD	Min	Max
Premorbid IQ (T0)					
Educational	99	103.19	9.38	77	115
VIS	59	108.76	12.23	82	134
First hospitalization (T1)					
Verbal	80	103.95	13.98	57	133
Performance	80	99.10	16.59	60	136
Total	80	101.59	15.06	54	132
Follow-Up (T2)					
Verbal	47	107.65	18.29	58	141
Performance	48	107.57	17.83	66	140
Total	45	109.33	17.18	66	141

Table 4. Mean IQ scores for the low and high IQ subgroups at T0, T1 and T2.

	T0	T1	T2
Total IQ	119.0	109.0	118.7
high IQ subgroup			
Total IQ	98.3	96.4	101.7
low IQ subgroup			
Verbal IQ	119.0	111.8	118.0
high IQ subgroup			
Verbal IQ	98.3	98.2	101.8
low IQ subgroup			
Performance IQ	119.9	104.8	115.4
high IQ subgroup			
Performance IQ	99.0	95.8	100.7
low IQ subgroup			

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COGNITIVE IMPAIRMENT AS CANDIDATE ENDOPHENOTYPE

CHAPTER 3

THE ASSOCIATION BETWEEN COGNITION AND FUNCTIONAL OUTCOME IN FIRST-EPIISODE PATIENTS WITH SCHIZOPHRENIA: MYSTERY RESOLVED?

Ruud van Winkel^{a,b}, Inez Myin-Germeys^b, Marc De Hert^a, Philippe Delespaul^b, Joseph Peuskens^a, Jim van Os^{b,c}

^aUniversity Psychiatric Center Katholieke Universiteit Leuven, Leuvensesteenweg 517, 3070 Kortenberg, Belgium.

^bDepartment of Psychiatry and Neuropsychology, EURON, South Limburg Mental Health Research and Teaching Network, Maastricht University; PO box 616, 6200 MD Maastricht, The Netherlands.

^cDivision of Psychological Medicine, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK.

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Abstract

Introduction: The presence of a prospective association between cognition and functional outcome in first episode patients with schizophrenia is much debated. **Method:** Associations between Intelligence Quotient (IQ) measures and functional outcome were assessed at the first hospitalization and after ten years follow-up. **Results:** Functional outcome was associated with estimated premorbid IQ and IQ at ten-year follow-up, but not with IQ assessed at first hospitalization. **Conclusion:** The presence of a prospective as well as a cross-sectional relationship of the global cognitive measure IQ with 10-year functional outcome could be established. However, assessing associations between cognitive measures assessed at first hospitalization and subsequent functional outcome, can give inconclusive results due to non-uniform intellectual deterioration from premorbid level in the period preceding the first hospitalization.

Keywords: Intelligence, Schizophrenia, Outcomes Research

Introduction

It is generally accepted that cognitive measures are associated with functional outcome in patients diagnosed with schizophrenia (Green et al., 2000). However, the evidence regarding the direction of effects over time remains conflicting. Although there is considerable evidence suggesting that baseline cognitive functioning predicts later functional outcome in chronic patients (Green et al., 2004), first episode studies have found no evidence for such a prospective association (Bilder et al., 2000; Stirling et al., 2003; Verdoux et al., 2002). The reason first episode studies failed to confirm an association between cognitive measures and outcome may be related to evidence suggesting that premorbid cognition deteriorates in the period prior to the first episode (Rabinowitz et al., 2000a; Reichenberg et al., 2005; Jones et al., 1994; Fuller et al., 2002), but that the level of deterioration is not the same for high and low premorbid IQ patients. Thus, a recent ten-year follow-up study (van Winkel et al., 2006), suggested that the decline in cognition prior to the first episode, expressed as IQ, was particularly noticeable in individuals with high estimated premorbid IQ, with subsequent recovery of IQ over the next ten years. In individuals with low estimated premorbid IQ, however, IQ levels were stable in the period prior to the first episode and at ten-year follow-up (see figure 1). As depicted in figure 1, the contrast in IQ between individuals with low and high estimated premorbid IQ is less informative at the first episode than it is in the premorbid period and at long-term follow-up, so that the power to detect associated differences in outcome is reduced.

Given this heterogeneity in course of IQ, it is attractive to hypothesize that premorbid IQ and IQ at long-term follow-up may be better predictors of functional outcome than IQ assessed at the first hospitalization.

The current study investigated the association between estimated premorbid IQ, IQ at first hospitalization and IQ at ten year follow-up on the one hand, and subsequent functional outcome on the other in a 10-year follow-up study of a sample of 100 first episode patients diagnosed with schizophrenia.

Methods

Measures

One-hundred consecutive first-episode patients from the university psychiatric hospital in Kortenberg were followed for an average period of 10.7 years ($SD=1.6$). Of these 100 patients, 70 were male and 30 were female. Since a diagnosis of schizophrenia implicates a certain duration and a certain severity, it is not always possible to diagnose patients accurately at their first episode of psychosis, as is widely recognised. It was chosen not to include only patients who could already be diagnosed with schizophrenia at their first episode of psychosis, since this approach would predominantly include patients with early negative and/or deficitary symptoms. Instead, the recruited subjects were consecutively admitted patients from the rehabilitation ward for first-episode patients with psychosis. As an admission on the rehabilitation ward was considered necessary for recruited patients, it was

ascertained that their first episode of psychosis had relatively large implications for psychosocial functioning (severity criterion), over a time-period of at least several months (time criterion), indicating that over time, the vast majority of these patients was assumed to be diagnosed with schizophrenia. Diagnoses were evaluated at follow-up, and all patients that did not meet DSM-IV criteria of schizophrenia or schizoaffective disorder at this assessment were excluded from the analyses. All patients were informed about the purpose of the study and provided written informed consent.

Intellectual functioning was assessed at the first hospitalization (T1) using the Flemish translation and norms of the full scale Wechsler Adult Intelligence Score (WAIS) (Stinissen et al., 1970). The T1 IQ was assessed when patients achieved clinical stability, indicating i) that patients had had an adequate treatment for their psychotic symptoms, meaning that they had a remission of psychotic symptoms, or in case of non-remission, that large improvements in psychotic symptoms were no longer anticipated, and ii) that patients were able to leave the hospital independently without danger (for example during the weekends). After a mean follow-up period of 10.7 years (T2; range 6-14 years; SD=1.6), patients were invited to be interviewed for a formal assessment of (lifetime) diagnosis according to DSM-IV criteria, a WAIS IQ assessment and an assessment of estimated premorbid IQ. All assessments were conducted by a trained psychologist. None of the patients had a WAIS IQ testing between T1 and T2. Premorbid IQ (T0) was assessed using the Vragenlijst voor Intellectuele Status (VIS), an algorithm to assess premorbid IQ based on reading ability (Mas, 1979). The use and validity of the VIS, as well as an extensive description of the methodology of the study are discussed in an earlier paper on the same sample (van Winkel et al., 2006). The patients who were interviewed at T2 (n=53) had diagnoses of schizophrenia (n=43), schizoaffective disorder (n=8) and schizophreniform disorder (n=2). For the remainder of the patients, diagnoses were assessed by contacting their psychiatrist and/or family, or by chart review. These patients had clinical diagnoses of schizophrenia (n=36), schizoaffective (n=6) or schizophreniform (n=4) disorder and unspecified psychosis (n=1). The patients with diagnoses of schizophreniform disorder (n=6) and unspecified psychosis (n=1) were excluded from the analyses. Both at T1 and at T2, the WHO Life Chart was used to rate functional outcome (WHO, 1992). Functional outcome was the composite score of living situation, working situation, relational status, and social contacts at T2, based on information from the Life Chart. Each outcome area received a score ranging from 0 to 2, with 0 being the worst and 2 being the best outcome. Area scores were then added up, resulting in a eight-point scale (table 1). Likewise, functional status at T1 was the composite score of living situation, working situation and relational status on a six-point scale, since there was insufficient information on the status of social contacts at T1.

Sample

At T1, 20 patients did not have their IQ tested because they remained floridly psychotic or left the hospital against medical advice before they could be tested. At T2, 11 patients had died. All other

patients (n=89) were contacted. Fifty-three agreed to be interviewed for a WHO Life Chart assessment. Two of these patients were diagnosed with schizophreniform disorder and were excluded from the analyses. Of the remaining 51 patients, 47 also consented to do a WAIS IQ testing, which could be completed in 44 patients. In 4 of these 44 patients with a WHO Life Chart and a complete T2 WAIS testing, no VIS data could be obtained, yielding a sample of 40 patients with a VIS IQ assessment, a T2 WAIS assessment and the WHO Life Chart. Another 19 patients were willing to fill in questionnaires on demographic variables and do a VIS testing, but refused a formal interview with a WAIS IQ testing, so that for 59 patients a VIS IQ assessment was obtained. Of the 40 patients with complete VIS and T2 WAIS IQ data, there were no T1 WAIS IQ data for 10 patients, yielding a sample of 30 patients with complete T0, T1, T2 IQ data and a WHO Life Chart assessment. For the assessment of functional outcome at T2 for the patients that could not be interviewed directly, information was obtained from questionnaires that were sent to them by mail (for 7 patients), from the medical file (for 17 patients), or from their parents and/or treating doctor (for 12 patients). Five of the patients that could not be interviewed directly were excluded from the analyses because they had clinical diagnoses of schizophreniform disorder (n=4) or unspecified psychosis (n=1). For 70 patients, sufficient information was available to assess functional outcome at T2, of whom 66 patients had a diagnosis of schizophrenia or schizoaffective disorder (table 2). This resulted in a risk set of 51 patients at T0, 53 patients at T1 and 43 patients at T2 with a diagnosis of schizophrenia or schizoaffective disorder for whom both an IQ assessment at this given time-point and functional outcome at T2 was available; the associations between IQ and functional outcome were assessed using these risk sets.

Analysis

Associations between IQ measures and functional outcome at T2 were determined using linear regression analysis, with functional outcome as dependent variable and premorbid IQ, IQ at T1 and IQ at T2 as independent variables. Standardized regression coefficients (β) are displayed. The models were adjusted for the following *a priori* selected possible confounding variables: duration of untreated psychosis, gender, age at onset and functional status at T1. Duration of untreated psychosis was conceptualized as the elapsed time between the first experienced psychotic symptom and the first administration of antipsychotic medication. This was assessed by asking the patient, or in case the patient was not able to answer, by asking the family.

Given the unequal availability of IQ measures at T0, T1 and T2, a sensitivity analysis was done with a stable risk set consisting of the 30 patients with complete T0, T1, T2 IQ data and a WHO Life Chart assessment. The aim of this analysis was to determine whether the unequal availability of IQ measures at T0, T1 and T2 would affect the association with the T2 functional outcome measure, and thus, to investigate the robustness of the possible associations.

Results

The mean age of the patients at T1 was 23.2 years (SD=4.0). No large or significant differences in gender, age or estimated premorbid IQ (assessed at T2) were found between patients who could be tested for IQ at T1 and those who could not (van Winkel et al., 2006b). Similarly, no large or significant differences were found between patients that could and could not be tested at T2. The mean IQ scores were 108.8 at T0 (SD=12.2), 101.6 at T1 (SD=15.1) and 109.3 at T2 (SD=17.2). The functional outcome at T2 is shown in table 2. A suggestive association was found between estimated premorbid IQ and functional outcome after 10 years ($\beta = 0.24$, 95% CI: -0.02-0.50, $p=0.07$), which was significant after adjustment ($\beta = 0.30$, 95% CI: 0.02-0.59, $p=0.04$). However, no significant or large association, although directionally similar, was found between IQ at T1 and functional outcome at T2 ($\beta = 0.08$, 95% CI: -0.17-0.33, $p=0.52$). At T2, IQ again was associated with outcome ($\beta = 0.28$, 95% CI: 0.02-0.55, $p=0.04$), also after adjustment for confounders ($\beta = 0.33$, 95% CI: 0.02-0.63, $p=0.04$) (figure 2). A sensitivity analysis on a stable risk set of the 30 patients with non-missing data on IQ measures at T0, T1 and T2, and on functional outcome at T2, confirmed these findings (estimated premorbid IQ: $\beta = 0.31$, 95% CI: -0.03-0.65, $p=0.07$; IQ at T1: $\beta = 0.19$, 95% CI: -0.20-0.57, $p=0.33$; IQ at T2: $\beta = 0.34$, 95% CI: 0.02-0.69, $p=0.06$).

Discussion

The current data show a consistent association between both estimated premorbid IQ and IQ at follow-up on the one hand and functional outcome on the other after a mean illness duration of ten years. IQ assessed at the first hospitalization, however, was not associated with functional outcome at ten years follow-up.

These findings are in line with our hypothesis and confirm the existence of a prospective as well as a cross-sectional relationship of the global cognitive measure IQ with functional outcome, and may help to explain the controversy in the literature regarding the prospective relationship between cognitive measures and subsequent functional outcome between chronic and first episode patients. They also support the hypothesis that the use of cognitive measures taken at first hospitalization for the prediction of subsequent functional outcome is less informative, due to a non-uniform rate of deterioration of premorbid IQ preceding the first hospitalization (van Winkel et al., 2006), although other approaches to explain the apparently contradictory findings have also been formulated.

Addington and colleagues stressed the importance of taking symptoms into account, as the relationship between cognition and outcome no longer existed, when it was (cross-sectionally) controlled for symptoms (Addington et al., 2005). However, it may not be meaningful to control for symptoms when investigating a possible predictive relationship, because symptoms tend to change considerably over the course of the illness and their evolution cannot be reliably predicted. An additional problem is the interrelationship of negative, depressive and positive symptoms in the presence of a psychotic episode, which makes the assessment of negative symptoms at the first hospitalisation problematic (Lieberman

et al., 1996). Nevertheless, the finding that the relationship between cognition and outcome no longer existed when it was controlled for symptoms (Addington et al., 2005), points to the importance of symptomatology for the functional outcome of patients with schizophrenia. The design of the current study did not allow to investigate the possibility that the lack of association of the T1 WAIS IQ measure with functional outcome at T2 could be due to the presence of psychotic symptomatology and the accompanying stress and use of sedative medication at the first hospitalization, as symptomatology was not assessed at T1. However, patients were only tested after they achieved clinical stability, as is the case in most studies on first-episode patients. This implicates that, given the good response to antipsychotic medication in first-episode patients, the vast majority of patients thus had little or no remaining psychotic symptoms at the time when they were tested at T1, making it unlikely that the presence of psychotic symptomatology at T1 in these patients would solely explain the lack of association between IQ at T1 and later functional outcome.

Despite the fact that the underlying reason for the lack of association between IQ at T1 and subsequent functional outcome thus could not be directly tested, the current study is important as it shows that the reliability of the assessment of cognition at the first episode of psychosis is questionable and not very indicative for the prognosis of patients, whereas estimated premorbid IQ may be a more reliable reflection of future cognitive abilities and functional outcome. The possible replication of this finding would have important implications to the assessment of prognosis and treatment for future patients who present with a first episode of psychosis.

One could argue that the association between estimated premorbid IQ and subsequent functional outcome could be confounded by functional status at first hospitalization, given the expectation that high premorbid IQ would be associated with a better functional status at first hospitalization. Recent research supports this claim, showing the importance of functional status prior to the first hospitalization for psychosis for later outcome (Meng et al., 2006). A recent study on first-episode patients with psychosis who did find an association between full scale WAIS IQ assessed at the first hospitalization and functional outcome after 3 years (measured by the Global Assessment of Functioning), failed to control for this possibly confounding factor (Carlsson et al., 2006). In the current study, the association between estimated premorbid IQ and functional outcome remained significant, even after controlling for the possible confounding effect of functional status at first hospitalization, and other possible confounders. This is in line with findings reported by Munro and colleagues, who found an association between measured childhood IQ and outcome after a mean period of 21 years in subjects who attended psychiatric services as a child and were later diagnosed with schizophrenia (Munro et al., 2002), which underscores the importance of estimated premorbid IQ for the long-term functional outcome in patients with schizophrenia.

The present study also has some limitations. First, not all patients could be tested at their first hospitalization (T1) because they left the hospital unplanned or were clinically unstable. Furthermore, a substantial group were lost to follow-up after ten years (T2). However, no large or significant

differences in gender, age or premorbid IQ were found between the study patients and the patients who could not be tested, both at T1 and at T2. Second, functional status at T1 consisted of the sumscore of living situation, work situation and relational status, but we failed to include information on social status. Third, the mean estimated premorbid and T2 WAIS IQ scores of 109 suggest that the current sample of first onset patients with schizophrenia may not be representative for patients with schizophrenia in general, since patients diagnosed with schizophrenia were reported to function at a below-average intellectual level in several studies (Caspi et al., 2003; Rabinowitz et al., 2000b). However, the standardization of the WAIS for Belgium was done in 1970. Since then, no restandardization was done until 1997, with the introduction of WAIS-III (Wechsler, 1997), meaning that for the WAIS IQ scores of the current sample, the Flynn-effect was not taken into account. This phenomenon consists of a mean estimated rise in IQ scores of 15 IQ points per generation (30 years) (Flynn, 1987). This effect was present in every country for which IQ follow-up data were available, including Belgium. Therefore, at the time this cohort had their first-episode WAIS IQ assessment (1985-1989), the average IQ in the general population in Belgium can be estimated at around 108 (15 to 19 years since standardization in 1970, times 0.5 IQ points gained per year), suggesting that the mean T2 WAIS IQ score of 109 actually represents an average score. In addition, the high T2 WAIS IQ scores probably also reflect the particular demographic characteristics of the catchment area, as this catchment area mainly serves the area around the city of Leuven. This is a small city with approximately 90 000 inhabitants, that harbours the largest university of Belgium with around 30 000 students. As a result, 47 of the 100 first-episode patients were students, thus considerably raising the mean IQ of our cohort. Fourth, the cognitive assessment only included IQ measures, but no measures of executive functioning and episodic memory.

In conclusion, the current data show a consistent association between both estimated premorbid IQ and IQ at follow-up on the one hand and functional outcome on the other after a mean illness duration of ten years. IQ assessed at the first hospitalization, however, was not associated with functional outcome at ten years follow-up. Clearly, these findings need replication, but they may shed light on the apparently conflicting evidence regarding the prospective relationship between cognition and subsequent functional outcome in first episode patients.

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Table 1. Conceptualization of the T2 functional outcome measure.*

	0	1	2
Living situation	Address in psychiatric hospital	With family or sheltered housing	Alone or with partner
Working situation	No job	Voluntary or sheltered work	Paid work or student [°]
Relational status	No relationship	Relationship for more than 6 months but no contractual engagement	Married or living as married [#]
Social contacts	Almost none	Only with family and/or colleagues at work	Large network of social contacts

*The T2 functional outcome measure is the sumscore of the scores on living situation, working situation, relational status and social contacts.

[°]Or graduated less than six months prior to T2.

[#]With contractual engagement.

Table 2. Functional outcome at T2.

	All patients (N)	Mean (SD)	SCZ/SA (N)	Mean (SD)
Living situation	80	1.13	74	1.05
Address in psychiatric hospital	22	(0.8)	22	(0.8)
With family	15		15	
Sheltered housing	11		11	
Alone	17		16	
With partner	15		10	
Working situation	80	0.60	74	0.53
No job	49	(0.8)	48	(0.8)
Voluntary work	9		9	
Sheltered work	5		4	
Paid work parttime	1		1	
Paid work fulltime	16		12	
Student°	0		0	
Relational status	76	0.42	70	0.31
None	53	(0.7)	53	(0.6)
Without contractual engagement, >6 months	14		12	
Married or living as married#	9		5	
Social contacts	70	0.91	66	0.89
Almost none	22	(0.7)	22	(0.7)
Only with family and/or colleagues at work	32		29	
Large network of social contacts	16		15	
Functional outcome*	70	3.01 (2.2)	66	2.83 (0.8)

*The T2 functional outcome measure is the sumscore of the scores on living situation, working situation, relational status and social contacts.

°Or graduated less than six months prior to T2.

#With contractual engagement.

SCZ/SA: patients with diagnoses of schizophrenia or schizoaffective disorder at T2

Figure 1. Course of IQ in patients with high and low premorbid IQ, as found in a recent ten-year follow-up study on the same sample (van Winkel et al., 2006), suggesting that the decline in cognition prior to the first episode, expressed as IQ, was particularly noticeable in individuals with high estimated premorbid IQ, with subsequent recovery of IQ over the next ten years. In individuals with low estimated premorbid IQ, however, IQ levels were stable in the period prior to the first episode and at ten-year follow-up.

T0: estimated premorbid IQ

T1: IQ at first hospitalization

T2: IQ at ten-years follow-up

Pairwise comparisons T0-T1 and T1-T2: * $p < 0.01$, ** $p < 0.001$

Figure 2. Associations between functional outcome at T2 and IQ measures at T0 (estimated premorbid IQ), T1 (at first hospitalization) and T2 (at ten-years follow-up). The standardized regression coefficients are displayed.

* $p < 0.05$

duration of untreated psychosis, gender, age at onset and functional status at T1

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STRESS-SENSITIVITY AS CANDIDATE ENDOPHENOTYPE

CHAPTER 4

EVIDENCE THAT THE COMT VAL158MET POLYMORPHISM MODERATES SENSITIVITY TO STRESS IN PSYCHOSIS: AN EXPERIENCE-SAMPLING STUDY.

**Ruud van Winkel^{a,b}, Cécile Henquet^b, Araceli Rosa^{c,d}, Sergi Papiol^e, Lourdes Fañanás^c,
Marc De Hert^a, Joseph Peuskens^a, Jim van Os^{b,e}, Inez Myin-Germeys^{b,f}**

^aUniversity Psychiatric Center Katholieke Universiteit Leuven, Leuvensesteenweg 517, 3070 Kortenberg, Belgium.

^bDepartment of Psychiatry and Neuropsychology, EURON, South Limburg Mental Health Research and Teaching Network, Maastricht University; PO box 616, 6200 MD Maastricht, The Netherlands.

^cUnitat d'Antropologia, Facultat de Biologia, Universitat de Barcelona, Avinguda Diagonal 645. 08028 Barcelona, Spain.

^dUnitat de Biologia Evolutiva, Facultat de Ciències de la Salut i de la Vida, Universitat Pompeu Fabra, Doctor Aiguader 80. 08003 Barcelona, Spain.

^eDivision of Psychological Medicine, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK.

^fSchool of Psychological Sciences, University of Manchester, UK.

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Abstract

Background: Gene-environment interactions involving the Catechol-O-Methyltransferase *Val¹⁵⁸Met* polymorphism (COMT^{Val158Met}) have been implicated in the causation of psychosis. Evidence from general population studies suggests that *Met/Met* subjects are sensitive to stress, a trait associated with psychosis. We hypothesized that the *Met* allele would moderate the effects of stress on negative affect (NA) in controls, and on NA and psychosis in patients with a psychotic disorder. **Methods:** Thirty-one patients with a psychotic disorder and comorbid cannabis misuse and 25 healthy cannabis users were studied with the Experience Sampling Method (ESM), a structured diary technique assessing current context and emotional and psychotic experiences in daily life. **Results :** A significant interaction between COMT^{Val158Met} genotype and ESM stress in the model of NA was found for patients (interaction $\chi^2=7.4$, $p=0.02$), but not for controls (interaction $\chi^2=3.8$, $p=0.15$). In the model of ESM psychosis, a significant interaction between COMT^{Val158Met} genotype and ESM stress was also apparent (interaction $\chi^2=11.6$, $p<0.01$), with *Met/Met* patients showing the largest increase in psychotic experiences as well as NA in reaction to ESM stress. **Conclusion:** The findings suggest that the COMT^{Val158Met} polymorphism moderates affective and psychotic responses to stress in patients with psychosis, providing evidence for gene-environment interaction mechanisms in the formation of psychotic symptoms.

Key words: COMT, Schizophrenia, Psychosis, Gene-Environment Interaction, Stress, Experience Sampling Method

Introduction

The Catechol-O-Methyltransferase gene (COMT) has received much attention as a candidate gene in recent psychosis research, because of its function in inactivating catecholamines at postsynaptic sites in the human brain. COMT contains a functional polymorphism that results in a change from Valine (*Val*) to Methionine (*Met*) (COMT^{Val158Met}). The amino acid change affects the function of the enzyme: individuals with the *Val/Val* genotype have a 40% higher COMT enzyme activity in the brain than individuals with the *Met/Met* genotype (Chen et al., 2004a). However, the results from association studies attempting to examine the COMT^{Val158Met} polymorphism as a specific risk gene for schizophrenia have shown great inconsistency. Earlier studies found an association of schizophrenia with the *Met* allele (Park et al., 2002; Ohmori et al., 1998; Kotler et al., 1999), whereas later evidence favoured an association with the *Val* allele (Glatt et al., 2003; Wonodi et al., 2003; Kremer et al., 2003; Chen et al., 2004b; Sanders et al., 2005). Two recent meta-analyses found minimal or no evidence for an association between the COMT^{Val158Met} polymorphism and schizophrenia (Fan et al., 2005; Munafo et al., 2005), comparable to a recent study in two large samples (Williams et al., 2005). Recent studies have focused on gene-environment interactions involving COMT^{Val158Met} rather than genotypic main effects. These studies focused on the *Val* allele, providing evidence of synergism between the *Val* allele and exposure to cannabis in the causation of psychosis; carriers of the *Val* allele were most likely to exhibit psychotic symptoms and to develop schizophreniform disorder years after the initial exposure to cannabis in an epidemiological study (Caspi et al., 2005). *Val* carriers were also found to display more psychotic experiences in reaction to cannabis use in an experimental challenge study (Henquet et al., 2006) and an experience-sampling study (Henquet et al., submitted), consistent with interaction, although these findings were conditional on prior evidence of psychometric psychosis liability in both studies.

Therefore, rather than a main effect, the influence of COMT^{Val158Met} on behaviour may be better understood in terms of gene-environment interactions. Interestingly, a number of studies in general population samples suggested that carriers of the *Met* allele may be differentially affected by the environment, by showing larger sensitivity to stress. Oswald and colleagues, for example, found the *Met* allele to be associated with a greater stress hormone response to a physical stressor in 46 healthy controls (Oswald et al., 2004). A study of 35 healthy subjects by Smolka and colleagues showed greater brain activation in the limbic region to unpleasant stimuli (but not pleasant stimuli) in carriers of the *Met* allele, as measured by fMRI (Smolka et al., 2005). These findings were extended by the work of Drabant and colleagues in 100 healthy control subjects, who found a greater limbic reactivity in *Met* carriers using an emotional face processing task. Furthermore, the *Met* allele was associated with excessive hippocampal and prefrontal cortex activity (Drabant et al., 2006). In this study, *Met/Met* subjects also showed greater amygdala-orbitofrontal cortex connectivity that in turn was associated with low novelty seeking. In the context of provocative environments (eg stress), this could lead to an increased susceptibility for negative mood states (Drabant et al., 2006).

These studies suggest that *Met* carriers may have greater reactivity to situations that provoke negative affective states. This is in keeping with findings from the general population that the *Met* allele is associated with a propensity to anxiety (Enoch et al., 2003; Olsson et al., 2005; Stein et al., 2005; Mathew et al., 1980), reduced extraversion (Reuter and Hennig, 2005; Stein et al., 2005) and reduced novelty seeking (Reuter and Hennig, 2005; Tsai et al., 2004; Benjamin et al., 2000).

The findings connecting the *Met* allele to stress-responsivity are relevant to schizophrenia, as increased stress-sensitivity was found to be present not only in patients diagnosed with schizophrenia, but also in their relatives in an experience sampling study (Myin-Germeys et al., 2001). In addition, experience sampling studies also found that increased stress-sensitivity in schizophrenia is associated with increases in both affective and psychotic responses (Myin-Germeys et al., 2001; Myin-Germeys et al., 2005a) in both patients and their first degree relatives.

It can thus be hypothesized that the *Val* and *Met* allele are both, albeit differentially, implied in the development of psychopathology through divergent interactions with specific environmental stimuli. Whereas the *Val* allele may interact with cannabis in shaping the risk for psychotic disorder as shown previously (Henquet et al., submitted; Caspi et al., 2005; Henquet et al., 2006), the *Met* allele may be specifically associated with stress-sensitivity in terms of affective and psychotic responses to small stressors in the flow of daily life.

The Experience Sampling Method (Myin-Germeys et al., 2001), a self-assessment technique that is used to assess context, thoughts, affect and symptoms in the flow of daily life, can be used to investigate these hypothesized gene-environment interactions in a momentary, ‘real-world’ design. Using this method, the current study aimed to evaluate the relationship between sensitivity to stress and the COMT^{Val158Met} polymorphism in a sample of 31 patients with a clinical diagnosis of psychotic disorder and 25 nonpsychotic controls. The aim of the current study was to investigate the hypothesis that the *Met* allele would moderate affective responses to stressful events in daily life both in patients and control subjects. In addition, since stress also elicited psychotic reactions in patients, it was hypothesized that the *Met* allele would also moderate the effects of stress on psychotic symptoms in patients with a psychotic disorder but not in the control group.

Of note, this same sample has been previously shown to have an interaction between the *Val* allele and cannabis use in their effect on psychotic symptoms (Henquet et al., submitted).

Materials and methods

Sample

Thirty-one cannabis users with a clinical diagnosis of psychotic disorder according to DSM-IV criteria and 25 nonpsychotic cannabis users were recruited through inpatient and outpatient mental health service facilities in South-Limburg, The Netherlands, or were recruited from the general population as described previously (Henquet et al., 2006; Henquet et al., submitted). The diagnosis of patients was assessed according to the Research Diagnostic Criteria (RDC) using the OPCRIT computer program

(McGuffin et al., 1991). Patients had diagnoses of schizophrenia (n=6), schizoaffective disorder (n=23) and psychosis not otherwise specified (n=2).

Subjects attended a briefing session during which a complete description of the study was provided and written informed consent was obtained. In addition, past and current psychiatric illness and past and current substance use were assessed. Given the focus of the study by Henquet and colleagues on the effects of cannabis use on psychosis according to genotype (Henquet et al., submitted), the following exclusion criteria were applied in order to reduce possible confounding by the use of other substances, and to minimize health risks: alcohol use in excess of 5 units per day; use of illicit drugs (other than cannabis) during the 6 consecutive days of the study; respiratory, cardiovascular or neurological disease. Pregnant women were also excluded. A positive family history for psychosis was a further exclusion criterion for the control group. The study was carried out in accordance with the World Medical Association's Declaration of Helsinki (Edinburgh modification, 2000) and was approved by the local Medical Ethics Committee.

COMT^{Val158Met} genotyping

Buccal mucosa was obtained from all the individuals by brushing of a large surface inside both cheeks by means of a cotton swab. DNA was extracted using a BuccalAmp DNA Extraction Kit.

COMT^{Val158Met} genotype was assayed by polymerase chain reaction (PCR) and enzymatic digestion with NlaIII followed by Acrylamide gel electrophoresis as described by Daniels and colleagues (Daniels et al., 1996).

Experience Sampling Method (ESM)

The Experience Sampling Method (ESM) has been described in previous reports (Myin-Germeys et al., 2001; Myin-Germeys et al., 2005a; Myin-Germeys et al., 2005b). It is a self-assessment technique that is used to assess current context, thoughts, mood and symptoms in the flow of daily life. Subjects are provided a wrist-watch and a set of booklets (one booklet for each day). At random moments, the watch emits a 'beep', after which subjects are asked to report their current context, thoughts, appraisals and mood. In the current study, the watch emitted a beep 12 times a day, during 6 consecutive days. Beeps occurred at random, between 7.30 am and 0.30 pm. Self-assessments were rated on a 7-point Likert scale.

The ESM procedure was explained to the subjects during an initial briefing session, and a practice form was filled in to confirm that subjects were able to understand the 7-point Likert scale format. Subjects were asked to complete their reports immediately after the beep and to record the time at which they completed their report, in order to minimize memory distortions. For reasons of reliability and validity as described in detail before (Delespaul, 1995), all reports completed more than 15 minutes after the beep and/or subjects with fewer than 24 reports were excluded from the analysis. In

line with earlier reports (Myin-Germeys et al., 2001, Myin-Germeys et al., 2005a), recruited patients were clinically remitted. This strategy was chosen because i) the completing and adequacy of the reports was assumed to be better in clinically remitted patients and ii) clinically remitted patients were assumed to be less likely to quit the study because of paranoid ideas interfering with the research protocol.

Measures

As described in previous work, stress reactivity was conceptualized as affective and psychotic reactivity to daily life events and minor disturbances in daily life (Henquet et al., submitted; Myin-Germeys et al., 2001; Myin-Germeys et al., 2002; Myin-Germeys et al., 2005a; Myin-Germeys et al., 2005b). Measures of stress, affective response, and psychotic symptoms were derived from the experience sampling reports as described below.

Assessment of stress

Stress in the model of ESM (hereafter ‘ESM stress’) was conceptualized as the subjective appraised stressfulness of distinct events in the natural flow of daily life. Subjects were asked to report the most important event that happened between the current and the previous report, and to rate this event on a 7-point scale (-3: very unpleasant; 0: neutral; 3: very pleasant). ESM stress was linearly defined with most stress being related to the ‘unpleasant’ side of the continuum and least stress being associated with the ‘pleasant’ side of the continuum. In order to allow high scores to reflect high ESM Stress, responses were recoded (-3: very pleasant; 0: neutral; 3: very unpleasant).

Assessment of psychosis

Psychotic experiences were assessed with 9 ESM items rated on 7-point Likert scales (1: not at all; 7: very). To allow self-reported assessments, these 9 items included aspects of the mental state that subjects are aware of and that are directly associated with psychotic experiences such as delusions and hallucinations. These 9 items were: ‘auditory hallucinations’, ‘visual hallucinations’, ‘preoccupation’, ‘suspicion’, ‘feeling unreal’, ‘feeling controlled’, ‘difficulty of expressing thoughts’, ‘racing thoughts’ and ‘fear of losing control’. As previous reports have shown that subjects with hallucinatory experiences can distinguish between hearing real voices and auditory hallucinations (Delespaul, 1995; Escher et al., 2002), the presence of hallucinations was asked directly (“Do you hear voices?”, “Do you see things that others cannot see?”). Guided by a previous paper addressing the presence of psychotic symptoms using ESM (Myin-Germeys et al., 2005a), the presence of delusions was assessed with the use of items that assess aspects of mental states that are directly related to delusional ideation in psychosis. These were: ‘preoccupation’, ‘suspicion’, ‘feeling unreal’ and ‘feeling controlled’. Finally, three items were added that are related to psychosis in general. These were: “I have difficulty expressing my thoughts”, “My thoughts are racing” and “I am afraid to lose control”. The sum of these

nine items formed the variable ‘ESM psychosis’ (Cronbach’s $\alpha = 0.77$). A sumscore was preferred over other approaches (eg using the highest symptom score as measure for psychosis) because the ESM psychosis measure had to allow to pick up subtle fluctuations in psychotic symptomatology reactive to small, daily life stressors; a score that ranges from 9 to 63 (as in a sumscore) is more likely to allow this than a score that only ranges from 1 to 7 (as in the highest psychotic symptom score). Furthermore, the use of a sumscore was chosen because of its consistency with previous ESM studies that examined psychotic reactivity to daily life stressors (Myin-Germeys et al., 2005a; Myin-Germeys et al., 2005b).

Factor analysis of these 9 psychosis items yielded two factors with eigenvalues greater than 1. The first factor loaded high on the items that assessed hallucinations and consisted of the mean of the items ‘auditory hallucinations’ and ‘visual hallucinations’ (‘ESM hallucinations’; Cronbach’s $\alpha = 0.70$). The second factor loaded high on items that were intended to assess delusions or thought disorder, and consisted of the mean of the items ‘preoccupation’, ‘suspicion’, ‘feeling controlled’, ‘racing thoughts’, ‘feeling unreal’, ‘fear of losing control’ and ‘difficulty expressing thoughts’ (‘ESM delusions’; Cronbach’s $\alpha = 0.76$).

Assessment of affect

The affective states reported after each beep were assessed with 9 mood-related items, that were rated on 7-point Likert scales (1: not at all; 7: very). In line with previous reports (Myin-Germeys et al., 2001; Myin-Germeys et al., 2002), affective states were expressed as ‘positive affect’ and ‘negative affect’. The items ‘happy’, ‘cheerful’, ‘relaxed’, and ‘satisfied’ formed the positive affect scale (PA), (Cronbach’s $\alpha=0.85$); the items ‘down’, ‘guilty’, ‘insecure’, ‘lonely’ and ‘anxious’ formed the negative affect scale (NA), (Cronbach’s $\alpha=0.80$). As there was no a priori hypothesis regarding PA, only the results with regard to NA are shown.

Statistical analyses

ESM data are hierarchically structured: multiple observations (level 1) are nested within subjects (level 2). Since observations from the same subject are more similar than observations from other subjects, conventional regression techniques are not suited for analyzing ESM data. Therefore, multilevel linear random regression was used, hereby taking into account the variance components at two levels (ESM-beep level and subject level) (Goldstein, 1987).

As it is also necessary to correct for autocorrelation of data in a time-series like the ESM data, data were analyzed with the XTREGAR module in Stata (StataCorp, 2005), that takes the possibility of autocorrelation into account. The β is the fixed regression coefficient, and can be interpreted in the same fashion as the parameters of unilevel regression coefficients. In order to test the hypothesis that COMT^{Val158Met} genotype moderates the psychotic response to daily life stress, multilevel linear random

regression analyses were conducted with ESM psychosis, ESM delusions and ESM hallucinations as the respective dependent variables, COMT^{Val158Met} genotype (0= *Val/Val*; 1=*Val/Met*; 2=*Met/Met*) and ESM stress as independent variables, as well as their interaction term. Similarly, in order to test the hypothesis that COMT^{Val158Met} genotype moderates the affective response to daily life stress, a multilevel linear random regression was performed with negative affect as the respective dependent variable, and COMT^{Val158Met} genotype and ESM stress as independent variables, as well as their interaction term. As the current study was performed in a sample of cannabis users (Henquet et al., submitted), ESM cannabis use was included in the analyses as a time-dependent covariate.

Antipsychotic use was included in the analyses as a time-independent covariate. Furthermore, use of sedative medication related to perceived stress as indicated by the subject ('ESM stress'), was included in the analyses as a time-dependent potential confounder. Both benzodiazepines and first-generation, sedative antipsychotics that were not prescribed on a daily basis were defined as 'sedative medication'.

In order to estimate effect sizes for each genotype separately, the appropriate linear combinations were calculated from the interaction terms using the STATA LINCOM routine, after fitting the stressXgenotype interaction term with genotype as two dummy variables, using *Val/Val* as reference category. Main effects and interactions were assessed by Wald test (Clayton and Hills, 1993). As there was no a priori hypothesis regarding the type of psychotic symptoms related to the hypothesized gene-stress interaction, the results were corrected for multiple testing using the Simes' correction, which in the case of correlated outcomes represents an improvement over the Bonferroni procedure (Simes, 1986). According to the Simes' procedure, observed p-values greater than Simes' p-values are considered statistically non-significant. Simes' p-values are shown for p-values below 0.05. Since it was hypothesized that the increased responses to stress associated with *Met* would differ between patients and controls, stratified analyses were conducted.

Results

Subjects

All subjects had used cannabis in the past 12 months with a frequency of use of once a day or more in 84% of subjects. No illicit drugs other than cannabis were used during the study. In the patient group, 7 patients were taking typical antipsychotics, 12 were taking atypical antipsychotics and 12 were not taking antipsychotic medication. There were no differences between patients and controls with regard to frequency of cannabis use, age at onset of cannabis use, gender or living situation, but patients were significantly older and had less education (table 1). Patients had significantly more ESM symptomatology, but did not experience more ESM stress. The number of completed ESM reports did not significantly differ between patients and controls (table 1). Of all ESM moments, cannabis use was reported in 40.6%. The use of sedative medication was not confined to patients, but patients were much more likely to use sedative medication ($t = -4.0$, $p < 0.001$).

COMT^{Val158Met} genotype

The COMT^{Val158Met} genotype distribution was in Hardy-Weinberg equilibrium for both patients and controls, with the *Met/Met* genotype being present in 14.3% of subjects (n=8; 5 patients (16.1%); 3 controls (12.0%)), *Val/Met* in 55.4% (n=31; 18 patients (58.1%); 13 controls (52.0%)) and *Val/Val* in 30.4% (n=17; 8 patients (25.8%); 9 controls (36.0%)). Genotype was not associated with sex, ESM cannabis use, ESM psychosis, ESM hallucinations, ESM delusions or ESM stress, but there was a significant main effect of genotype on NA (table 2).

Models for NA in patients and controls

The main effect of genotype on NA was significant in controls ($\beta = 0.27$, 95% CI 0.03- 0.51, $p=0.03$), but failed to reach significance in patients, although the relationship was directionally similar ($\beta = 0.37$, 95% CI -0.02- 0.76, $p=0.07$), with subjects of the *Met/Met* genotype having the highest NA scores in both groups (Table III). ESM stress had a significant main effect on NA in the total group ($\beta = 0.03$, 95% CI 0.02- 0.04, $p<0.001$). Stratified analyses revealed that this effect was also significant for patients, but just failed to reach significance for controls (table 3).

A significant interaction effect was found for COMT^{Val158Met} genotype and ESM stress in the model of NA for patients (interaction $\chi^2=7.4$, $p=0.02$) but not for controls (interaction $\chi^2=3.8$, $p=0.15$), indicating that COMT^{Val158Met} genotype moderated the affective response to ESM stress in patients only. The *Met/Met* patients reported a larger increase in NA in reaction to ESM stress than the patients of the other genotypes (table 3). Although the interaction between COMT^{Val158Met} genotype and ESM stress in the model of NA was only statistically significant for patients, the fit of the model improved in both groups after the addition of the interaction term (table 3).

Models for ESM psychosis in patients and controls

In the patient group, ESM stress was significantly associated with the ESM psychosis measure ($\beta=0.18$, 95% CI: 0.05-0.32, $p<0.01$; table 4). ESM stress was not associated with the ESM psychosis measure in controls (table 4). In the model of ESM psychosis, a significant interaction was apparent for patients between COMT^{Val158Met} genotype and ESM stress (interaction $\chi^2=11.6$, $p<0.01$; < Simes'p of 0.016), indicating that in patients, the psychotic response to ESM stress was moderated by COMT^{Val158Met} genotype. The *Met/Met* patients showed a significantly greater increase in psychotic experiences in reaction to ESM stress than the patients of the *Val/Met* or *Val/Val* genotype (table 4). Similar results were also found for ESM delusions (interaction $\chi^2=12.4$, $p<0.01$; < Simes'p of 0.033), but not for ESM hallucinations (interaction $\chi^2=4.9$, $p=0.08$). As expected, there was no interaction between COMT^{Val158Met} genotype and ESM stress in the model of ESM psychosis in controls (interaction $\chi^2=3.3$, $p=0.20$).

Discussion

Findings

The current study aimed to test two main hypotheses. First, it was hypothesized that the *Met* allele would moderate the effects of stress on negative affect in healthy controls as well as in patients with a psychotic disorder. This hypothesis was only partly supported, as a significant interaction effect for COMT^{Val158Met} genotype and ESM stress in the model of NA was found for patients but not for controls. Nevertheless, the fit of the model improved in both groups after the addition of the interaction term, suggesting that a lack of power may explain the lack of significant interaction in the controls group. As hypothesized, the *Met/Met* patients reported a larger increase in NA in reaction to ESM stress than the patients of the other genotypes.

Second, it was hypothesized that the *Met* allele would moderate the effects of stress on psychotic symptoms in patients only. In the model of ESM psychosis, a significant interaction between COMT^{Val158Met} genotype and ESM stress was indeed apparent for patients, indicating that the psychotic response to ESM stress was also moderated by COMT^{Val158Met} genotype in patients. Again, the *Met/Met* patients showed a significantly greater increase in psychotic experiences in reaction to ESM stress than the patients of the *Val/Met* or *Val/Val* genotype. Similar results were also found for ESM delusions, but not for ESM hallucinations, probably because of a relative scarcity of hallucinations in the patient group (table 1). As hypothesized, there was no evidence for an interaction between COMT^{Val158Met} genotype and ESM stress in the model of ESM psychosis in the controls group. ESM stress had a significant main effect on NA and on ESM psychosis in patients but not in controls. These findings suggest that patients with psychosis react more strongly to stress, showing an increase in psychotic and affective symptoms. Interestingly, the model containing ESM stress, genotype and their interaction term predicted the symptomatic response clearly better than the main model only containing ESM stress, indicating the importance of taking gene-environment interaction into account in explaining transitions in momentary symptomatology in psychosis. The observation that the interaction between ESM stress and COMT^{Val158Met} was only present in patients is in line with findings regarding the interaction between the COMT^{Val158Met} *Val* allele and cannabis use, where the cannabis X genotype interaction was dependent on a pre-existing liability to psychosis (Henquet et al., submitted; Henquet et al., 2006). Given these findings, it can be hypothesized that the *Met* allele can be a causal factor not only for depression and bipolar disorder as shown by Mandelli and colleagues (Mandelli et al., 2006), but also for psychosis, specifically in subjects with a pre-existing liability to psychosis. Whereas the effect of genotype on NA in patients was only apparent in interaction with ESM stress, a significant main effect of genotype on NA was found in controls. Since the effect of ESM stress on measures of symptomatology was only shown in patients, it is unclear whether the effect of genotype on NA in the controls group was independent of ESM stress, or alternatively, whether the perceived stress for controls during the ESM registration was insufficient to provoke and detect these kind of

gene-environment interactions. The observation that the fit and statistical significance of the model containing the interaction term was clearly better than the fit of the main effect model (table 3) could be in line with the latter possibility.

COMT^{Val158Met} polymorphism and emotional processing

These findings support the hypothesized role of the COMT^{Val158Met} polymorphism in sensitivity to stress in the patients with a psychotic disorder and its possible contribution to symptomatology in the general population, and are in line with previous findings connecting the *Met* allele with sensitivity to stress. The findings support the involvement of the COMT^{Val158Met} polymorphism in the emotional processing of environmental stimuli, with *Met* carriers experiencing more difficulties. The tonic-phasic dopamine model may provide an underlying biological rationale for COMT^{Val158Met} interactions with the environment. According to this model, the enzyme containing *Val* favours reduction in tonic dopamine but increases in phasic dopamine. A milieu characterized by predominance of phasic over tonic dopamine may give rise to reduced cognitive stability, but increased cognitive flexibility. For the enzyme containing *Met*, the opposite would hold (Blasi et al., 2005; Stefanis et al., 2005; Nolan et al., 2004; Bruder et al., 2005; Rosa et al., 2004). It has been suggested that cognitive stability in *Met* carriers would be adaptive in circumstances where holding information is demanded (eg working memory), but dysfunctional in circumstances where rapid adjustments to changing external stimuli are required (Bilder et al., 2004; Tunbridge et al., 2006). The lack of an allele dosage effect in the current study, meaning that the *Val/Met* individuals clustered with *Val/Val* individuals rather than being intermediate between homozygote groups, is interesting in this regard, and supports the idea that excessive cognitive stability, that is only present in subjects with two *Met* alleles, could be problematic in these circumstances. The current study is the first to demonstrate the relevance of these emotional processing difficulties in *Met* carriers for psychopathological symptoms such as psychosis and negative affect. It extends the findings of Mandelli and colleagues, who showed that the *Met* allele was associated with depression following adverse life events in a large sample of patients with major depression and bipolar disorder (Mandelli et al., 2006).

COMT^{Val158Met} polymorphism and psychosis

The current findings also add evidence to the theoretical framework that links dopamine to the development of psychosis through aberrant salience (Kapur, 2003; Kapur, 2004), in the sense that a part of the 'dopamine system' (the COMT^{Val158Met} polymorphism, that regulates breakdown of intrasynaptic dopamine) was shown to moderate the psychotic response to daily life stressors. These daily life stressors were shown to interact with COMT^{Val158Met} genotype to increase momentary delusional ideas, which indeed suggests some kind of attribution of aberrant salience to these daily life stressors and, given the interaction with COMT^{Val158Met} genotype, also suggests a role for dopamine in the development of this aberrant salience. The current results also suggest that the attribution of

aberrant salience is not ‘context-independent’, as hypothesized by Kapur and colleagues, but rather that the more stressful these daily life stressors are perceived, the greater the chance that they are being interpreted in a ‘context-inappropriate’, delusional way. Interestingly, COMT has its effect primarily in the prefrontal cortex, whereas aberrant salience is considered to occur through excess striatal dopamine. Future research will have to investigate this issue more specifically.

Strengths and caveats

First, a major strength of the current study is the use of the Experience Sampling Method for the assessment of a gene-environment interaction between the COMT^{Val158Met} polymorphism and the responsivity to stress. This method allows gathering insight in the course of symptoms and the influence of genes and environmental stimuli in a momentary, ‘real-world’ design. The use of the Experience Sampling Method facilitated the test of the hypothesis that both the COMT^{Val158Met} *Val* and *Met* allele differentially moderated the psychotic response to different specific environmental stimuli. Although this finding needs to be replicated, the confirmation of this hypothesis by the current data clearly provides greater insight in the role of the COMT^{Val158Met} polymorphism in the occurrence and course of psychopathological symptoms. In future research, the Experience Sampling Method could also provide an attractive paradigm to study the influence of several other candidate genes, including gene-gene and gene-environment interactions.

A second strength of the current study is that it was specifically performed in a sample in which it was previously shown that the *Val* allele moderated the psychotic response to cannabis (Henquet et al., submitted). In this study on the same sample as that of the current study, subjects with the *Val/Val* genotype, but not those with one or more *Met* alleles, showed an increase in hallucinations after cannabis exposure, that was conditional on prior evidence of psychometric psychosis liability. These findings allowed the test of the hypothesis that within an identical sample, both the COMT^{Val158Met} *Val* and *Met* allele moderate differential vulnerabilities in interaction with specific environmental factors. However, apart from being a strength of the current study by allowing to directly test this hypothesis, the approach of testing COMT^{Val158Met} moderation of stress reactivity in severe cannabis smokers also represents the main limitation of the current study, as it obviously limits the generalizability of our findings. Although limited data are available, cannabis use has been suggested to result in increased synaptic dopamine activity, at least as a short term effect (Voruganti et al., 2001). Furthermore, chronic cannabis use was found to induce a prefrontal hypodopaminergic state (Eldreth et al., 2004) and desensitization of CB1 receptors (Sim-Selley, 2003). Therefore, a replication of our findings in a sample of subjects abstinent of any drug use is needed.

A second limitation is the cross-sectional nature of the analyses, which makes it impossible to establish causal relationships. Therefore it is impossible to determine whether stress measures influenced affect or psychotic symptoms, or whether affect and psychotic symptoms influenced the subjective appraisal of stress. However, either explanation has clinical relevance. A third limitation is

the unequal use of sedative medication in patients and controls, which could have biased the results, as could the use of antipsychotic medication in patients. However, the therapeutic effect of these drugs is intended to be stress-reducing and antipsychotic. This implies that if the current results are indeed biased by the unequal intake of these drugs in patients and controls, the bias is most likely to reduce the results towards the null rather than to create spurious results.

In conclusion, the current results provide evidence for a gene-environment interaction between COMT^{Val158Met} genotype and stressful events in the flow of daily life in patients with psychosis and comorbid cannabis abuse, with *Met/Met* patients showing the largest increase in psychotic experiences as well as NA in reaction to ESM stress. The findings of this study need replication in samples abstinent of any drug use in order to confirm these gene-stress interactions.

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Table 1. Sociodemographic characteristics and descriptives.

	Patients	Controls	t, p
Age (SD)	36.2 (9.6)	26.1 (6.6)	t= -4.3, p<0.001
Gender (male/female)	23/8	22/3	t= -1.3, p=0.20
Education (n=58)			t= 2.6, p=0.01
Elementary school	5	3	
Secondary school	21	11	
Higher education	2	11	
Living situation (n=61)			t= -0.6, p=0.57
Alone	15	12	
With partner	6	5	
With parents or family	5	8	
Protected housing	5	0	
Frequency of cannabis use*			t= -0.15, p=0.88
1-2 times per week	2	0	
3-4 times per week	2	5	
one time per day	5	3	
more than 1 time per day	22	17	
Age of onset cannabis use	18.3 (6.9)	16.0 (1.8)	t= -1.6, p=0.11
Number of ESM reports	41.9 (1.9)	44.2 (2.1)	t= 0.8, p=0.43
ESM psychosis	17.5 (7.6)	12.9 (4.3)	t= -2.7, p=0.01
ESM delusions	2.2 (1.0)	1.6 (0.6)	t= -2.5, p=0.02
ESM hallucinations	1.3 (0.7)	1.0 (0.1)	t= -2.5, p=0.02
ESM stress	-1.3 (1.8)	-1.5 (1.6)	t= -1.1, p=0.28
ESM positive affect	4.5 (1.3)	5.1 (1.2)	t= 2.1, p=0.04
ESM negative affect	1.7 (1.0)	1.3 (0.7)	t= -2.3, p=0.03

*over the last year

Table 2. Sociodemographic characteristics and Experience Sampling Method (ESM) measures by genotype

	Val/Val	Val/Met	Met/Met	P
Age (SD)	32.2 (8.4)	31.3 (10.4)	27.7 (8.2)	0.26
Sex (M/F)	16/3	24/8	8/2	0.67
Number of ESM reports (SD)	42.7 (8.5)	47.1 (10.8)	44.5 (8.2)	0.45
ESM cannabis use*	48.8%	36.7%	39.7%	0.25
ESM psychosis (SD)	14.9 (6.3)	15.6 (7.0)	14.8 (6.2)	0.79
ESM delusions (SD)	1.8 (0.9)	1.9 (0.9)	1.8 (0.8)	0.95
ESM hallucinations (SD)	1.1 (0.4)	1.1 (0.6)	1.3 (0.6)	0.23
ESM stress (SD)	-1.5 (1.6)	-1.4 (1.8)	-1.1 (1.7)	0.21
ESM negative affect (SD)	1.3 (0.5)	1.6 (0.9)	1.8 (1.0)	0.03

*percentage of ESM moments where cannabis use is reported

Table 3. Effect sizes and fit of different models[#] including ESM stress and COMT genotype on Negative Affect. In the composite models, only genotype effect sizes are displayed.

Model	Patients		Controls	
	Effect size (β , p)(SE)	Model fit (Wald χ^2 ; p)	Effect size (β , p)(SE)	Model fit (Wald χ^2 ; p)
‘ESM stress only’	0.04; p<0.001 (0.01)	25.3; p<0.001	0.01; p=0.07 (0.01)	9.1; p=0.06
‘Genotype only’		7.3; p=0.30		13.7; p=0.02
Val/Val	0.00*		0.00*	
Val/Met	0.55; p=0.07 (0.30)		0.07; p=0.66 (0.16)	
Met/Met	0.68; p=0.09 (0.40)		0.69; p<0.01 (0.24)	
‘Genotype+ESM stress’		26.6; p<0.001		17.6; p<0.01
Val/Val	0.05; p<0.001 (0.01)		0.01; p=0.32 (0.01)	
Val/Met	0.57; p=0.05 (0.29)		0.07; p=0.65 (0.15)	
Met/Met	0.74; p=0.05 (0.39)		0.73; p=0.001 (0.22)	
‘Genotype*ESM stress’		35.1; p<0.001		21.2; p<0.01
Val/Val	0.05; p=0.13 (0.03)		0.01; p=0.49 (0.02)	
Val/Met	0.03; p<0.01 (0.01)		0.00; p=0.92 (0.01)	
Met/Met	0.12; p<0.001 (0.03)		0.08; p=0.04 (0.04)	

* Val/Val is the reference category

[#] The Wald χ^2 ’s and their statistical significance can be used to compare the fit of the models. The reported effect sizes are relative effect sizes as compared to the Val/Val reference category, that can only be interpreted within a given model and not across models. Models were adjusted for the following confounders: cannabis use, use of sedative medication and antipsychotic use.

Table 4. Effect sizes and fit of different models[#] including ESM stress and COMT genotype on ESM psychosis. In the composite models, only genotype effect sizes are displayed.

Model	Patients		Controls	
	Effect size (β , p)(SE)	Model fit (Wald χ^2 ; p)	Effect size (β , p)(SE)	Model fit (Wald χ^2 ; p)
‘ESM stress only’	0.18; p=0<0.01 (0.07)	10.5; p=0.06	-0.03; p=0.52 (0.05)	2.8; p=0.59
‘Genotype only’		1.5; p=0.96		4.5; p=0.47
Val/Val	0.00*		0.00*	
Val/Met	1.83; p=0.47 (2.51)		-0.45; p=0.74 (1.36)	
Met/Met	2.87; p=0.39 (3.34)		-2.26; p=0.28 (2.10)	
‘Genotype+ESM stress’		5.1; p=0.65		6.6; p=0.36
Val/Val	0.15; p=0.07 (0.08)		-0.12; p=0.05 (0.06)	
Val/Met	1.99; p=0.44 (2.57)		-0.56; p=0.68 (1.36)	
Met/Met	3.11; p=0.37 (3.45)		-2.41; p=0.25 (2.08)	
‘Genotype*ESM stress’		16.7; p=0.05		10.1; p=0.26
Val/Val	0.25; p=0.30 (0.24)		-0.11, p=0.27 (0.10)	
Val/Met	0.01; p=0.95 (0.09)		-0.08, p=0.32 (0.08)	
Met/Met	0.77; p<0.001 (0.21)		-0.56, p=0.03 (0.25)	

*Val/Val is the reference category

[#] The Wald χ^2 ’s and their statistical significance can be used to compare the fit of the models. The reported effect sizes are relative effect sizes as compared to the Val/Val reference category, that can only be interpreted within a given model and not across models. Models were adjusted for the following confounders: cannabis use, use of sedative medication and antipsychotic use.

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STRESS-SENSITIVITY AS CANDIDATE ENDOPHENOTYPE

CHAPTER 5

EVIDENCE THAT THE COMT VAL158MET POLYMORPHISM MODERATES SUBCLINICAL PSYCHOTIC AND AFFECTIVE SYMPTOMS IN FIRST-DEGREE RELATIVES OF PATIENTS WITH SCHIZOPHRENIA.

Ruud van Winkel^{a,b*}, Pilar Isusi^{c*}, Paloma Galdos^c, Elena Echevarria^c, José Ramón Bilbao^d, Ainhoa Martín-Pagola^d, Luis Castaño^d, Sergi Papiol^e, Ron Mengelers^b, Lydia Krabbendam^b, Jim van Os^{b,f}, Inez Myin-Germeys^{b,g}

*contributed equally

^a University Psychiatric Center Katholieke Universiteit Leuven, Leuvensesteenweg 517, 3070 Kortenberg, Belgium.

^b Department of Psychiatry and Neuropsychology, EURON, South Limburg Mental Health Research and Teaching Network, Maastricht University; PO box 616, 6200 MD Maastricht, The Netherlands.

^c Centro de Salud Mental de LLodio, Llodio, Spain.

^d Unidad de Investigación, Universidad del País Vasco / Hospital de Cruces, Barakaldo, Bizkaia.

^e Unitat d'Antropologia, Departament Biologia Animal, Facultat de Biologia, Universitat de Barcelona, Diagonal 645, 08028 Barcelona, Spain.

^f Division of Psychological Medicine, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK.

^g School of Psychological Sciences, University of Manchester, UK.

Submitted

Abstract

Objectives: Psychotic patients with COMT^{Val158Met} *Met* alleles were recently found to display more intense psychotic and affective responses to daily life stressors. We aimed to test the hypothesis that the *Met* allele is implicated in the development of affective and psychotic symptomatology in subjects genetically at risk for schizophrenia, by testing if first-degree relatives of patients with schizophrenia who share a *Met* allele have greater concordance of symptomatology than relatives not sharing a *Met* allele. **Methods:** Relatives (n=38) were arranged in as many genetically related pairs as possible (n=26), and *Met*-sharing between Index Subject (IS) and Related Subject (RS) was assessed. Psychopathology was assessed with the Brief Psychiatric Rating Scale (BPRS) total score. **Results:** Multilevel regression revealed an interaction between RS BPRS score and *Met*-sharing in the model of IS BPRS score (interaction $\chi^2= 3.46$, $p=0.06$). Stratified analyses revealed that IS-RS total BPRS scores were significantly associated in case of *Met*-sharing ($B= 0.53$, 95% CI: 0.20-0.87, $p=0.002$), but were not when there was no *Met*-sharing. **Conclusion:** These findings support the hypothesis that the *Met* allele may be involved in the causation of psychopathology, at least in populations with a genetic predisposition to psychosis.

Keywords: COMT, schizophrenia, psychosis, affective symptoms

Introduction

A *Val*¹⁵⁸*Met* functional polymorphism in the Catechol-O-Methyltransferase (COMT) gene has received much attention in recent psychiatric research, because of a 40% reduction of dopamine catabolism in individuals homozygous for the *Met* variant. Much of the research on this polymorphism was focused on psychosis, as dopamine is considered as one of the key neurotransmitters in the pathophysiology of psychosis (Kapur, 2004; Kapur, 2003) and because of its genomic localization in the 22q11 region, a region which is deleted in the velo-cardial-facial syndrome, of which the psychiatric presentation resembles the clinical syndrome of schizophrenia (Shprintzen et al., 1992; Bassett et al., 2003). The results of studies examining COMT^{Val158Met} as a specific risk gene for schizophrenia, however, have shown great inconsistency. Earlier studies found an association of schizophrenia with the *Met* allele (Park et al., 2002; Ohmori et al., 1998; Kotler et al., 1999), while the latest evidence favors an association with the *Val* allele (Glatt et al., 2003; Wonodi et al., 2003; Kremer et al., 2003; Chen et al., 2004; Sanders et al., 2005). Two recent meta-analyses found minimal or no evidence for an association between COMT^{Val158Met} and schizophrenia (Fan et al., 2005; Munafo et al., 2005), as did a recent study using two large samples (Williams et al., 2005).

An interesting approach to overcome the problems associated with simple gene-disorder association analyses in large samples is the use of smaller samples consisting of pairs of relatives, in order to study the association between allele sharing and a certain illness, or alternatively, the influence of a candidate polymorphism on continuous or dichotomous measures of psychopathology. This widely used approach allows to examine the potential causal role of genetic polymorphisms (Sham, 1998), by testing whether sharing of a polymorphism among relatives is associated with greater levels of sharing of continuous or dichotomous measures of psychopathology. Comparable methods have already been productively applied in schizophrenia (eg (Kohn et al., 2004; Schwab et al., 1997; Gill et al., 1996)). A current hypothesis in the literature with regard to the functional implications of COMT^{Val158Met} is the ‘Warrior versus Worrier’ hypothesis, that states that in the general population, *Val* alleles may be associated with an advantage in the processing of aversive stimuli (Warrior strategy), while *Met* alleles may be associated with an advantage in memory and attention tasks (Worrier strategy) (Stein et al., 2006). Under conditions of increased dopamine release (eg, stress, administration of dopamine agonists), individuals with *Val* alleles may have improved dopaminergic transmission and better performance, whereas individuals with *Met* alleles may have less efficient neurotransmission and worse performance (Stein et al., 2006; Tunbridge et al., 2006; Bilder et al., 2004; Mattay et al., 2003). Interestingly, the *Val* allele has also been associated with reduced brain volume and worse cognition in patients with schizophrenia (Mata et al., 2006; Ohnishi et al., 2005) and in subjects at high risk for schizophrenia (McIntosh et al., 2006), whereas the *Met* allele has been associated with increased sensitivity to stress in patients with psychosis, both in terms of the psychotic as well as the affective response to daily life stressors (van Winkel et al., 2007). These findings seem to be in keeping with the ‘Warrior versus Worrier’ hypothesis, and also with evidence suggesting that sensitivity to stress and

cognitive impairments may act through different pathways in the formation of psychotic symptoms (Myin-Germeys et al., 2002). In patients with schizophrenia, sensitivity to stress has been associated with increases in psychotic symptoms in reaction to daily life stressors (Myin-Germeys et al., 2005), and also with increases in affective symptoms (Myin-Germeys et al., 2001). Furthermore, the development of depressed mood was found to increase the risk for psychosis in individuals at risk, for example in individuals who report hallucinatory experiences (Krabbendam et al., 2005; Krabbendam and van Os, 2005; Hanssen et al., 2005). Given these findings, it is attractive to hypothesize that the *Met* allele is involved in the causation of symptomatology in individuals with a genetic predisposition for psychosis, and that this symptomatology is not restricted to psychotic symptoms, but also includes affective and anxious symptoms.

An interesting population to study this hypothesis are healthy relatives of patients with schizophrenia, since on the one hand they have been found to display schizotypic symptomatology directly related to the symptomatology in their relative with schizophrenia (Mata et al., 2000), but on the other hand are not treated with dopamine agonists. Moreover, the interpretation of data is not troubled by the possibility of reverse causality as it is in patients with schizophrenia.

Thus, if the *Met* allele is implicated in the vulnerability to develop psychotic, affective and anxious symptoms in subjects with a predisposition to psychosis, then healthy relatives of patients with schizophrenia sharing the *Met* allele should have greater levels of concordance of a range of (subclinical) psychopathological symptoms including anxiety, mood symptoms and psychotic symptoms than relatives not sharing the *Met* allele. The current study aimed to test this hypothesis in a sample of 38 healthy relatives of patients with schizophrenia.

Methods

Sample

First-degree relatives of patients with a clinical diagnosis of schizophrenia were asked to participate in the present study. They were recruited via the catchment area Community Mental Health Centre in the city of Llodio, which their relative with schizophrenia was attending. Llodio is a village with a population of 19.000 inhabitants in the rural province of Avila in the Basque region of Spain. All first-degree relatives were in good mental health. The study was approved by the local ethics committee and all subjects provided written informed consent. The level of psychopathology was assessed with the Brief Psychiatric Rating Scale (Lukoff et al., 1986). This is a 24-item scale that was chosen because it includes a broad range of affective as well as psychotic and psychosis-related symptoms. Since the study was performed in healthy relatives with a relatively low expected level of mood and psychotic symptomatology, the total BPRS score was used as measure for the level of psychopathology, in order to optimize variability in scores between subjects.

COMT genotyping

Genomic DNA was extracted by standard procedures. COMT^{Val158Met} was genotyped using a 5'-nuclease assay on an ABI-PRISM 7700 Sequence Detection System (Applied Biosystems, Foster City-CA, USA). Flanking amplification primers (5'-TCGTGGACGCCGTGATTCAGG-3' and 5'-AGGTCTGACAACGGGTCAGGC-3') and two fluorescent probes [5'-6FAM-CGCTGGCGTGAAG-3' (*Val*) and 5'-TET-TTTCGCTGGCATGAA-3' (*Met*)] were designed using *PrimerExpress* v.2.0 software (Applied Biosystems) and reactions were performed using the *Taqman® Universal PCR master mix* (Applied Biosystems) following the manufacturer's instructions. All assays were run in duplicate and alleles were called by the *SDS* v.1.9.1 software (Applied Biosystems) using pre-sequenced DNA samples homozygous for either the *Val* or *Met* alleles as standards.

Statistical analyses

The subjects were arranged in as many unique genetically related pairs as possible, resulting in sib-sib, father-sib and mother-sib pairs. For every pair, it was assessed whether subjects shared a *Met* allele (sharing of *Met* allele = '1'; no sharing of *Met* allele = '0'; 'no *Met*-sharing' as reference category). Since the data were hierarchically structured, with individuals being clustered within families, standard errors were corrected for familial clustering using multilevel random regression analysis (Goldstein, 1987). Data were analyzed with the XTREG module in Stata (StataCorp, 2005). The regression analysis was conducted with the BPRS score of the first subject of the pair (Index Subject: IS) as the dependent variable, the BPRS score of the second subject (Related Subject: RS), *Met*-sharing and the interaction as independent variables. From the model containing the interaction term, stratified effects were calculated by applying the appropriate linear combinations using the STATA LINCOM routine.

Results

The sample consisted of 38 first-degree relatives pertaining to 17 families (table 1). The 38 relatives could be arranged in 26 genetically related pairs: 14 mother-sib, 6 father-sib and 6 sib-sib pairs. Their mean total BPRS score was 26.4 (range 24-35; SD 2.9).

There was no main effect of COMT^{Val158Met} genotype on BPRS score ($B = -1.50$, 95% CI: -6.95- 0.84, $p=0.18$). Multilevel random regression revealed a suggestive interaction effect between RS BPRS score and *Met*-sharing in the model of IS BPRS score (interaction $\chi^2 = 3.46$, $p=0.06$). Stratified analyses revealed that when IS and RS shared at least one *Met* allele, their BPRS scores were significantly associated ($B = 0.53$, 95% CI: 0.20-0.87, $p=0.002$), whereas the IS-RS BPRS scores were not associated if there was no *Met*-sharing ($B = -0.54$, 95% CI: -1.62-0.54, $p=0.33$).

Discussion

The current study found evidence that healthy relatives of patients with schizophrenia who share a *Met* allele have greater levels of concordance of subclinical psychiatric symptomatology than relatives not sharing a *Met* allele. These findings support the hypothesis that the *Met* allele may be involved in the causation of psychopathology, at least in populations with an increased risk for psychiatric illness.

This is in line with a study by Mandelli and colleagues (Mandelli et al., 2006), who found that the *Met* allele was associated with first-onset depressive disorder following exposure to a major life event in a large sample of patients with depression or bipolar disorder.

The current study did not differentiate between subclinical psychotic symptomatology and affective symptomatology, as the sample was too small to allow for this differentiation, certainly when taking the low total BPRS scores in these healthy relatives into account. Nevertheless, a recent study in patients with psychotic disorder (van Winkel et al., 2007) revealed that the *Met* allele moderated both the psychotic and the affective reaction to daily life stressors, with *Met/Met* subjects displaying the strongest reactivity. These findings, as well as the findings of the current study, support the hypothesis that the *Met* allele may be associated with a relatively broad vulnerability to develop psychiatric symptomatology including mood symptoms and anxiety (Stein et al., 2006), and indicate that the *Met* allele may also be involved in the causation of psychosis in subjects with an increased genetic risk.

The neurobiological mechanism underlying this vulnerability is much debated. A possible neurobiological mechanism can be found in the inverted-U shape of the functional response curve to increasing dopamine signalling in the prefrontal cortex (Mattay et al., 2003), meaning that dopamine could impact on prefrontal function in such way that the response is optimized within a narrow range of dopamine activity, with too little or too much dopamine having a relatively deleterious effect. Thus, under conditions of increased dopamine release (eg, stress), individuals with *Val* alleles may have improved dopaminergic transmission and better cognitive performance, whereas individuals with *Met* alleles may have less efficient neurotransmission and worse cognitive performance. Recent evidence suggests that this could not only be reflected in worsening cognitive performance in *Met* subjects under conditions of increased dopamine release, induced by amphetamine administration (Mattay et al., 2003), but also in an increased risk for methamphetamine-induced psychosis (Suzuki et al., 2006). However, other researchers have pointed to the possible role of the tonic-phasic dopamine model (Tunbridge et al., 2006; Bilder et al., 2004). According to this model, the enzyme containing *Val* favours reduction in tonic dopamine but increases in phasic dopamine. A predominance of phasic over tonic dopamine may give rise to reduced cognitive stability, but increased cognitive flexibility. For the enzyme containing *Met*, the opposite would be true (Blasi et al., 2005; Stefanis et al., 2005; Nolan et al., 2004; Bruder et al., 2005; Rosa et al., 2004). It has thus been suggested that cognitive stability in *Met* carriers would be adaptive in circumstances where holding information is demanded (eg working memory), but dysfunctional in circumstances where rapid adjustments to changing external stimuli are required (Bilder et al., 2004; Tunbridge et al., 2006), possibly leading to a ruminative, worrisome

coping style. This, in turn, could explain the greater stress-sensitivity found in patients with psychosis with the *Met/Met* genotype (van Winkel et al., 2007), and the greater response to negatively connotated stimuli in healthy *Met* carriers, in terms of prefrontal, hippocampal and limbic neural activation (Drabant et al., 2006; Smolka et al., 2005). More research is certainly needed in order to fully understand the nature of the interactions between COMT^{Val158Met} and environmental factors such as daily life stressors, adverse life events, cannabis- and amphetamine abuse and the etiopathological mechanism underlying these complex gene-environment interactions.

The current study also has some limitations. The sample was relatively small, and subjects had low levels of symptomatology as measured by the total BPRS score. Therefore, it was not possible to differentiate between subclinical psychotic and subclinical affective/anxious symptomatology in these subjects. Furthermore, the current study did not evaluate the neurobiological mechanism underlying these findings, and did not evaluate the cognitive coping styles that could possibly mediate the influence of COMT^{Val158Met} on symptomatology. Future research will have to address these issues more specifically.

In conclusion, the current study found evidence that healthy relatives of patients with schizophrenia who share a *Met* allele have greater levels of concordance of subclinical psychiatric symptomatology than relatives not sharing a *Met* allele. These findings support the hypothesis that the *Met* allele may be involved in the causation of psychopathology, at least in populations with a genetic predisposition to psychosis.

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Table 1. Demographic and genetic variables.

	Subjects (n=38)
Male sex (n, %)	14 (36%)
Years of full-time education (SD)	10.4 (6.4)
Age (SD)	50.3 (16.0)
Genotype (n, %)	
Val/Val	8 (21.1%)
Val/Met	16 (42.1%)
Met/Met	14 (36.8%)

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METABOLIC DISTURBANCES AS CANDIDATE ENDOPHENOTYPE

CHAPTER 6

SCREENING FOR DIABETES AND OTHER METABOLIC ABNORMALITIES IN PATIENTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER: EVALUATION OF INCIDENCE AND SCREENING METHODS.

Ruud van Winkel^{a,b}, Marc De Hert^a, Dominique Van Eyck^a, Linda Hanssens^c, Martien Wampers^a, Andre Scheen^d, Joseph Peuskens^a

^aUniversity Psychiatric Center Katholieke Universiteit Leuven, Leuvense Steenweg 517, 3070 Kortenberg, Belgium

^bDepartment of Psychiatry and Neuropsychology, EURON, South Limburg Mental Health Research and Teaching Network, Maastricht University; PO box 616, 6200 MD Maastricht, The Netherlands.

^cDepartment of Epidemiology and Public Health, University Liege, Belgium

^dDepartment of Diabetes, Nutrition and Metabolic Disorders, CHU Sart Tilman, University Liege, Belgium

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Abstract

Objective: to assess the diagnostic properties of two different screening guidelines for the detection of diabetes in patients diagnosed with schizophrenia. **Methods:** Over a two-year period, 415 patients with schizophrenia were screened with a full laboratory screening and a 75 g Oral Glucose Tolerance Test (OGTT). The sensitivity of two screening strategies was compared to the 'Gold Standard': the OGTT. The two strategies were: 1) assessing fasting glucose in all patients, as suggested by the American Psychiatric Association/American Diabetes Association (APA/ADA) and 2) a screening strategy derived from the guidelines of the World Health Organization (WHO) of assessing fasting glucose in all patients (step one), and subsequently performing an OGTT in patients with impaired fasting glucose (step two).

Results: Of the total sample, 6.3% (n=26) met criteria for diabetes, resulting in a mean annual incidence of diabetes of 3.15% (6.3% incident cases/2 years). A screening based on the APA/ADA guidelines detected diabetes in 12 of the 26 cases (46.2%) identified by the OGTT. The proposed two-step strategy detected 25 out of 26 cases (96.2%). **Conclusion:** The data suggest a high incidence of diabetes in patients diagnosed with schizophrenia. However, the guidelines to detect diabetes as proposed by the APA/ADA, did not sufficiently detect diabetes in this specific high risk group. The alternative two-step strategy was able to detect the vast majority of diabetes cases and should therefore be considered in the clinical routine of screening and monitoring patients with schizophrenia.

Key words: Schizophrenia, Diabetes, Metabolic Syndrome, Physical Health

Introduction

In recent years, there has been a growing interest in the occurrence of medical co-morbidity in patients diagnosed with schizophrenia (Goldman, 1999; Jones et al., 2004; Lambert et al., 2003; Marder et al., 2004). This is certainly the case for diabetes, as numerous case reports and some retrospective cohort studies provided evidence for an increased risk of diabetes in patients diagnosed with schizophrenia, or more broadly, in patients treated with atypical antipsychotics (Henderson et al., 2005a; Caro et al., 2002; Citrome and Jaffe, 2003; Gianfrancesco et al., 2003; Hedenmalm et al., 2002; Henderson, 2002; Lindenmayer et al., 2003; Melkersson and Dahl, 2004; Newcomer et al., 2002; Carlson et al., 2006). Given this amount of evidence, there is a large consensus that patients treated with atypical antipsychotics are at high risk of developing diabetes, specifically diabetes type 2 (Lean and Pajonk, 2003). Schizophrenic patients treated with antipsychotics indeed display many risk factors for diabetes type 2 such as a sedentary lifestyle, overweight and unhealthy dietary habits. In addition to these risk factors, all atypical antipsychotics are to some degree associated with weight gain, although their liability to induce weight gain varies from relatively low to relatively high, depending on the individual drug. Furthermore, antipsychotic drugs may even induce insulin resistance (Bergman and Ader, 2005; Henderson et al., 2005b), although insulin resistance was also found in drug-naïve patients with schizophrenia (Ryan et al., 2003). Another major health concern in patients with schizophrenia is the metabolic syndrome, which comprises abnormalities in glucose metabolism, lipid metabolism, body weight/fat distribution and blood pressure. The metabolic syndrome is present in as much as 40% of patients diagnosed with schizophrenia, and its presence significantly increases the risk for diabetes and other glucose abnormalities (De Hert et al., 2006a; Basu et al., 2004; Cohn et al., 2004; Heiskanen et al., 2003; McEvoy et al., 2005; De Hert et al., 2006b).

A recent American consensus conference proposed much awaited guidelines to screen and monitor patients treated with an atypical antipsychotic (American Diabetes Association and American Psychiatric Association, 2004). Importantly, the consensus conference also acknowledged the need to acquire additional data in order to further improve screening and treatment guidelines. This is especially relevant because of two reasons. First, preliminary evidence suggests that the use of the proposed guidelines may result in an underdiagnosis of diabetes and other glucose abnormalities in high risk groups, when compared to the ‘gold standard’ of the Oral Glucose Tolerance Test (OGTT) (De Hert et al., 2006a; Adam and Tarigan, 2004; Botas et al., 2003). Second, early detection of glucose abnormalities in patients diagnosed with schizophrenia could well be of eminent importance, as prediabetic abnormalities and even frank diabetes are shown to be potentially reversible in this specific population, at least in cases in which the onset of diabetes was most likely related to antipsychotic treatment (Ananth et al., 2002; Rigalleau et al., 2000; Peuskens et al., 2004; De Hert et al., 2007).

However, the standard use of an OGTT as a screening instrument in all patients treated with antipsychotics may not be an achievable goal in all treatment settings. Therefore, a two-step strategy

derived from the guidelines of the World Health Organization (WHO) (World Health Organization, 1999) was developed, that could serve as an alternative for the standard use of an OGTT in patients treated with antipsychotics.

The current study reports on the baseline data of a cohort of 415 prospectively monitored schizophrenic patients treated with antipsychotics. The aim of the current study was twofold: first, to assess metabolic abnormalities in a large sample of patients diagnosed with schizophrenia; second, to assess the sensitivity of two different screening guidelines for the detection of diabetes. These two strategies were: 1) assessing fasting glucose in all patients, as suggested by the American Psychiatric Association/American Diabetes Association (APA/ADA) consensus guidelines and 2) the screening strategy derived from the guidelines of the WHO of assessing fasting glucose in all patients (step one), and subsequently performing an OGTT in patients with impaired fasting glucose (IFG)(step two). In line with the previous literature on screening for diabetes in the general population (Botas et al., 2003; Adam and Tarigan, 2004; Hilton et al., 2002; Tai et al., 2000; Cheng et al., 2006), it was hypothesized that the use of the consensus screening guidelines, but not the use of the two-step strategy, would result in a large underdiagnosis of diabetes and other glucose abnormalities in the present sample of patients diagnosed with schizophrenia.

Methods

Over a two-year period, both inpatients (73.7%) and outpatients (26.3%) with a diagnosis of schizophrenia or schizoaffective disorder who were in contact with the services of the University Centre St. Jozef (Kortenberg, Belgium), were asked to participate in the present study. All included patients were on stable medication treatment for at least three months and were not diagnosed with diabetes mellitus prior to the baseline screening. All patients were informed about the purpose of the study and provided written informed consent. The study was approved by an ethical committee. The baseline screening consisted of a full laboratory screening including fasting insulin and a 75 g Oral Glucose Tolerance Test (OGTT). For the OGTT, patients were instructed to fast overnight and were observed by a nurse during the OGTT, in order to ensure the reliability of the test results. All laboratory analyses were performed in the same laboratory. For the diagnosis of diabetes and impaired glucose tolerance, the ADA criteria were used (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003), meaning that diabetes was defined as a fasting glucose level > 125 mg/dl and/or a 2-hour post-glucose load > 199 mg/dl. Prediabetes was defined as impaired fasting glucose (IFG: fasting glucose level 100-125 mg/dl) and/or impaired glucose tolerance (IGT: 2-hour post-glucose load 140-199 mg/dl). Insulin resistance was assessed using fasting plasma glucose and insulin levels and a homeostatic model (HOMA-IR). Glycosylated hemoglobin (HbA1c) levels were assessed in diabetic patients. For all patients that were identified with a glucose level that met the criteria for diabetes, a new OGTT was performed within two weeks to confirm the diagnosis. To assess the diagnostic properties of two different screening strategies, the diabetes cases identified by means of

the OGTT were used as the 'gold standard' for comparison. The two strategies were: 1) assessing fasting glucose in all patients, as suggested by the APA/ADA and 2) a screening strategy derived from the guidelines of the WHO (World Health Organization, 1999). The WHO guidelines suggest the use of an OGTT in patients presenting with fasting glucose above 109 mg/dl. Following the lower diagnostic fasting glucose levels recommended by the ADA (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003), we modified this WHO strategy to the use of an OGTT in patients presenting with a fasting glucose level above 100 mg/dl (further referred to as impaired fasting glucose or IFG).

The presence of the metabolic syndrome was assessed using the adapted National Cholesterol Education Program – Adult Treatment Panel III (ATP-III) criteria (Expert Panel on Detection and Evaluation of Treatment of High Blood Cholesterol in Adults, 2001; Grundy et al., 2005). This is a recent commentary on the original ATP-III criteria, that proposes to use a fasting glucose limit of 100 instead of 110 mg/dl and to include drug treatment for hypertension, hyperlipidemia and hyperglycemia as criteria for the metabolic syndrome. Descriptive statistics were applied for basic demographic and clinical characteristics. An analysis of variance was done to evaluate the influence of the metabolic syndrome on measures of the OGTT.

Results

Subjects

The mean age of the patients was 34.7 years (SD=11.3), and they had been ill for a mean of 10.8 years (SD=10.2). The majority of the sample was male (67%) and 99% were Belgian natives and of Caucasian descent. The mean Global Assessment of Functioning (GAF) score was 60.6 (SD=9.1). Patients had been admitted a mean of 5.1 times (SD=4.5), with the mean age of first admission being 23.9 years (SD=6.6). Of all patients, 68% were smokers, and many patients had a family history of diabetes (31.1%), dyslipidaemia (34.7%) or cardiovascular disorders (47.5%).

All patients but 2 patients were treated with antipsychotic medication at the moment of assessment. First-generation antipsychotics were used by 19.3% (n=80) of patients, second-generation antipsychotics by 91.1% (n=378). The majority of patients were on monotherapy (84.1%, n=349), with 90.0% of this group receiving a second-generation antipsychotic and 10.0% a first-generation antipsychotic (table 1). Patients received a mean of 3.2 (SD=2.0) different medications. Antipsychotics were combined with anticholinergics (16.1%), antidepressants (38.3%), benzodiazepines (35.7%), mood stabilisers (21.2%) and non-psychoactive medications (40.9%). Of the non-psychoactive medications, 24.4% were related to metabolic disturbances, with 7 patients (1.7%) taking a statin (3.5% of all non-psychoactive medications) and 42 patients (10.1%) taking antihypertensive medication (20.9% of all non-psychoactive medications).

Metabolic abnormalities

Only a minority of patients had a normal body mass index (BMI) (47.2%). Overweight (BMI 25-30) was present in 34.2% of patients, an additional 18.6% even had a BMI of more than 30. The mean BMI was 25.8 (SD=5.0). An increased waist circumference (> 102 cm for men, > 88 cm for women) was present in 36.1% of patients. Female patients were more likely than male patients to be overweight or obese and to have an increased waist circumference ($\chi^2=30.6$, $p<.0.0001$). Lipid abnormalities were also highly prevalent: 47.9% had elevated total cholesterol (> 190 mg/dl), 41.2% elevated triglycerides (>150 mg/dl), 28.9% low high-density lipoprotein (HDL; men: < 40 mg/dl; women: < 50 mg/dl) and 45.1% elevated low-density lipoprotein (LDL; >115 mg/dl). In the total sample, 6.3% (n=26) met criteria for diabetes. Since the inclusion and screening of patients were performed over a period of two years, this results in a mean annual incidence of diabetes of 3.15% (6.3% incident cases/2 years). Of the patients meeting criteria for diabetes, 12 (46.2%) met the criterion of fasting glucose >125 mg/dl, 18 (69.2%) met the criterion of glucose >199 mg/dl at 120 min in the OGTT, and 4 (15.4%) met both these criteria. All 26 diabetes cases had another OGTT within two weeks, that confirmed the diagnosis in all patients. IFG was present in another 79 patients (19.0%). IGT was present in 53 patients (12.8%), of whom 31 (58.5% of all IGT cases) had a normal fasting glucose. Prediabetic abnormalities, defined as IFG and/or IGT, were present in 97 patients in total (table 2). The prevalence of diabetes and pre-diabetic abnormalities was significantly higher in the patients treated with clozapine ($\chi^2=23.87$, df 4, $p<.0001$) (table 3), and the use of clozapine was significantly associated with the presence of glucose abnormalities ($\chi^2=13.15$, df 1, $p<.001$; controlled for the possible confounders age, gender and BMI).

The metabolic syndrome was present in 30.6% of patients. Its prevalence was significantly higher in diabetic subjects (84.6%) compared to patients with prediabetic abnormalities (51.1%) and patients without glucose abnormalities (18.8%). Patients with the metabolic syndrome were more likely to meet criteria for diabetes or prediabetic abnormalities (table 4).

As expected, all parameters evaluated in the OGTT (glucose and insulin values fasting, at 30 minutes, at 60 minutes and at 120 minutes) as well as HOMA-IR and HbA1c levels were significantly higher in patients with the metabolic syndrome ($p<.0001$). Similar highly significant differences were found on all fasting serum lipid values and calculated lipid risk factors for cardiovascular disease (cholesterol, triglycerides, HDL, LDL, total cholesterol/HDL and LDL/HDL) ($p<.0001$). There were no significant differences between antipsychotics for any of the metabolic parameters.

Diagnostic properties of the screening guidelines

In a screening based on the APA/ADA guidelines, 12 of the 26 diabetes cases (46.2%) were identified, as they had a fasting glucose that was higher than 125 mg/dl, and 79 patients (19.0%) showed IFG.

When compared to the consensus screening strategy of fasting glucose alone, the screening according to the WHO-derived guidelines resulted in the detection of an extra 13 diabetes cases (25 of 26 or 96.2% of all diabetes cases).

Thus, the difference between the two strategies was most striking with regard to the number of missed diabetes cases or 'false negatives' (3.8% for the WHO-derived guidelines against 53.8% for the APA/ADA guidelines), resulting in a lower sensitivity for the APA/ADA guidelines. The number needed to diagnose (NND), which is the expression of how many tests one has to do in order to get 1 correct test result (either negative or positive), was much higher in the consensus screening. Ideally, NND equals 1, which means that every test gave a correct result. The sensitivity, specificity, percentage of false negatives and NND of the two strategies compared to the 'gold standard' are shown in table 5.

Discussion

The present study, which describes the baseline data of 415 patients, is the largest study as of today, using an OGTT to assess glucose abnormalities in patients treated with antipsychotics. A screening based on the consensus guidelines showed that diabetes was present in 12 patients (2.9%), and impaired fasting glucose in another 79 patients (19.0%). However, in line with our hypothesis, these cases represented only 46.2% of diabetes cases and 69.3% of prediabetes cases (IGT and/or IFG) of the cases identified by means of an OGTT. In total, 6.3% (n=26) met criteria for diabetes, resulting in a mean annual incidence of diabetes of 3.15% (6.3% incident cases/2 years).

These data confirm that metabolic abnormalities are highly prevalent in a relatively young sample of schizophrenic patients treated with antipsychotics. Compared to the estimated prevalence of diabetes in the Belgian general population, the prevalence in this sample is about double (Walckiers et al., 1992; Hortulanus-Beck et al., 1990). Two large scale naturalistic studies however revealed that the screening and diagnosis of these abnormalities in patients treated with antipsychotics still have not become routine practice, and that therefore, these abnormalities frequently remain untreated (Wampers et al., 2004; Hanssens et al., 2006).

Moreover, one has to take into account that all patients who were screened were not diagnosed with diabetes prior to this baseline screening, so that the diagnosed cases are newly detected or *incidence* cases. As the screening was performed over the period of two years, the current data suggest a mean annual incidence of diabetes of 3.15% (6.3% incident cases/2 years). One could argue that at the start of an extensive screening program, there is a possibility that in addition to new cases, already existing but previously undiagnosed cases are detected. However, before the start of the current screening program, subjects were regularly screened with fasting plasma glucose assessments as a part of clinical routine, and none of the included subjects had diabetes according to these assessments. Therefore, the newly detected cases most likely indeed represent *incidence* cases. This interpretation is being strengthened by a sensitivity analysis for the 250 patients for whom data on the first year of follow-up

were already available. Of these 250 patients, 10 (4.0%) were diagnosed with diabetes at the baseline screening. Of the remaining 240 patients (that did not have diabetes at baseline), another 10 developed diabetes during the first year of follow-up (4.17%), indicating that the rate reported on the whole sample (3.15%) is not likely to be an overestimation of the actual incidence rate. Furthermore, the reported incidence rate is in line with other incidence rates in patients treated with antipsychotics that ranged from 4.4% to 6.9% (Leslie and Rosenheck, 2004; Miller et al., 2005; Lambert et al., 2006), although the methods that were used to derive incidence rates in these studies were less extensive and the screening was performed in other regions, which makes a comparison across studies difficult. The data of the current study suggest that, even when screened according to the APA/ADA guidelines, 53.8% of patients with diabetes would not have been recognized and thus, would not have been adequately treated. This is in line with previous research (Adam and Tarigan, 2004; Botas et al., 2003; Hilton et al., 2002; Tai et al., 2000), and underscores the need for a more thorough screening in high-risk populations. Clearly, schizophrenic patients treated with antipsychotics ought to be considered at a very high risk of developing diabetes (Lean and Pajonk, 2003), as was convincingly shown by the current data. The results of the present study also suggest that the use of OGTT's to screen and monitor glucose abnormalities in this high risk population should be encouraged. This is especially so since it has been shown that patients with postload hyperglycemia are at risk for cardiovascular morbidity, even in the absence of impairments in fasting glucose (DECODE Study Group; on behalf of the European Diabetes Epidemiology Group), which further underscores the usefulness of the OGTT.

However, since the use of OGTT's as the standard screening instrument may not be an achievable practice in all treatment settings due to concerns of inconvenience and high cost (Lorenzo et al., 2003; Stern et al., 2002), the diagnostic properties of an alternative, two-step strategy was assessed. The WHO-derived two-step strategy of performing an OGTT in patients with IFG detected 96.2% of diabetes cases. The loss of sensitivity that is inherent to a two-step strategy, as one tries to identify a certain risk group within a larger sample, was limited to 3.8% or 1 diabetes case that had a fasting glucose <100 mg/dl. This limited loss of sensitivity resulted in a superior sensitivity and NND when compared to the APA/ADA consensus guidelines, suggesting that the two-step strategy would provide a substantial improvement over the currently used APA/ADA consensus screening guidelines. To our knowledge, the cost-effectiveness of this two-step strategy has not been investigated before. Nevertheless, a study by the CDC Diabetes Cost-Effectiveness Study Group (CDC Diabetes Cost-Effectiveness Study Group, 1998) revealed that screening for diabetes type 2 is especially cost-effective when done in subgroups at high risk for developing diabetes and in younger patients, resulting in a reduction of lifetime complications such as end-stage renal disease, blindness and lower extremity amputations. Since the population of patients diagnosed with schizophrenia fits both the characteristics of relatively young age and high risk for diabetes, this suggests that a more extensive screening in this specific population could be cost-effective and would result in a limitation of lifetime

major complications and an increase in Quality-Adjusted-Life-Years (QALY's) (CDC Diabetes Cost-Effectiveness Study Group, 1998). Preliminary evidence (Ananth et al., 2002; Rigalleau et al., 2000; Peuskens et al., 2004) even suggests that in those cases where there is a rapid onset of diabetes following the start of antipsychotic medication, screening for diabetes could possibly result in reversal of diabetes by allowing a rapid switch to another antipsychotic. These findings provide additional arguments to stress the importance of adequately screening and treating diabetes in patients diagnosed with schizophrenia, and underscore the potential relevance of a more thorough screening in this specific population.

Although investigating the prevalence of diabetes and prediabetes per drug treatment was not the primary aim of the study, these data are interesting, since they give 'real world' information on the prevalence of glucose abnormalities in a large sample of patients with schizophrenia. Especially for clozapine, these real world data support the clinical impression of a higher risk for glucose abnormalities, with not even half of the patients treated with clozapine having a normal glucose metabolism, and are in line with previous naturalistic studies (Gianfrancesco et al., 2006; Henderson et al., 2005a). However, one has to be cautious in interpreting the possible causality of the high prevalence of glucose abnormalities, which is especially true for the antipsychotic drugs other than clozapine. Indeed, the explanation for the high prevalence of glucose abnormalities in patients with schizophrenia and schizoaffective disorder probably is multifactorial, since in addition to the possible iatrogenic influence of antipsychotic medication, schizophrenic patients also display many risk factors for diabetes such as bad dietary habits, lack of exercise and obesity. Furthermore, it is difficult to draw firm conclusions regarding the causality of the reported glucose abnormalities because of the relatively low number of patients per treatment group and the impossibility to control for other factors such as dietary habits and exercise.

In addition to diabetes, there was a high prevalence of the metabolic syndrome, which is in line with earlier reports (Basu et al., 2004; Cohn et al., 2004; De Hert et al., 2006b; McEvoy et al., 2005). The high prevalence of diabetes and other metabolic abnormalities including the metabolic syndrome may in part explain the high mortality rates in this population (Brown, 1997; Joukamaa et al., 2001), and especially why 50% of the excess mortality in this population is caused by cardiovascular disease (Osby et al., 2000).

The current study also has some limitations. First, it is a cross-sectional study and therefore the adequacy of the current screening guidelines can not be assessed in a longitudinal fashion. It is possible that some diabetes or prediabetes cases would have been detected with a fasting glucose test in a follow-up screening. Second, this study was restricted to one site, indicating that the interpretation of the incidence and prevalence rates of metabolic abnormalities needs to be done with caution, since large regional differences in metabolic parameters have been reported in the literature (Ford et al., 2005). Third, although this is the largest study as of today that used the OGTT to evaluate the different screening strategies (n=415), the number of patients with both schizophrenia or schizoaffective

disorder and diabetes is relatively low (n=26), meaning that the interpretation of these results needs to be done with caution. On the other hand, the findings of the current study are in line with previous literature on screening methods for diabetes in the general population. Moreover, the relatively low number of patients with diabetes in the current study is the consequence of the fact that both schizophrenia and diabetes have a relatively low prevalence. In order to collect larger numbers of patients with schizophrenia and diabetes to evaluate these screening guidelines, even larger, multi-site studies need to be conducted. As of today, no such studies have been undertaken, probably because of the enormous cost of doing OGTT's in 1000 or more patients.

In conclusion, metabolic abnormalities are highly prevalent in schizophrenic patients treated with antipsychotics. The importance of actively screening for these abnormalities needs to be emphasized and, by consequence, the widespread use of adequate screening guidelines is crucial. However, the guidelines as proposed by the APA/ADA(American Diabetes Association and American Psychiatric Association, 2004) did not sufficiently detect diabetes in this specific high risk group. In contrast, the alternative two-step strategy was able to detect the vast majority of diabetes cases and should therefore be considered in the clinical routine of screening and monitoring patients with schizophrenia.

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Table 1. Antipsychotic (AP) treatment

Antipsychotic treatment	% (n)
Only first generation*	8.4 % (35)
Only second generation*	80.2% (333)
Combination of FGA [#] and SGA ^{\$}	10.8% (45)
Only 1 antipsychotic	84.1 % (349)
First-generation AP	10.0% (35)
Second generation AP	90.0% (314)
Second generation AP	91.1% (378)
Second generation (N= 400 prescriptions)	
Amisulpride (n=32)	7.7%
Aripiprazole (n=4)	1.0%
Clozapine (n=74)	17.8%
Risperidone (n=98)	23.6%
Quetiapine (n=53)	12.8%
Olanzapine (n=139)	33.5%

[#]FGA=first generation antipsychotic; ^{\$}SGA=second generation antipsychotic

*within-class combinations (FGA-FGA or SGA-SGA) included

Table 2. Overlap of glucose abnormalities identified by means of fasting glucose (column) and by means of the 120-min glucose in the OGTT (row) in 415 patients diagnosed with schizophrenia.

	NI fasting glucose (<100 mg/dl)	IFG (≥100<126 mg/dl)	Diabetes (≥126 mg/dl)	All
Normal OGTT (glucose ^{120min} <140 mg/dl)	292 (70.4%)	48 (11.6%)	4 (1.0%)	344 (82.9%)
IGT (glucose ^{120min} ≥140<200mg/dl)	31 (7.5%)	18 (4.3%)	4 (1.0%)	53 (12.8%)
Diabetes (glucose ^{120min} ≥200 mg/dl)	1 (0.2%)	13 (3.1%)	4 (1.0%)	18 (4.3%)
All	324 (78.1%)	79 (19.0%)	12 (2.9%)	415 (100%)

This table describes the overlap between the fasting glucose results and the OGTT results. For example: 18 subjects meet the 120 minutes OGTT criterion for diabetes, 12 subjects meet the fasting glucose criterion for diabetes. Of these 12, 4 also meet the 120 minutes OGTT criterion. Thus, the total amount of patients with diabetes is 18 (OGTT criterion) + 12 (fasting glucose criterion) – 4 (subjects that meet both criteria) = 26.

Table 3. Glucose abnormalities in relation to antipsychotic treatment

	Diabetes (n=26)	Prediabetes (n=97)	Normal values (n=292)
Only FGA (n=35)	8.6% (3)	25.7% (9)	65.7% (23)
Combination FGA + SGA (n=45)	2.2% (1)	28.9% (13)	68.9% (31)
Combination SGA (n=19)	5.3% (1)	21.0% (4)	73.7% (14)
Only 1 SGA (n=314)	6.7% (21)	22.6% (71)	70.7% (222)
Amisulpride (n=26)	0% (0)	3.9% (1)	96.1% (25)
Aripiprazole (n=3)	0% (0)	0% (0)	100% (3)
Clozapine (n=54)	9.3% (5)	42.6% (23)	48.1% (26)
Risperidone (n=75)	6.6% (5)	22.7% (17)	70.7% (53)
Quetiapine (n=44)	11.4% (5)	9.1% (4)	79.5% (35)
Olanzapine (n=112)	5.4% (6)	23.2% (26)	71.4% (80)

Table 4. Glucose abnormalities in relationship with the metabolic syndrome*

	Normal values	Pre diabetes	Diabetes	Total	P#
No	82.3% (237)	16.3% (47)	1.4% (4)	69.4% (288)	0.0001
Yes	43.3% (55)	39.4% (50)	17.3% (22)	30.6% (127)	

*Criteria are: 1) waist circumference >102 (male subjects)/ >88 (female subjects); 2) blood pressure $\geq$ 130/85 or treatment with antihypertensive medication; 3) HDL <40 mg/dl (male subjects)/ <50 mg/dl (female subjects) or treatment with antihyperlipidemic medication; 4) triglycerides $\geq$ 150 mg/dl or treatment with antihyperlipidemic medication; 5) fasting glucose $\geq$ 100 mg/dl or treatment with antihyperglycemic medication. The metabolic syndrome is present if at least 3 criteria are met.

#ANOVA

Table 5. Diagnostic properties of the different screening strategies for diabetes

Screening strategy	Baseline assessment	Subsequent OGTT	Sensitivity (a)	Specificity (b)#	False negatives (c)	Number needed to diagnose (NND) (d)
'Gold Standard'*	Weight (BMI) Waist circumference Blood pressure Fasting glucose Fasting lipids + OGTT	Not applicable	100.0%	100.0%	0%	1
APA/ADA consensus guidelines	Weight (BMI) Waist circumference Blood pressure Fasting glucose Fasting lipids	No	46.2%	100.0%	53.8%	2.16
Two-step Strategy	Weight (BMI) Waist circumference Blood pressure Fasting glucose Fasting lipids	In patients with IFG (n=79)	96.2%	100.0%	3.8%	1.04

- (a) Sensitivity: the probability of an individual with the condition having a positive test (true positives divided by true positives plus false negatives)
- (b) Specificity: the probability of an individual without the condition having a negative test (true negatives divided by false positives plus true negatives)
- (c) False negatives: undiagnosed or 'missed' diabetes cases
- (d) Number needed to diagnose: the expression of how many tests one has to do in order to get 1 correct test result (either negative or positive). Ideally, NND equals 1, which means that every test gave a correct result.

*The 'Gold Standard' is defined as being 100% specific and sensitive

#There were no false positives, since 1) the diagnosis of diabetes is defined by abnormal glycemic levels (fasting or at 120 minutes in the OGTT) and 2) all values that were above the diabetes diagnosis threshold were double-checked and confirmed in all cases. As there were no false positives, the specificity by definition is 100% for all strategies.

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METABOLIC DISTURBANCES AS CANDIDATE ENDOPHENOTYPE
CHAPTER 7

MAJOR CHANGES IN GLUCOSE METABOLISM, INCLUDING NEW-ONSET DIABETES, WITHIN 3 MONTHS AFTER INITIATION OF OR SWITCH TO ATYPICAL ANTIPSYCHOTIC MEDICATION IN PATIENTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER.

Ruud van Winkel^{a,b}, Marc De Hert^a, Martien Wampers^a, Dominique Van Eyck^a, Linda Hanssens^c, Andre Scheen^d, Joseph Peuskens^a

^aUniversity Psychiatric Center Katholieke Universiteit Leuven, Leuvense Steenweg 517, 3070 Kortenberg, Belgium

^bDepartment of Psychiatry and Neuropsychology, EURON, South Limburg Mental Health Research and Teaching Network, Maastricht University; PO box 616, 6200 MD Maastricht, The Netherlands.

^cDepartment of Epidemiology and Public Health, University Liege, Belgium

^dDepartment of Diabetes, Nutrition and Metabolic Disorders, CHU Sart Tilman, University Liege, Belgium

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Abstract

Objective: to investigate 3-month changes in glucose metabolism in a naturalistic sample of patients with schizophrenia newly started on or switched to specific atypical antipsychotic medication.

Methods: 183 patients were evaluated before initiation and 3 months after with a 75gr glucose load Oral Glucose Tolerance Test (OGTT). **Results:** 8 patients developed new-onset diabetes within 3 months (4.4%). Initiation of clozapine resulted in a significantly higher risk for new-onset glucose abnormalities than initiation of aripiprazole (odds ratio 67.29, 95% CI: 5.23 – 866.49). Significant drug X time interactions were found for all OGTT glucose assessments (fasting: $F(5, 177) = 6.79$, $p < .0001$, 30 minutes: $F(5, 177) = 3.89$, $p = .0023$, 60 minutes: $F(5, 177) = 5.03$, $p = .0002$, 120 minutes: $F(5, 177) = 3.78$, $p = .0028$), with the evolution of glucose levels being significantly worse in patients initiated on clozapine (fasting, 30 minutes, 60 minutes), olanzapine (fasting, 60 minutes, 120 minutes) and quetiapine (fasting, 60 minutes) than in patients initiated on aripiprazole ($p < .05$). Clozapine was also significantly more deleterious than risperidone and amisulpride for fasting glucose changes ($p < .05$). Type of initiation (start or switch) did not affect any of the metabolic parameters.

Conclusions: the incidence of new-onset glucose abnormalities including diabetes in the first 3 months after newly starting or switching of atypical antipsychotic medication is high and may be markedly influenced by type of prescribed antipsychotic. The importance of accurately screening for new-onset glucose abnormalities after initiation of an atypical antipsychotic is emphasized.

Key words: Schizophrenia, Diabetes, Metabolic Syndrome, Physical Health

Introduction

High prevalence rates of diabetes have consistently been reported in patients with schizophrenia (Cohen et al., 2006; De Hert et al., 2006a), with growing evidence suggesting a direct diabetogenic effect of atypical antipsychotic medication (De Hert et al., 2006b; Henderson et al., 2005; Newcomer and Haupt, 2006; Scheen and De Hert, 2007). Evidence however also suggests that a diagnosis of schizophrenia may be a relevant factor for the development of diabetes independently of medication effects. Increased central obesity (Thakore et al., 2002), decreased insulin sensitivity (Cohn et al., 2006), impaired fasting glucose (Ryan et al., 2003) and impaired glucose tolerance (Spelman et al., 2007) were also shown at increased rates in unmedicated subjects presenting with a first episode of psychosis. Furthermore, high prevalence rates of diabetes and cardiovascular morbidity were reported in unaffected relatives (Mukherjee et al., 1989; De Hert et al., 2006a; Lamberti et al., 2004; Spelman et al., 2007). These findings not only support the high liability to develop diabetes in patients with schizophrenia, but also underscore the possible relevance of diagnostic homogeneity. Next to medication effects (Newcomer and Haupt, 2006), shared genetic factors could partly underlie reported associations (Gough and O'Donovan M, 2005; Bellivier, 2005), although not all studies found evidence for insulin resistance in drug-naïve patients (Arranz et al., 2004; Zhang et al., 2004). In two diagnostically mixed samples treated with atypical antipsychotics, annual incidence rates of new-onset diabetes were 4.7% (Miller et al., 2005) and 6.9% (Lambert et al., 2006a). In a sample consisting only of patients with schizophrenia, Leslie and Rosenheck observed an annual incidence rate of 4.4% in patients on a stable regimen of antipsychotic treatment (Leslie and Rosenheck, 2004). Likewise, in a study using the Oral Glucose Tolerance Test (OGTT), an annual incidence rate of 4.2% was found in 240 schizophrenia patients with OGTT-confirmed non-diabetic status at baseline who were on stable treatment (van Winkel et al., 2006).

Whereas these incidence studies only included patients on a stable antipsychotic regimen for at least 3 months (van Winkel et al., 2006; Leslie and Rosenheck, 2004), information on the exact timing of the development of diabetes after initiation of an atypical antipsychotic is scarce. So far, only one study addressed this issue (Lambert et al., 2006b), by identifying all new antipsychotic users with schizophrenia in the database of the U.S. Veterans Health Administration, and prospectively following-up any diagnosis of diabetes or antidiabetic treatment, as recorded in the database. In this study, that examined only patients newly initiated on haloperidol, risperidone, olanzapine and quetiapine, one year incidence rates of a database diagnosis of diabetes or treatment with antidiabetic medication were 2% in patients started on haloperidol, 3.2% in patients with risperidone, 3.3% in patients with olanzapine and 3.6% in patients with quetiapine. The available data thus confirm that the development of new-onset diabetes represents a major health problem in patients with schizophrenia and suggest that the development of new-onset diabetes may occur rather quickly after initiation of an atypical antipsychotic. However, there have been no studies that have assessed the early changes in glucose metabolism following initiation of atypical antipsychotics in detail by using the OGTT.

The aim of the current study was to investigate the early changes in glucose metabolism, including the 3-month incidence of new-onset diabetes, in a naturalistic sample of patients with schizophrenia with OGTT-confirmed non-diabetic status who were initiated on a specific atypical antipsychotic. Furthermore, we were interested in differential effects of antipsychotic medication on the evolution of glucose metabolism, given the evidence that some antipsychotics, especially clozapine and olanzapine, could be more deleterious than others (Newcomer and Haupt, 2006). We hypothesized that substantial changes in glucose metabolism would occur within 3 months after initiation of an atypical antipsychotic, and that these changes would be most severe in patients initiated on clozapine and olanzapine.

Methods

Study cohort

At our hospital and affiliate services, all patients treated with antipsychotic medication (AP) are being screened and monitored prospectively for metabolic abnormalities. The vast majority of patients are part of an extensive clinical metabolic screening and monitoring protocol, which was started in November 2003 (van Winkel et al., 2006; De Hert et al., 2006a; De Hert et al., 2006c; De Hert et al., 2007). The study population is a dynamic, naturalistic cohort. Decisions regarding antipsychotic medication are made by the treating psychiatrist and the patient, including dose reduction, dose augmentation and switch strategies. These changes are recorded, and patients are monitored for metabolic abnormalities by means of laboratory tests, Oral Glucose Tolerance Tests (OGTT) and clinical examinations. The baseline characteristics of the first 415 included patients of this dynamic cohort that were screened with an OGTT are described in detail elsewhere (van Winkel et al., 2006; De Hert et al., 2006a). The sample of the current study was derived from this large, dynamic cohort. Patients were included if i) they had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder as established by their treating psychiatrist, ii) if they were newly initiated on a specific atypical antipsychotic, meaning they did not take any antipsychotic medication and were then newly started on a specific atypical antipsychotic ('starters') or were switched from an other antipsychotic and newly initiated on a specific atypical antipsychotic with complete discontinuation of the previous antipsychotic within 3 weeks ('switchers') and iii) did not have diabetes before initiation of the specific atypical antipsychotic as confirmed with an OGTT. As one of the aims of the study was to assess differential medication effects on glucose metabolism, patients for whom the initiated atypical antipsychotic was added to existing antipsychotic medication ('add-on', or 'antipsychotic polypharmacy') were excluded from the analyses. The study was approved by an ethical committee and all patients gave written informed consent.

Metabolic screening

Patients were evaluated 2 times with a full metabolic screening, which included a 75gr glucose load OGTT after an overnight fast: at baseline before the initiation of the atypical antipsychotic and 3 months after initiation of the new antipsychotic drug. Insulin resistance (HOMA-IR) was assessed using fasting plasma glucose and insulin levels and a homeostatic model (Matthews et al., 1985). For the diagnosis of diabetes and prediabetic abnormalities the American Diabetes Association criteria were used: diabetes (fasting plasma glucose > 125 mg/dl and/or 2-h OGTT plasma glucose > 199 mg/dl), Impaired fasting glucose (IFG; 100-125 mg/dl) and Impaired Glucose Tolerance (IGT, glucose 140-199 mg/dl at 2 hours in the OGTT) (American Diabetes Association, 2006).

Statistical analyses

Descriptive statistics were computed for the basic demographic and clinical variables as well as for the variables relevant for the evaluation of metabolic abnormalities. Differences between treatment groups at baseline were evaluated through one-way analysis of variance (ANOVA). The influence of known diabetes risk factors and type of medication on the occurrence of glucose abnormalities (diabetes + pre-diabetes) was modelled through logistic regression in patients without glucose abnormalities at baseline (n=153). Known risk factors for diabetes, as measured at baseline, were included in the model (fasting glucose, glucose at 120 minutes in the OGTT, Body Mass Index (BMI), a family history of diabetes, High Density Lipoprotein (HDL) cholesterol blood level, Low Density Lipoprotein (LDL) cholesterol blood level, HDL/LDL ratio and triglycerides blood level) (American Diabetes Association, 2006). Drug (6) X time (2) repeated measures ANOVAs were performed to evaluate changes in glucose and insulin levels and in HOMA-IR as a function of antipsychotic medication over the follow-up period. Pairwise comparisons between antipsychotic treatment groups were evaluated through Tukey's studentized range test at an alpha level of .05.

Results

Subjects

In 220 patients a specific atypical antipsychotic was newly initiated. Of these, 12 were diagnosed with diabetes at the OGTT that was performed before initiation. As one of the aims of the current study was to examine the incidence of new-onset diabetes, these patients were excluded from the analyses. Of the remaining 208 subjects, the initiated atypical antipsychotic was added to existing antipsychotic medication in 25 patients ('add-on', or 'antipsychotic polypharmacy'). The 25 patients with polypharmacy were also excluded in order to be able to reliably assess differential medication effects, resulting in a final sample of 183 patients. Of these 183, 126 were not treated with antipsychotic medication before study entry because they were drug-naïve first-episode patients (n = 22) or because of non-compliance with their previous treatment (n = 104). Duration of non-compliance was not recorded. The remaining 57 patients were treated with antipsychotic medication (20 with risperidone,

18 with olanzapine, 6 with amisulpride, 5 with a typical antipsychotic, 4 with quetiapine, 3 with clozapine and 1 with bifeprunox) and were switched to the specific atypical medication under study. No significant differences in age, sex, Clinical Global Impression (CGI), Global Assessment of Functioning (GAF) score and number of different medications were found between starters and switchers, but starters did have a significantly shorter duration of illness ($F(1, 181) = 4.51, p = .0350$) and a significantly lower mean BMI ($F(1, 181) = 16.42, p < .0001$).

Olanzapine was initiated in 50 patients (27.3%), risperidone in 48 patients (26.2%), quetiapine in 24 patients (13.1%), aripiprazole in 22 patients (12.0%), clozapine in 21 patients (11.5%) and amisulpride in 18 patients (9.8%). Anticholinergic medication was prescribed in 13.7% of patients, antidepressants in 32.8%, benzodiazepines in 33.9%, mood stabilizers in 23.0%, antihypertensive medication in 10.4% and statins in 1.1%. No significant differences in age, duration of illness, Global Assessment of Functioning (GAF) score or Clinical Global Impression (CGI) were found for the different antipsychotic treatment groups, but there was a significant main effect of BMI ($F(5, 147) = 3.28, p = .0078$), although only the contrast between patients initiated on aripiprazole and on olanzapine reached significance, with patients initiated on aripiprazole having a significantly higher baseline BMI than patients treated with olanzapine ($p < .05$).

Patients had DSM-IV diagnoses of schizophrenia (76.0%) and schizoaffective disorder (24.0%). Their mean age was 33.7 years ($SD=11.6$), and they had been ill for a mean of 7.5 years ($SD=9.4$). The majority of the sample was male (60.7%). Many patients had a family history of diabetes (31.2%), dyslipidaemia (37.7%) or cardiovascular disorders (50.8%).

Incidence of new-onset diabetes

8 patients developed diabetes within 3 months after the start of the atypical antipsychotic, resulting in a 3-month incidence rate of 4.4% (8/183). Patients with new-onset diabetes were initiated on clozapine (2 of the 21 treated patients, 9.5%), olanzapine (4 of the 50 treated patients, 8.0%), quetiapine (1 of the 24 treated patients, 4.2%) and risperidone (1 of the 48 treated patients, 2.1%), whereas no new cases developed in the group treated with aripiprazole and amisulpride. Of the 8 new-onset diabetes cases, 2 already had IFG at baseline, 1 had IGT at baseline, 2 had both IFG and IGT, indicating that 16.7% of patients with prediabetic abnormalities developed diabetes (table 1). The remaining 3 had no glucose abnormalities at baseline (table 1). Prediabetic abnormalities regressed in 12 patients (40% of patients with pre-existing glucose abnormalities), mainly in patients initiated on aripiprazole, whereas prediabetic abnormalities developed in 29 patients (18.9% of normoglycemic patients), mainly in patients initiated on clozapine and olanzapine (table 1).

Three-month evolution of glucose, weight and insulin

The repeated measures drug (6) X time (2) ANOVA on glucose and insulin levels and HOMA-IR revealed significant main effects of time on glucose at 120 min ($F(1, 177) = 4.76, p = .0304$) and

insulin at 60 min ($F(1, 177) = 4.38, p = .0378$). There were no significant main effects of drug. There were no significant differences in the evolution of any of the metabolic parameters between switchers and starters.

For fasting glucose, a significant drug X time interaction was observed ($F(5, 177) = 6.79, p < .0001$) (table 2). Patients initiated on clozapine had a significantly greater increase of fasting glucose than patients initiated on risperidone, aripiprazole or amisulpride ($p < .05$). Fasting glucose changes in patients initiated on aripiprazole differed significantly from changes observed in patients on olanzapine or quetiapine ($p < .05$). The drug X time interaction for glucose at 30 min also reached significance ($F(5, 177) = 3.89, p = .0023$), with decreased levels in patients initiated on aripiprazole significantly different from increased levels in patients on clozapine. There was a significant drug X time interaction for glucose at 60 minutes ($F(5, 177) = 5.03, p = .0002$) with a decrease in patients on aripiprazole significantly different from increases in patients on clozapine, olanzapine and quetiapine ($p < .05$). Finally, we observed a significant drug X time interaction for glucose at 120 min ($F(5, 177) = 3.78, p = .0028$) with decreases in patients on aripiprazole significantly different from increases in patients treated with olanzapine ($p < .05$).

A significant drug X time interaction was also found for BMI ($F(5, 177) = 43.60, p < .0001$) and waist circumference ($F(5, 177) = 26.03, p < .0001$) (table 2). For waist circumference, the decrease in patients initiated on aripiprazole was significantly different from increases in patients initiated on olanzapine, quetiapine, risperidone and amisulpride ($p < .05$) but not from increases in patients initiated on clozapine. For BMI, the decrease in patients initiated on aripiprazole was significantly different from increases in patients treated with any of the other atypicals ($p < .05$). The increase of both waist circumference and BMI in patients initiated on olanzapine was significantly larger than in patients initiated on risperidone ($p < .05$). There were no significant drug X time interactions for insulin measures and HOMA-IR (table 2).

Prediction of new-onset glucose abnormalities

At baseline, 153 patients were normoglycemic, both in the fasting state and after the glucose load. The logistic regression model predicting the incidence of any new-onset glucose abnormality (IFG, IGT, diabetes) based on type of antipsychotic agent and known diabetic risk factors was significant ($\chi^2(14) = 42.26, p < .0001$). Baseline glucose at 120 min ($\chi^2(1) = 4.61, p = .0318$) and type of antipsychotic ($\chi^2(5) = 18.40, p = .0025$) were significantly associated with new-onset glucose abnormalities. None of the known risk factors for diabetes were associated with new-onset glucose abnormalities, although the effect of age just failed to reach significance ($\chi^2(1) = 3.79, p = .0515$). Type of initiation (start or switch) did not significantly predict new-onset glucose abnormalities ($\chi^2(1) = 0.32, p = .5704$). Higher baseline values for glucose at 120 min slightly increased the risk for the development of glucose abnormalities (OR = 1.023, 95% CI: 1.003-1.044). A post-hoc analysis failed to find an association between weight change over the 3-month period and new-onset glucose abnormalities (χ^2

(1) = .27, $p = .604$), nor did including weight change in the predictive model change the significant associations with type of antipsychotic medication (χ^2 (5) = 17.31, $p = .0039$) and baseline glucose at 120 min in the OGTT (χ^2 (1) = 4.81, $p = .0284$).

Patients treated with clozapine had a significantly higher risk of developing glucose abnormalities at 3 months follow-up as compared to patients on aripiprazole (odds ratio (OR)= 67.29, 95% CI: 5.23 – 866.49). The risk of developing new-onset glucose abnormalities in patients on olanzapine, risperidone, amisulpride, and quetiapine did not significantly differ from the risk for patients on aripiprazole.

Discussion

Findings

To our knowledge, this is the first study to examine the incidence of new-onset diabetes and early changes in glucose metabolism in patients with schizophrenia who were initiated on a specific atypical antipsychotic, by means of the OGTT. A 3-month incidence rate of new-onset diabetes of 4.4% was found. Most patients with new-onset diabetes already had baseline prediabetic abnormalities (5/8, 62.5%), although a substantial number did not (3/8, 37.5%). Initiation of clozapine resulted in a significantly higher risk of developing glucose abnormalities at 3-months follow-up as compared to patients on aripiprazole. There were significant drug X time interactions for all glucose assessments in the OGTT (fasting, 30 min, 60 min, 120 min), with the evolution of glucose levels being significantly worse in patients treated with clozapine (fasting, 30 min, 60 min), olanzapine (fasting, 60 min, 120 min) and quetiapine (fasting, 60 min) than in patients treated with aripiprazole. Clozapine was also significantly worse than risperidone and amisulpride at the fasting glucose assessment ($p < .05$). Type of initiation (start or switch) did not affect the evolution of any of the metabolic parameters. Interestingly, the development of new-onset glucose abnormalities was not associated with BMI or weight change over the 3-month follow-up period.

Incidence

As a 10-year OGTT study in a European general population sample of 837 subjects aged between 40 and 79 in the village of Bruneck (Italy) revealed a yearly incidence rate of 0.72% (Bonora et al., 2004), a 3-month incidence of new-onset diabetes of 4.4% in a representative sample of patients with schizophrenia with a mean age of 34 years is disturbingly high. This supports the claim that compared to the general population, patients with schizophrenia treated with atypical antipsychotics are at a considerably increased risk to develop diabetes (De Hert et al., 2006a), although it needs to be noted that the reasons for this increased risk are likely multifactorial, including differences in known risk factors such as BMI and dietary habits. Compared to the 1-year incidence rate of 4.2% reported in the identically screened sample of 240 patients that was on stable medication (van Winkel et al., 2006), the current 3-month 4.4% incidence rate is strikingly similar, despite a much shorter follow-up period.

This suggests that the chance of developing diabetes is especially high in the first months after initiation of antipsychotic medication, which underscores the importance of accurately screening for new-onset glucose abnormalities after the initiation of an atypical antipsychotic (De Nayer et al., 2005; Newcomer, 2006). Indeed, our data convincingly show that even patients without abnormalities at baseline can develop prediabetic abnormalities and even frank diabetes within a 3-month period.

Compared to the only other study so far in patients with schizophrenia who were newly started on a second-generation antipsychotic (Lambert et al., 2006b), the current 3-month incidence rate of 4.4% is higher than the reported 1-year incidence rates of 3.2% in patients started on risperidone, 3.3% in patients started on olanzapine and 3.6% in patients started on quetiapine. However, this was an epidemiological study that used the Veterans Health Administration database to identify new users of atypical antipsychotics and to assess the incidence of new-onset diabetes. This also represents the main limitation of the latter study, as convincing evidence exists that a large proportion of incident diabetes cases remain undiagnosed for years (Samuels et al., 2006), making it likely that the reported incidence rates are an underestimation of the actual incidence rates. In contrast, the diagnostic accuracy of the current study is very high, as new-onset diabetes was assessed by means of the ‘Gold Standard’: the OGTT. However, whereas the study by Lambert and colleagues had a sample of 15.767 patients (Lambert et al., 2006b), our study only included 183 patients. Given the low incidence rates typically reported for diabetes, this is a relatively low number.

Risk factors for new onset glucose abnormalities and differential medication effects

The finding that clozapine was significantly associated with new-onset glucose abnormalities is in line with earlier evidence, with naturalistic studies finding glucose abnormalities in more than half of patients on stable clozapine treatment for at least 3 months (van Winkel et al., 2006) and even frank diabetes in almost half of clozapine-treated patients after 10 years of treatment (Henderson et al., 2005). The available data also suggest that aripiprazole is safer in this regard (De Hert et al., 2007), which was confirmed by the finding that the evolution of OGTT glucose levels was significantly better in patients initiated on aripiprazole than in patients initiated on clozapine, olanzapine and quetiapine. Interestingly, none of the known risk factors for diabetes were associated with the development of new-onset glucose abnormalities, although the effect of age just failed to reach significance. A post-hoc analysis also failed to find an association between weight change over the 3-month period and new-onset glucose abnormalities, nor did including weight change in the predictive model change the significant associations with type of antipsychotic medication and baseline glucose at 120 min in the OGTT.

The absence of significant associations between known risk factors and glucose abnormalities is in contrast to our research on patients on stable medication (van Winkel et al., 2006), where age and BMI were significantly associated with glucose abnormalities. First, this supports the importance of

differential antipsychotic medication effects in the development of new-onset glucose abnormalities in patients with schizophrenia. Second, although speculative, it may also suggest two possible mechanisms for the development of new-onset diabetes in patients treated with antipsychotic medication: a slower onset related to weight gain, leading to insulin resistance and gradual beta-cell decompensation (Haupt et al., 2007), and a quick onset more directly related to antipsychotic treatment effects, possibly via a specific effect on beta-cell function, where the influence of known risk factors is much less prominent. This claim is supported by the finding that the latter type may be reversible following a medication switch to aripiprazole (De Hert et al., 2006b), or amisulpride (De Hert et al., 2005). These findings also suggest that certain antipsychotic medications, especially clozapine, should be considered as medication that can induce diabetes (American Diabetes Association, 2006).

Next to type of antipsychotic medication, glucose level at 120 minutes in the OGTT was the only significant predictor of subsequent glucose abnormalities, which further underscores the usefulness of the OGTT in patients treated with atypical antipsychotics as reported earlier (van Winkel et al., 2006; De Hert et al., 2006d; Cohen et al., 2006), certainly when taking into account that IGT (Qiao et al., 2003), but not IFG (Rijkkelijkhuizen et al., 2007), was shown to be associated with increased cardiovascular mortality in the absence of diabetes in the general population.

Limitations

The current study also has some limitations. As previously stated, the sample was relatively small to assess the low incidence rates typically reported for diabetes. This is especially true for differences between atypical antipsychotics, although the demonstrated differences are in line with previous research. Furthermore, the current study is a naturalistic study, meaning that there was no random allocation of antipsychotic medication. It is thus likely that patients' and caregivers' views of anticipated metabolic side-effects have influenced their choice for an antipsychotic. Although we have tried to minimize such influence by controlling for known diabetes risk factors, it is still possible that this has biased our results to some extent. Nevertheless, the data provide 'real-world' evidence that a significant proportion of a representative, naturalistic sample of patients with schizophrenia develops new-onset diabetes and prediabetic abnormalities within 3 months after initiation of a second-generation antipsychotic, which is of major clinical significance. The importance of accurately screening for diabetes in patients with schizophrenia therefore needs to be stressed.

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Table 1. Three-month glucose abnormalities in a naturalistic sample of patients with schizophrenia who were normoglycemic (n=153) and prediabetic (IFG and/or IGT; n=30) at baseline.

NORMOGLYCEMIC PATIENTS			PREDIABETIC PATIENTS		
(n=153)			(n=30)		
	No abnormality	121 (79.1%)		No abnormality	12 (40.0%)
	IFG and/or IGT	29 (18.9%)		IFG and/or IGT	13 (43.3%)
	Diabetes	3 (2.0%)		Diabetes	5 (16.7%)
Amisulpride (n=14)			Amisulpride (n=4)		
	No abnormality	12 (85.7%)		No abnormality	2 (50.0%)
	IFG and/or IGT	2 (14.3%)		IFG and/or IGT	2 (50.0%)
	Diabetes	0 (0.0%)		Diabetes	0 (0.0%)
Aripiprazole (n=17)			Aripiprazole (n=5)		
	No abnormality	16 (94.1%)		No abnormality	5 (100.0%)
	IFG and/or IGT	1 (5.9%)		IFG and/or IGT	0 (0.0%)
	Diabetes	0 (0.0%)		Diabetes	0 (0.0%)
Clozapine (n=18)			Clozapine (n=3)		
	No abnormality	8 (44.4%)		No abnormality	0 (0.0%)
	IFG and/or IGT	9 (50.0%)		IFG and/or IGT	2 (66.7%)
	Diabetes	1 (5.6%)		Diabetes	1 (33.3%)
Olanzapine (n=39)			Olanzapine (n=11)		
	No abnormality	31 (79.5%)		No abnormality	3 (27.3%)
	IFG and/or IGT	8 (20.5%)		IFG and/or IGT	4 (36.4%)
	Diabetes	0 (0.0%)		Diabetes	4 (36.4%)
Quetiapine (n=23)			Quetiapine (n=1)		
	No abnormality	17 (73.9%)		No abnormality	1 (100.0%)
	IFG and/or IGT	5 (21.7%)		IFG and/or IGT	0 (0.0%)
	Diabetes	1 (4.4%)		Diabetes	0 (0.0%)
Risperidone (n=42)			Risperidone (n=6)		
	No abnormality	37 (88.1%)		No abnormality	1 (16.7%)
	IFG and/or IGT	4 (9.5%)		IFG and/or IGT	5 (83.3%)
	Diabetes	1 (2.4%)		Diabetes	0 (0.0%)

IFG: Impaired Fasting Glucose (fasting glucose 100-125 mg/dl)

IGT: Impaired Glucose Tolerance (glucose 140-199 mg/dl at 2 hours in the OGTT)

Table 2. Evolution of OGTT measures, BMI and waist circumference per treatment group in 183 patients initiated on an atypical antipsychotic.

	Amisulpride (n=18)		Aripiprazole (n=22)		Clozapine (n=21)		Olanzapine (n=50)		Quetiapine (n=24)		Risperidone (n=48)		DrugXtime interaction*
	Baseline, mean (SD)	3 months, mean (SD)	Baseline, mean (SD)	3 months, mean (SD)	Baseline, mean (SD)	3 months, mean (SD)	Baseline, mean (SD)	3 months, mean (SD)	Baseline, mean (SD)	3 months, mean (SD)	Baseline, mean (SD)	3 months, mean (SD)	
Glucose fasting (mg/dl)	88.8 (11.4)	85.5 (6.3)	92.0 (8.1)	86.3 (7.4)	88.4 (9.6)	98.8 (14.1)	88.9 (11.5)	92.1 (15.6)	83.9 (6.7)	88.3 (9.4)	87.8 (7.5)	88.2 (8.1)	p < .0001
Glucose 120min (mg/dl)	109.5 (41.0)	107.6 (30.8)	96.3 (35.5)	84.5 (20.8)	95.4 (37.8)	112.2 (43.1)	89.2 (32.7)	111.7 (48.3)	96.0 (28.7)	101.2 (42.7)	93.1 (28.3)	98.9 (40.0)	p = .0028
Insulin fasting (mg/dl)	14.5 (9.7)	12.0 (7.1)	12.6 (12.9)	8.4 (4.6)	15.2 (14.1)	17.1 (14.0)	12.4 (16.7)	15.0 (20.1)	13.6 (18.1)	10.7 (4.2)	10.7 (6.9)	11.4 (7.8)	NS
Insulin 120 min (mg/dl)	56.6 (48.0)	42.7 (39.4)	42.3 (40.9)	28.0 (20.1)	53.9 (64.0)	78.8 (160.2)	46.1 (55.0)	54.8 (60.0)	44.4 (39.0)	39.5 (37.0)	42.0 (54.5)	55.3 (110.7)	NS
HOMA-IR	3.3 (2.7)	2.6 (1.7)	3.0 (3.3)	1.8 (1.0)	3.4 (3.2)	4.4 (4.3)	3.2 (6.4)	3.6 (5.5)	2.9 (4.3)	2.3 (1.0)	2.4 (1.7)	2.5 (1.9)	NS
BMI (kg/m ²)	26.5 (4.3)	27.9 (3.5)	28.4 (5.7)	27.3 (5.2)	24.8 (4.9)	26.5 (5.2)	23.5 (4.9)	25.8 (5.1)	25.2 (6.1)	26.8 (7.2)	24.9 (3.7)	25.8 (4.1)	p < .0001
Waist (cm)	95.1 (11.1)	99.1 (10.0)	99.2 (16.0)	96.4 (14.9)	93.6 (13.0)	96.7 (13.0)	87.7 (11.8)	94.6 (11.4)	91.0 (13.3)	97.0 (16.4)	90.5 (11.2)	93.0 (10.7)	p < .0001

*Drug X time interaction in the repeated measures drug (6) X time (2) analysis of variance

NS: non-significant

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METABOLIC DISTURBANCES AS CANDIDATE ENDOPHENOTYPE

CHAPTER 8

PREVALENCE OF DIABETES AND THE METABOLIC SYNDROME IN A SAMPLE OF PATIENTS WITH BIPOLAR DISORDER.

Ruud van Winkel^{a,b}, Marc De Hert^a, Dominique Van Eyck^a, Linda Hanssens^c, Martien Wampers^a, Andre Scheen^d, Joseph Peuskens^a

^aUniversity Psychiatric Center Katholieke Universiteit Leuven, Leuvense Steenweg 517, 3070 Kortenberg, Belgium

^bDepartment of Psychiatry and Neuropsychology, EURON, South Limburg Mental Health Research and Teaching Network, Maastricht University; PO box 616, 6200 MD Maastricht, The Netherlands.

^cDepartment of Epidemiology and Public Health, University Liege, Belgium

^dDepartment of Diabetes and Metabolic Disorders, CHU de Sart Tilman, University Liege, Belgium

Bipolar Disorders, in press

Abstract

Objective: The presence of metabolic abnormalities is an important risk factor for cardiovascular disease and diabetes. There are limited data on the prevalence of the metabolic abnormalities in disorders other than schizophrenia in which antipsychotic medication is part of routine treatment. **Methods:** Sixty consecutive patients with bipolar disorder at our university psychiatric hospital and affiliate services were entered in an extensive prospective metabolic study including an oral glucose tolerance test. The prevalence of the metabolic syndrome was assessed based on the National Cholesterol Education Program Adult Treatment Protocol criteria (ATP III), the adapted ATP-III criteria using a fasting glucose threshold of 100mg/dl, and the recently proposed criteria from the International Diabetes Federation (IDF). **Results:** The analysis of 60 patients showed a prevalence of the metabolic syndrome of 16.7% (ATP-III), 18.3% (adapted ATP-III) and 30.0% (IDF), respectively. 6.7% of the patients met criteria for diabetes and 23.3% for prediabetic abnormalities. **Conclusion:** The metabolic syndrome and glucose abnormalities are highly prevalent among patients with bipolar disorder. They represent an important risk for cardiovascular and metabolic disorders. Assessment of the presence and monitoring of metabolic abnormalities and its associated risks should be part of the clinical management of patients with bipolar disorder.

Key words: Bipolar disorder, Metabolic Syndrome, Diabetes, Physical Health

Introduction

Since the introduction of second generation antipsychotics and their association with metabolic abnormalities, there has been a rise of interest into the occurrence of metabolic abnormalities in patients treated with these drugs, although the main focus of research was on patients diagnosed with schizophrenia (Jin et al., 2004; Allison and Casey, 2001; Meyer and Koro, 2004). The issue of abnormalities in glucose metabolism has received most attention (Jin et al., 2002; Jin et al., 2004; Haupt and Newcomer, 2001; Scheen and De Hert, 2005; Newcomer, 2005; De Nayer et al., 2005; De Hert et al., 2006a).

Next to diabetes, there has been a surge of interest into other medical conditions such as cardiovascular morbidity, abnormal lipid metabolism and obesity that also have a serious impact on the physical health. In patients with schizophrenia, recent research has demonstrated a prevalence of 40 to 50% of the metabolic syndrome, which comprises abnormalities in glucose metabolism, lipid metabolism, obesity and blood pressure (Heiskanen et al., 2003; Basu et al., 2004; De Hert et al., 2006b).

In contrast to patients diagnosed with schizophrenia, research on metabolic abnormalities in patients with bipolar disorder has been relatively scarce. Three retrospective chart reviews of patients with bipolar disorder (Lilliker, 1980; Cassidy et al., 1999; Regenold et al., 2002), one of which also investigated diabetes prevalence in patients with schizoaffective disorder and schizophrenia (Regenold et al., 2002), found evidence for an increased prevalence of diabetes in these patients, when compared to the general population. It has been previously shown, however, that a large proportion of diabetes cases remain undetected when patients are not actively screened for these abnormalities (van Winkel et al., 2006; Taylor et al., 2005; Sernyak et al., 2005; De Hert et al., 2006c), which implicates that the actual prevalence of diabetes in patients with bipolar disorder could even be higher than the rates reported in these studies.

With respect to the metabolic syndrome, a study by Fagiolini and colleagues evaluated the prevalence of the metabolic syndrome in 171 patients with bipolar disorder, and found a prevalence of 30%, using ATP III criteria (Fagiolini et al., 2005). Furthermore, there is convincing evidence for an increased prevalence of obesity in bipolar patients (Elmslie et al., 2000; McElroy et al., 2002; Fagiolini et al., 2002; Fagiolini et al., 2003), and possibly also for different dietary habits, with bipolar patients consuming more sugars and carbohydrates than controls (Elmslie et al., 2001). These data clearly show the relevance of investigating metabolic abnormalities in patients with bipolar disorder.

To our knowledge, no study has specifically addressed the prevalence of metabolic abnormalities in bipolar patients with a comprehensive metabolic screening using an oral glucose tolerance test. The aim of the current study was to investigate the prevalence of metabolic abnormalities and the metabolic syndrome in a sample of 60 patients with bipolar disorder.

Methods

At the University Psychiatric Center Katholieke Universiteit Leuven in Kortenberg (Belgium) and its affiliate services, according to international guidelines, patients treated with antipsychotic medication are being asked to participate in an extensive screening and prospective follow-up study of metabolic parameters. The vast majority of patients treated with antipsychotic medication and in follow-up in our hospital or its affiliate

services are part of this extensive metabolic study, which was started in November 2003. This screening program was described extensively elsewhere (De Hert et al., 2007; van Winkel et al., 2006; De Hert et al., 2006b; De Hert et al., 2006c; De Hert et al., 2006d). In short, the study population is a dynamic, naturalistic cohort. Referral by the treating psychiatrist for metabolic screening and monitoring is a clinical routine in our hospital and its affiliate services, certainly for hospitalized patients and to a lesser extent for ambulatory patients. Although no systematic data are being recorded on patients who refuse this monitoring, the clinical experience learns that very few patients do so. Decisions regarding medication are made by the treating psychiatrist together with the patient, including dose reduction, dose augmentation, and switch strategies. These changes are recorded and patients are being monitored by means of laboratory tests, Oral Glucose Tolerance Tests and clinical examinations. The baseline characteristics of the first 430 patients with schizophrenia or schizoaffective disorder of this cohort were previously reported (De Hert et al., 2006b). The current study describes the baseline characteristics of the first 60 patients with bipolar disorder. As the diagnosis is a clinical diagnosis recorded by the treating psychiatrist, and no structured diagnostic interview was done, it was not possible to distinguish bipolar I and bipolar II patients.

At baseline, patients received a full fasting laboratory screening, clinical measurements and an ECG. A 75gr glucose load Oral Glucose Tolerance Test (OGTT) was performed in all patients. Patients were initiated on an overnight fast and were monitored during the OGTT. All laboratory analyses were performed in the same laboratory.

The presence of the metabolic syndrome was assessed using the ATP-III criteria, the adapted ATP-III criteria (fasting glucose criterion of ≥ 100 instead of ≥ 110 mg/dl, plus including treatment for hypertension, -lipidemia and -glycemia as criteria) and the recent IDF criteria (for overview see table 4) (Expert Panel on Detection and Evaluation of Treatment of High Blood Cholesterol in Adults, 2001; Grundy et al., 2005; IDF, 2005). For the diagnosis of diabetes and prediabetic abnormalities, we used the criteria of the American Diabetes Association (Impaired fasting glucose (IFG): fasting glucose 100-125 mg/dl and Impaired Glucose Tolerance (IGT), glucose 140-199 mg/dl at 2 hours in the OGTT) (American Diabetes Association, 2006). Patients were not known with diabetes prior to the baseline metabolic screening.

Descriptive statistics were computed for the basic demographic and clinical variables as well as for the variables relevant for the evaluation of metabolic abnormalities. The influence of the presence/absence of the metabolic syndrome and the presence/absence of glucose abnormalities on continuous variables was assessed by means of an independent samples t-test. The association between categorical variables was evaluated by a chi-square test. The study was approved by an ethical committee and all patients gave written informed consent.

Results

Subjects

The mean age of the patients was 45.3 years (std 13.0) and the mean duration of illness was 9.4 years (std 10.9). Of these patients, 26 were male (43.3%), and all patients were caucasians. All subjects completed the assessments. The majority of patients was able to live independently in the community (n=55, or 91.7%) and

17 patients also had a job (28.3%). There was a high prevalence of family history for cardiovascular and metabolic disorders (table 1). The majority of patients had a normal weight, and obesity was only present in 5 patients (8.3%). Except for 7 patients, all patients were treated with antipsychotic medication. The most frequently used antipsychotics were olanzapine and quetiapine (table 2). On average, patients received 3.2 (std 1.5) different medications. Next to antipsychotic medication, patients were treated with anticholinergics (5%), antidepressants (46.5%) and benzodiazepines (35.0%). Thirty patients received mood stabilisers: 20 patients received valproic acid, 10 lithium, 3 lamotrigine and 1 carbamazepine (4 patients took 2 mood stabilizers). Twenty patients took not-psychoactive medication, which was relevant for metabolic disturbances in 9 patients, who all took antihypertensive medication. Except for these 9 patients, no other patients were known with hypertension prior to the baseline screening; similarly, no patients were known with diabetes or lipid disorders prior to the baseline screening.

Metabolic abnormalities

The prevalence of the metabolic syndrome according to the different definitions is shown in table 3. There was no significant difference in the prevalence of the metabolic syndrome according to sex, although female patients were significantly more likely to meet the increased waist criterion according either to ATP-III ($\chi^2 = 4.67$, $p < .0307$) or IDF criteria ($\chi^2 = 5.98$, $p < .0144$). Abnormal lipid values were frequently observed: 35 patients (58.3%) had elevated cholesterol, 31 patients (51.7%) elevated LDL cholesterol, 16 (26.7%) elevated triglycerides and 13 (21.7%) low HDL cholesterol, with all of these elevated measures being uncovered for the first time. Patients meeting criteria for the metabolic syndrome were significantly more likely to take a second-generation antipsychotic, except for patients meeting criteria for the metabolic syndrome according to the IDF definition (ATP III: 7 of 10 patients, $\chi^2 = 9.4$, $p < .01$; adapted ATP III: 8 of 11 patients, $\chi^2 = 8.1$, $p = .0175$; IDF: 16 of 18 patients, $\chi^2 = 2.4$, $p = .31$). Patients with the metabolic syndrome were significantly more likely to be overweight or obese than patients that did not meet criteria for the metabolic syndrome (ATP III: 8 of 10 patients, $\chi^2 = 17.3$, $p < .001$; adapted ATP III: 9 of 11 patients, $\chi^2 = 21.4$, $p < .0001$; IDF: 10 of 18 patients, $\chi^2 = 12.2$, $p < .01$).

According to ADA criteria, 4 patients (6.7%) met criteria for diabetes and another 14 (23.3%) met criteria for prediabetes (14 IFG, of whom 9 also had IGT). Of the patients with diabetes, 3 were treated with quetiapine and 1 with quetiapine combined with olanzapine. Two of the patients who met criteria for diabetes were not treated with a mood stabilizer, the other two were treated with lithium. Patients with diabetes were significantly older than patients without diabetes ($F(1, 58) = 4.9$, $p = .0314$). Similarly, patients that met criteria for the metabolic syndrome, regardless of the definition applied, were significantly older than patients not meeting criteria for the metabolic syndrome (ATP III: $F(1, 58) = 14.5$, $p < .001$; adapted ATP III: $F(1, 58) = 10.8$, $p < .01$; IDF: $F(1, 58) = 4.3$, $p = .0422$). Of the patients with prediabetic abnormalities, 3 were treated with risperidone, 2 with clozapine, 3 with quetiapine, 5 with olanzapine and 1 without antipsychotic medication (who took two mood stabilizers and an antidepressant). Patients with the metabolic syndrome were more likely to meet criteria for diabetes or prediabetic abnormalities in all definitions applied (table 4). Patients with the metabolic syndrome according to the IDF criteria were more likely to have a family history of

diabetes ($\chi^2=4.9$, $p=.0269$), but this was not found for patients meeting criteria for the metabolic syndrome according to the ATP III or adapted ATP III criteria, or for patients that met criteria for diabetes. Likewise, the presence of a family history of lipid disorders or cardiovascular disease was not significantly different in patients with or without diabetes, or in patients with or without the metabolic syndrome for all definitions applied.

Discussion

To our knowledge, this is the first non-retrospective study to directly assess the prevalence of diabetes in patients with bipolar disorder, by the use of an OGTT. Furthermore, the metabolic syndrome and other metabolic abnormalities were assessed. High rates of diabetes, the metabolic syndrome and metabolic abnormalities were found. These results confirm the high prevalence of the metabolic syndrome in patients with bipolar disorder, reaching as much as twice the prevalence of the general Belgian population matched for age (Rietzschel et al., 2005). The prevalence of diabetes in the current sample was 3 times higher than the rate of drug-treated diabetes in the general population (Walckiers et al., 1992). Therefore, these data clearly demonstrate the need for screening for the metabolic syndrome and diabetes, not only in patients diagnosed with schizophrenia, as suggested in the literature (Marder et al., 2004; De Hert et al., 2006a; De Nayer et al., 2005; van Winkel et al., 2006), but also in patients with bipolar disorder, or at least those who are being treated with second generation antipsychotics. The importance of such screening is underlined by the rates of newly detected and previously untreated hypertension in 33% of patients and hypercholesterolemia in 58% of patients, which is in line with high rates of non-treatment in patients with schizophrenia (Nasrallah, 2006).

Despite these increased prevalence rates when compared to the general population, the prevalence of the metabolic syndrome in the current sample of bipolar patients was considerably lower than the prevalence reported by Fagiolini and colleagues (Fagiolini et al., 2005). These differences in prevalence rates are likely to be due to life style differences in the European versus the American population, but to our knowledge, no study has specifically handled this issue. Nevertheless, estimates of the metabolic syndrome in the general population have consistently been lower for European than for US populations (Ferreira et al., 2005; Boulogne and Vantighem, 2004; Hu et al., 2004; Ford et al., 2004; Ford et al., 2002).

When compared to patients with schizophrenia or schizoaffective disorder (De Hert et al., 2006b), the prevalence of the metabolic syndrome appears lower in the bipolar patient group. Interestingly, rates of glucose abnormalities were as high in bipolar patients as in schizophrenia patients (van Winkel et al., 2006), as was the presence of a family history of cardiovascular complications, diabetes and lipid disorders (De Hert et al., 2006e). The current results suggest that patients with bipolar disorder are also at high risk to develop metabolic abnormalities, and thus, that the increased risk for the development of these abnormalities is not limited to patients with schizophrenia. Interestingly, the current results suggest that the development of the metabolic abnormalities is only moderately associated with weight, since of the current sample, 43 of the 60 patients had a normal weight (body mass index between 20 and 25) and only 5 patients met criteria for obesity (body mass index above 30). An other interesting finding is the finding that female patients were more likely to have increased waist circumference in the current study, which is in line with studies in patients with

schizophrenia (De Hert et al., 2006b; McEvoy et al., 2005). Unfortunately, the sample size did not permit to investigate the liability to develop metabolic abnormalities according to the individual antipsychotic drugs.

The current study also has some limitations. First and most importantly, the current sample of patients with bipolar disorder is relatively small. Furthermore, it consisted mainly of patients that were treated with a second generation antipsychotic (almost 90%), and may thus not be representative for bipolar patients in general. Second, it is a cross-sectional study. We intent to follow-up this cohort prospectively, in order to assess metabolic changes during the course of the illness and in function of antipsychotic regimes. Third, we failed to include other parameters, such as dietary habits, physical activity level and psychopathological profile. Fourth, patient recruitment was restricted to one site, which could have influenced our results, since large regional differences in the prevalence of metabolic abnormalities have been reported, at least in the US (Ford et al., 2005). Future research should address these issues more specifically, in large, multi-site samples and with prospective study designs.

In conclusion, our data confirm the high prevalence of metabolic abnormalities, and especially glucose metabolism disturbances, for a European population of patients with bipolar disorder. Caregivers should carefully monitor and treat metabolic abnormalities in these patients.

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Table 1

Clinical and demographic data.

	All
Age	45.3 ($\pm$ 13.0)
Sex	
Female	56.7% (34)
Male	43.3% (26)
GAF	58.7 ($\pm$ 8.7)
Age first admission	35.9 ($\pm$ 12.3)
N admissions	3.3 ($\pm$ 2.5)
Duration of illness	9.4 ($\pm$ 10.9)
Number of different drugs	3.2 ($\pm$ 1.5)
BMI	24.4 ($\pm$ 4.2)
BMI segmentation	
Normal (20-25 kg/m ²)	70% (42)
Overweight (25-30 kg/m ²)	21.7% (13)
Obese (>30 kg/m ²)	8.3% (5)
Living situation	
Sheltered housing	3.3 % (2)
With family	20 % (12)
Partner	35% (21)
Alone	36.7% (22)
Residential facility	5% (3)
Occupation	
Work	28.3% (17)
Sheltered work	0% (0)
Study/training	3.3% (2)
None	68.3% (41)
Family history of CVD	40% (24)
Family history of diabetes	30% (18)
Family history of lipid disorder	30% (18)

Table 2

Medication characteristics.

	% (n)
Anticholinergic	5.0% (3)
Benzodiazepine	35.0% (21)
Antidepressant	46.6% (28)
Mood stabiliser*	50% (30)
Valproate	66.7% (20)
Lithium	33.3% (10)
Lamotrigine	10.0% (3)
Carbamazepine	3.3% (1)
No antipsychotic	11.7% (7)
Only first generation	0% (0)
Only second generation	78.3% (47)
Combination	10% (6)
Second generation antipsychotic	88.3% (53)
Second generation	
Aripiprazole	1.9% (1)
Clozapine	3.7% (2)
Risperidone	20.4% (11)
Quetiapine	31.5% (17)
Amisulpride	1.8% (1)
Olanzapine	40.7% (22)
No medication	0% (0)

*4 patients combine two mood stabilizers

Table 3

Metabolic syndrome criteria prevalence.

	All (n=60) % (n)	Male (n=26) % (n)	Female (n=34) % (n)	P
ATP-III*	16.7% (10)	19.2 % (5)	17.6% (5)	ns
Criteria:				
Waist (M>102, F>88)	30.0% (18)	15.4% (4)	41.4% (14)	0.03
Blood pressure ($\geq$ 130/85)	48.3% (29)	61.5% (16)	38.2% (13)	ns
HDL (M<40 mg/dl, F<50 mg/dl)	21.7% (13)	19.2% (5)	23.5% (8)	ns
Triglycerides ($\geq$ 150 mg/dl)	26.7% (16)	38.4% (10)	17.6% (6)	ns
Glucose ($\geq$ 110 mg/dl)	13.3% (8)	15.1% (4)	11.8% (4)	ns
Adapted ATP-III*	18.3% (11)	19.2% (5)	17.6% (6)	ns
Criteria:				
Waist (M>102, F>88)	30.0% (18)	15.4% (4)	41.4% (14)	0.03
Blood pressure ($\geq$ 130/85)***	48.3% (29)	61.5% (16)	38.2% (13)	ns
HDL (M<40 mg/dl, F<50 mg/dl)	21.7% (13)	19.2% (5)	23.5% (8)	ns
Triglycerides ($\geq$ 150 mg/dl)	26.7% (16)	38.4% (10)	17.6% (6)	ns
Glucose ($\geq$ 100 mg/dl)****	28.3% (17)	23.1% (6)	32.4% (11)	ns
IDF**	30.0% (18)	34.6% (9)	26.5% (9)	ns
Criteria:				
Waist (M $\geq$ 94, F $\geq$ 80)	60.0% (36)	30.6% (11)	69.4% (25)	0.01
Blood pressure ($\geq$ 130/85)	48.3% (29)	61.5% (16)	38.2% (13)	ns
HDL (M<40 mg/dl, F<50 mg/dl)	21.7% (13)	19.2% (5)	23.5% (8)	ns
Triglycerides ($\geq$ 150 mg/dl)	26.7% (16)	38.4% (10)	17.6% (6)	ns
Glucose ($\geq$ 100 mg/dl)	28.3% (17)	23.1% (6)	32.4% (11)	ns

*Metabolic syndrome if 3 of 5 criteria are met.

**Metabolic syndrome if 2 criteria AND the waist criterion are met (waist is obligatory).

***Or if treated with antihypertensive medication.

****Or if treated with insulin or glucose-lowering medication.

Table 4

The prevalence of glucose abnormalities depending on the absence ('No') or presence ('Yes') of the metabolic syndrome according to the different definitions.

	Normal values % (n)	Pre diabetes % (n)	Diabetes % (n)	Total % (n)	P
ATP-III					<0.001
No	78% (39)	20% (10)	2% (1)	83.3% (50)	
Yes	30% (3)	40% (4)	30% (3)	16.7% (10)	
Adapted ATP-III					<0.001
No	79.6% (39)	18.4% (9)	2% (1)	81.7% (49)	
Yes	27.3% (3)	45.4% (5)	27.3% (3)	18.3% (11)	
IDF					<0.001
No	83.3% (35)	16.7% (7)	0% (0)	70% (42)	
Yes	38.9% (7)	38.9% (7)	22.2% (4)	30% (18)	
Total	70% (42)	23.3% (14)	6.7% (4)		

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CHAPTER 9

DISCUSSION

Endophenotypes for schizophrenia research

Schizophrenia is a complex disorder, with genes and environmental factors likely to interact in its etiology, hereby complicating the search for causative genes. In an effort to reveal susceptibility genes, schizophrenia research has therefore turned to the endophenotype strategy, as endophenotypes are thought to reflect the actions of genes predisposing an individual to a disorder, even in the absence of diagnosable pathology. The underlying assumption is that individual endophenotypes are determined by fewer genes than the more complex and etiologically heterogeneous phenotype of schizophrenia, and that investigating endophenotypic outcomes would thus reduce the complexity of genetic analyses.

The advantage of the endophenotype strategy over straightforward gene-disorder association strategies is illustrated best by the example of COMT^{Val158Met}. Several findings make COMT a plausible candidate gene for schizophrenia: it is implicated in the catabolism of dopamine and contains a functional polymorphism that directly affects catabolic enzyme function (Chen et al., 2004). Furthermore, it maps to the 22q11 region that has been identified as one of three loci that had the highest likelihood of harbouring schizophrenia-risk genes in a meta-analysis of genome-wide linkage scans (Badner and Gershon, 2002) and is deleted in the velo-cardial-facial syndrome, of which the psychiatric presentation resembles the clinical syndrome of schizophrenia (Shprintzen et al., 1992; Bassett et al., 2003). Despite this evidence pointing towards a role of COMT^{Val158Met} in the etiology of schizophrenia, two meta-analyses disappointingly found minimal or no evidence for an association between the COMT^{Val158Met} polymorphism and schizophrenia (Fan et al., 2005; Munafo et al., 2005), as did a study in two large samples (Williams et al., 2005).

However, by using an endophenotypic approach, recent studies have suggested a role of COMT^{Val158Met} in (candidate) endophenotypes for schizophrenia such as P50 gating (Lu et al., 2007), schizotypy (Smyrnis et al., 2007; Schurhoff et al., 2007) and stress-sensitivity (chapter 4), which underscores the usefulness of endophenotypic rather than disorder outcomes.

This thesis aimed to explore clinical and genetic correlates of three candidate endophenotypes for schizophrenia, ie cognitive impairments, stress-sensitivity and metabolic disturbances. These endophenotypes were chosen because of their direct impact on treatment and outcome compared to other, more subtle endophenotypic markers.

Cognition for genetic research in schizophrenia

Cognition as an endophenotype for schizophrenia

Cognitive impairments are well established endophenotypic markers for schizophrenia (Gould and Gottesman, 2005; Gottesman and Gould, 2003; Snitz et al., 2006), for several reasons: because of their biological plausibility in the etiology of schizophrenia; because a meta-analysis revealed relatively large cognitive impairments in memory, attention and executive functioning and moderate impairments in vocabulary and

visual perceptive skills in 7420 patients with schizophrenia compared to 5865 controls (Heinrichs and Zakzanis, 1998); and because these cognitive impairments were also found, to a lesser degree, in first-degree relatives of patients with schizophrenia (Finkelstein et al., 1997; Gold, 2004). These findings show that cognitive impairments are associated with the illness (criterion 1 of the endophenotype concept as described in chapter 1), that these traits are presumably heritable (criterion 2), cosegregate with the illness within families (criterion 4) and are also found in a higher rate in unaffected relatives than in the general population (criterion 5).

However, this thesis suggested cognitive impairments may not be as stable, or 'state-independent' (criterion 3), as previously thought. Evidence suggests significant intellectual decline preceding the first episode of psychosis (Rabinowitz et al., 2000), especially in subjects with higher premorbid capacities (chapter 2). In those patients, catching up of cognitive function may take place later in the course of the illness, whereas those with the most severe premorbid impairments remain stable (chapter 2).

The cognitive instability around the first episode of psychosis in subjects with higher premorbid capacities makes the use of cognitive impairments as endophenotypic markers in these subjects potentially problematic, as cognitive assessments in this time-period may reflect illness-related, state-dependent characteristics rather than stable, endophenotypic traits suitable for genetic analyses.

Nevertheless, the global stability of cognitive measures from premorbid level up to at least ten years into the illness suggests that cognition could be a useful endophenotypic trait for genetic analyses, which is underscored by the finding that cognitive measures were able to differentiate between patients with a more neurodevelopmental and a more reactive profile (chapter 2) and had a direct relationship with functional outcome, cross-sectionally as well as prospectively (chapter 3), but only when premorbid or cognitive measures in patients with a certain illness duration were used.

Other points of consideration also need to be addressed. First, the type of cognitive test may be important when assessing cognition as an endophenotype. Estimates of heritability are particularly high for IQ measures (Wright et al., 2001), but recent evidence suggest that the often used Wisconsin Card Sorting Test may not be an ideal marker for cognitive heritability (Kremen et al., 2007). Second, the use of cognitive impairments as endophenotypic measures for schizophrenia within families assumes developmental equivalence; however, cognitive tests may not measure the same cognitive domain in children or older adults, and the heritability of cognitive skills likely destabilizes after the age of 50 (Kaprio and Koskenvuo, 2002). This illustrates the importance of carefully choosing the most adequate age range, balancing sample size and test- equivalence.

The use of subtypes for genetic analyses

Chapter 2 showed that cognitive measures, more specifically estimated premorbid IQ, could be used to distinguish patients with a more 'neurodevelopmental' and a more 'reactive' expression of the illness. Differences in clinical presentation between these patients have lead some researchers to put forward the concept of the 'deficit syndrome' consisting of patients with enduring, idiopathic negative symptoms (Kirkpatrick et al., 2001). The 'deficit syndrome' is suggested to identify individuals with a more homogeneous expression of the illness, or even a separate illness category (Kirkpatrick et al., 2001), although

the latter is in disagreement with a recent taxometric study on patients with schizophrenic and non-schizophrenic psychotic disorders (Cuesta et al., 2007). It has been suggested that genetic association analyses in these patients could prove to be productive (Hallmayer et al., 2005), but genetic studies so far have failed to find positive, 'deficit'-specific associations with candidate genes such as COMT, neuregulin, DTNBP1 (dysbindin), G72/G30, RGS4 and PIP5K2A (Bakker et al., 2007; Wonodi et al., 2006; Bakker et al., 2004). Although selection of specific subsamples within a certain clinical syndrome could be productive for the identification of disease genes, the importance of environmental factors in the expression or non-expression of psychosis in at-risk persons and the continuous rather than dichotomous distribution of positive, negative and desorganisation symptom domains of psychosis (Cuesta et al., 2007) could hamper the applicability of this approach for schizophrenia. Furthermore, this approach demands large samples of patients given the necessity to compare two patient samples ('deficit' versus 'non-deficit' patients). Studying endophenotypic outcomes in a more homogeneous 'deficit' sample would also reduce variability and thus the sensitivity of genetic analyses, making it unfavorable to study endophenotypic outcomes in homogeneous samples such as patients with the 'deficit syndrome' (Szatmari et al., 2007).

Stress-sensitivity as endophenotypic marker for schizophrenia

Stress-sensitivity: endophenotype?

Stress-sensitivity was only recently put forward as a possible endophenotype for psychosis (Lataster et al., 2007). A large body of evidence suggests a role of stress in the etiology of psychosis (Bebbington et al., 1993; Bebbington et al., 1996; Carr et al., 2000; Bebbington and Kuipers, 1994; Butzlaff and Hooley, 1998; Brown et al., 1972), making a possible role of stress-sensitivity biologically plausible. Quantification of stress-sensitivity by using ESM allowed to show that patients with schizophrenia are more stress-sensitive than controls, with first-degree relatives scoring intermediate (Myin-Germeys et al., 2001; Myin-Germeys et al., 2005). These studies also found evidence for state-independency, as they investigated stress-sensitivity in remitted patients. Furthermore, evidence was found for cosegregation within families (Lataster et al., submitted). These findings show that stress-sensitivity is associated with the illness (criterion 1), that it is presumably heritable (criterion 2), that it is state-independent (criterion 3), that it cosegregates with the illness within families (criterion 4) and is also found in a higher rate in unaffected relatives than in the general population (criterion 5). These findings suggest that stress-sensitivity is indeed a useful endophenotype for schizophrenia.

Nevertheless, some issues need to be considered. Although stress-sensitivity was present in remitted patients, which suggests state-independency, there have been no studies that have specifically assessed the stability of stress-sensitivity over longer periods of time. Concerns of within-person trait-stability, developmental equivalence and test-retest reliability therefore are concerns that need to be addressed.

Genes for stress-sensitivity in psychosis

This thesis was the first to show genetic moderation of stress-sensitivity in patients with psychosis, more specifically by COMT^{Val158Met} (chapter 4), and also suggested that COMT^{Val158Met} could have a relevant etiological role in the formation of psychotic and affective symptoms in at-risk persons (chapter 5).

These findings suggest that stress-sensitivity may be an important intermediate factor in gene-to-disorder pathways, that could play a crucial role in the development of both affective as well as psychotic symptomatology. Given the considerable overlap between affective and psychotic disorders in terms of genetic risk (Craddock et al., 2006; Cardno et al., 2002) and clinical comorbidity (Murray et al., 2004), understanding the role of stress-sensitivity in the formation of symptoms and its genetic underpinning could prove to be a large step forward in our understanding of the etiology of these disorders.

Of interest in this regard is a recent study in subjects with a varying degree of susceptibility to depression that investigated the influence of COMT^{Val158Met} on endocrine and subjective responses to a psychological stress task, showing an increased subjective response to psychological stress with increased *Met* loading in both healthy and depressed subjects, but a stronger endocrine response in controls with increased *Met* loading only (Jabbi et al., 2007a). These results do not only suggest that *Met* alleles are involved in subjective appraisals on situations that evoke negative affective states (ie stress-sensitivity), but the dissociation between subjective and endocrine responses to psychological stress in depressed subjects also suggests that it is in interaction with altered HPA axis functioning that this could lead to depression, although the issue of reverse causality needs to be addressed in future studies.

Further candidate genes for stress-sensitivity were reported by the same group, showing that next to COMT^{Val158Met}, polymorphic variations in genes coding for serotonin transporter (SERTPR), monoamine oxidase A (MAOA) as well as sex differences influence the regulation of hypothalamic-pituitary-adrenal (HPA)-axis response to acute psychological and endocrine challenges in subjects with a varying degree of susceptibility to depression (Jabbi et al., 2007b). Similar results were reported in a mixed sample of patients with depression and bipolar disorder, where both COMT^{Val158Met} and SERTPR were associated with the development of depression in reaction to life stressors in the preceding year, and significant interaction between COMT^{Val158Met} and SERTPR was also found (Mandelli et al., 2006).

Other interesting polymorphisms include a variable number tandem repeat in the dopamine transporter gene (DAT VNTR), given its role in dopamine reuptake, and a Val66Met polymorphism of Brain-Derived-Neurotrophic-Factor (BDNF), as there is growing evidence that stress decreases the expression of BDNF in limbic structures involved in affective regulation (Duman and Monteggia, 2006).

Metabolic disturbances for schizophrenia research

Metabolic disturbances as endophenotype?

Differential effects of antipsychotic treatment, as were also shown in this thesis (chapters 6 and 7), complicate the applicability of metabolic disturbances as a candidate endophenotype for schizophrenia. Therefore, this thesis focused on basic clinical questions, such as investigation of guidelines (chapter 6), incidence of new-

onset diabetes (chapters 6 and 7) and assessment of prevalence of metabolic disturbances in bipolar disorder (chapter 8), which confirmed the major clinical importance of these abnormalities.

Despite its questionable use for genetic research on schizophrenia, findings that metabolic disturbances are also consistently higher in unmedicated first-episode patients (Thakore et al., 2002; Cohn et al., 2006; Ryan et al., 2003; Spelman et al., 2007) and non-affected relatives (Mukherjee et al., 1989; De Hert et al., 2006; Lamberti et al., 2004) however confirm that these abnormalities are also present in the absence of antipsychotic medication and can thus be seen as biological markers of schizophrenia and possibly also bipolar disorder. The biological plausibility of metabolic disturbances as intermediate factors in gene-to-disorder pathways of psychosis is however far from clear.

A first clue on a possible biological mechanism relating metabolic disturbances and psychosis comes from a metabolic profiling study of cerebrospinal fluid (CSF) in 82 patients with psychosis, of whom 54 were first-episode, drug-naïve patients, and 70 healthy controls (Holmes et al., 2006). This study showed a significantly elevated concentration of glucose (and decreased concentrations of acetate and lactate) in the CSF of first-episode, drug-naïve patients compared to healthy controls, whereas serum glucose levels showed no difference, suggesting a brain-specific elevation of glucose levels in first-episode, drug-naïve patients. Short-term treatment for an average of about 9 days with atypical medication resulted in normalization of the CSF metabolic profile in 58% of these first-episode patients, whereas no normalization occurred in patients that were only treated with antipsychotic medication after their second psychotic episode, although it has to be noted that this was a very small group (n=7). Nevertheless, these data may suggest that brain-specific alterations in glucoregulation could be involved in the etiology and response to treatment of psychosis, and align with a postmortem brain tissue study (Prabakaran et al., 2004), that demonstrated significant alterations of pathways relating to glucoregulation and mitochondrial functioning in patients with schizophrenia.

Although these findings demonstrate that pathways of glucoregulation could be relevant for the etiology of schizophrenia, findings from this thesis suggest that its peripheral correlates, ie metabolic abnormalities, can not be considered as stable, ‘endophenotypic’ traits suited for genetic analyses aiming to investigate etiological mechanisms for schizophrenia, given the large and differential impact of atypical antipsychotics on prevalence and incidence rates of metabolic abnormalities, as was demonstrated in chapters 6 and 7.

Furthermore, the increase of metabolic abnormalities with age (developmental unequivalence) and the possibility of familial aggregation caused by non-genetic factors such as social class, lifestyle and dietary habits make the use of metabolic abnormalities as endophenotypic measures unfavorable.

Strategies for research on metabolic abnormalities in schizophrenia

Despite the conclusion that the use of metabolic abnormalities as endophenotypic measures is unfavorable, findings that suggest that brain-specific glucodysregulation could be involved in the etiology of schizophrenia imply that this area certainly merits further research. A potentially productive strategy could be to combine basic clinical research on metabolic abnormalities, such as examination of guidelines and assessment of risk factors for the development of metabolic abnormalities such as differential medication effects, dietary measures and life style changes, with fundamental research focusing on mechanisms that can be assumed to

be more proximal to the supposedly etiologically relevant effects of glucodysregulation than the peripheral metabolic abnormalities themselves. These studies could also more specifically address the question whether the increased rates of metabolic abnormalities in patients and unaffected relatives is under genetic control or is the result of shared environmental factors such as social class, lifestyle and dietary habits.

Furthermore, future studies could focus on interactions between drugs and susceptibility genes for metabolic disturbances or schizophrenia, ie pharmacogenetic studies. Studying interactions between metabolic genes and antipsychotics could give important answers to who is at risk for developing metabolic abnormalities, whereas studying interactions between schizophrenia susceptibility genes and antipsychotics could also guide the search for possibly shared etiological mechanisms between metabolic disturbances and schizophrenia. These type of studies could also provide a step forward in predicting the risk to develop metabolic abnormalities and could thus may be helpful in guiding treatment choices in the future. Studies investigating these kind of gene-drug interactions, for example, have found significant associations between a Leptin G2548A polymorphism and clozapine-induced weight gain (Zhang et al., 2007) and between a 5-HT_{2C} receptor C759T polymorphism and antipsychotic-induced weight gain (Ryu et al., 2007).

Are reported associations specific for schizophrenia?

The use of endophenotypes provides a potentially powerful approach in the search for schizophrenia susceptibility genes. As stated previously, the underlying assumption is that individual endophenotypes are determined by fewer genes than the more complex and etiologically heterogeneous phenotype of schizophrenia, and that investigating endophenotypic outcomes would thus reduce the complexity of genetic analyses. In other words, the rationale of the endophenotypic approach is to reduce complexity in order to increase sensitivity of genetic analyses.

Broadening the subject of genetic analyses to endophenotypes may however lead to loss of specificity. For example, increased stress-sensitivity (Myin-Germeys et al., 2003) has also been shown in bipolar disorder and major depression, and associations between COMT^{Val158Met} and affective regulation have also been shown in the general population (Drabant et al., 2006; Smolka et al., 2005).

This could indicate that the role of specific genes may be similar for patients with schizophrenia or affective disorders as for the general population, which can be considered as insufficient evidence to support a specific role of this particular gene in the etiology of schizophrenia. Study designs that assess genetic moderation of subclinical symptomatology in subjects at risk may help to clarify whether reported genetic associations could indeed be relevant for the etiology of the disorder. For instance, this thesis suggested that COMT^{Val158Met} is associated with stress-sensitivity in patients with psychosis (chapter 4), and that this could be a relevant mechanism for the development of psychotic and affective symptomatology in an at-risk population (chapter 5).

Furthermore, the role of specific genes may be quantitatively rather than qualitatively different for patients with schizophrenia versus patients with affective disorders or subjects from the general population. For instance, in the earlier reported comparative study on stress-sensitivity in subjects with diagnoses of non-affective psychosis, bipolar disorder, major depression and healthy subjects, significant quantitative differences

between groups were found for the degree of stress-sensitivity, with subjects with a diagnosis of non-affective psychosis being most vulnerable to the effects of daily life stress (Myin-Germeys et al., 2003).

This indicates that, although stress-sensitivity is likely to be involved in the etiology of psychosis, it is not specific for patients with schizophrenia, suggesting that the development of psychopathology does not follow diagnostic categories and that general psychopathological mechanisms such as stress-sensitivity may interact with other mechanisms to result in specific psychopathology. Thus, quantitative trait differences may only become relevant in the presence of specific environments and in interaction with (deficits in) other biological mechanisms. For stress-sensitivity, this was supported by the recent study of Jabbi and colleagues (Jabbi et al., 2007a) who found stronger subjective reactions to a psychological stress task with increased COMT^{Val158Met} *Met* loading in both healthy and depressed subjects (ie stress-sensitivity), but a stronger endocrine response in controls with increased *Met* loading only. These findings indicate that future genetic research will have to generate specific hypotheses in order to be able to study and understand the complex actions of genes, their interactions with other genes and the environment in the etiology of psychiatric disorders.

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SUMMARY

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The use of endophenotypes is a relatively novel approach to the genetics of complex disorders. For schizophrenia, several traits have been proposed as candidate endophenotypes for schizophrenia, yet the use of the term endophenotype has broadened over recent years to include traits that are biological markers rather than true endophenotypes. Furthermore, several candidate endophenotype have not been evaluated for key endophenotype characteristics. This thesis, *Evaluation of candidate endophenotypes for schizophrenia*, evaluates the usefulness of cognition, stress-sensitivity and metabolic disturbances as endophenotypes for schizophrenia.

Chapter 1 describes the phenomenology of schizophrenia and the as of yet relatively unsuccessful attempt to find genes underlying it. The failure to identify schizophrenia genes through genetic association studies have lead to alternative approaches such as studies taking into account gene-environment interaction and replacement of the dichotomous disorder-outcome with continuous, ‘endophenotypic’ outcomes. The concept of endophenotypes is introduced, as being quantifiable intermediate factors in the genes-to-behaviors pathways which make genetic and biological studies for disease categories more manageable. Five criteria distinguish endophenotypes from biological markers: 1. they are associated with the illness in the population, 2. they are heritable, 3. they are state independent, 4. they cosegregate with the illness within families and 5. an endophenotype identified in probands is found in their unaffected relatives at a higher rate than in the general population. Based on these criteria and available literature on the three candidate endophenotypes, specific research questions are delineated. *For cognitive impairments*, the aim was to evaluate the course of the global cognitive measure IQ in patients who presented with a first episode of psychosis and to investigate possible differences in course of IQ resulting from underlying phenotypic heterogeneity. A second aim was to investigate the relationship between IQ measures and functional outcome in this sample of first-episode patients. *For stress-sensitivity*, the aim was to evaluate whether COMT^{Val158Met} would moderate the psychotic and affective reaction to daily life stressors in a sample of patients with psychosis and controls, and to evaluate whether this possible COMT^{Val158Met} moderation could also be a causal mechanism in the development of psychosis, by assessing whether unaffected first-degree relatives of patients with schizophrenia who share a *Met* allele have greater concordance of subclinical symptomatology than relatives not sharing a *Met* allele. *For metabolic abnormalities*, aims were to assess the comparative adequacy of the widely used American Psychiatric Association/American Diabetes Association (APA/ADA) screening guidelines for detecting diabetes versus a screening guideline derived from the guidelines of the World Health Organization (WHO), to evaluate early changes in glucose metabolism after initiation of an atypical antipsychotic and to also assess the prevalence of metabolic abnormalities in a sample of patients diagnosed with bipolar disorder.

Following these specific research questions, **Chapter 2** described the longitudinal course of IQ in first episode patients diagnosed with schizophrenia. After ten years follow-up, there was no evidence for a deterioration of

IQ. The hypothesis that estimated premorbid IQ would moderate the course of IQ was confirmed. Dichotomization revealed that in the high IQ group, which was hypothesized to reflect the ‘episodic subtype’, IQ measures did not remain stable over the follow-up period. A significant deterioration at the first hospitalization was seen, followed by an improvement up to premorbid level. In the low IQ group, which was hypothesized to reflect the ‘neurodevelopmental subtype’ a stable course of IQ was found. **Chapter 3** assessed the presence of a prospective association between cognition and functional outcome in first episode patients with schizophrenia. The presence of a prospective as well as a cross-sectional relationship of the global cognitive measure IQ with 10-year functional outcome could be established. However, it was also found that assessing associations between cognitive measures at first hospitalization and subsequent functional outcome can give inconclusive results due to non-uniform intellectual deterioration from premorbid level in the period preceding the first hospitalization. These findings may help to explain the controversy in the literature regarding the prospective relationship between cognitive measures and subsequent functional outcome between chronic and first episode patients.

In Chapter 4, it was found that patients with psychosis and comorbid cannabis use react more strongly to stress than healthy cannabis users, showing an increase in psychotic and affective symptoms. Interestingly, there also was evidence for an interaction between stress and COMT^{Val158Met} genotyped on increases in psychotic and affective symptoms, with patients with the *Met/Met* genotype showing the largest increases in symptomatology. These findings indicate the importance of taking gene-environment interaction into account in explaining transitions in momentary symptomatology in psychosis. **In Chapter 5**, we aimed to test the hypothesis that the COMT^{Val158Met} *Met* allele is causally implicated in the development of affective and psychotic symptomatology in subjects genetically at risk for schizophrenia, by testing if first-degree relatives of patients with schizophrenia who share a *Met* allele have greater concordance of symptomatology than relatives not sharing a *Met* allele. The results showed that when relatives shared a *Met* allele, subclinical symptomatology showed significant concordance. This was not the case when relatives did not share a *Met* allele, which suggests that the *Met* allele may be involved in the causation of psychopathology, at least in populations with a genetic predisposition to psychosis.

In Chapter 6, the diagnostic properties of two different screening guidelines for the detection of diabetes in patients diagnosed with schizophrenia was evaluated: 1) assessing fasting glucose in all patients, as suggested by the American Psychiatric Association/American Diabetes Association (APA/ADA) and 2) a screening strategy derived from the guidelines of the World Health Organization (WHO) of assessing fasting glucose in all patients (step one), and subsequently performing an OGTT in patients with impaired fasting glucose (step two).

The screening based on the APA/ADA guidelines detected less than half of the diabetes cases identified by the OGTT, whereas the proposed two-step strategy detected all but 1 diabetes cases. The data also suggested a high incidence of diabetes in patients diagnosed with schizophrenia. **Chapter 7** investigated the early changes in glucose metabolism in a naturalistic sample of patients with schizophrenia newly started on or switched to

specific atypical antipsychotic medication. A significant proportion of these patients (4.4%) developed new-onset diabetes within 3 months. Initiation of clozapine resulted in a significantly higher risk for new-onset glucose abnormalities than initiation of aripiprazole. Furthermore, the evolution of glucose levels was significantly worse in patients initiated on clozapine, olanzapine and quetiapine than in patients initiated on aripiprazole. Clozapine was also significantly more deleterious than risperidone and amisulpride for fasting glucose changes. Type of initiation (start or switch) did not affect any of the metabolic parameters. **Chapter 8** showed that the metabolic syndrome and glucose abnormalities are not only highly prevalent in patients with schizophrenia but also in patients with bipolar disorder, implicating that assessment of metabolic abnormalities should be also part of the clinical management of patients with bipolar disorder.

Chapter 9 summarizes the evidence for and applicability of cognition, stress-sensitivity and metabolic abnormalities as endophenotypes for schizophrenia. The cognitive instability around the first episode of psychosis in subjects with higher premorbid capacities makes the use of cognitive impairments as endophenotypic markers in these subjects potentially problematic, as cognitive assessments in this time-period may reflect illness-related, state-dependent characteristics rather than stable, endophenotypic traits suitable for genetic analyses.

Nevertheless, the global stability of cognitive measures from premorbid level up to at least ten years into the illness suggests that cognition could be a useful endophenotypic trait for genetic analyses, which is underscored by the finding that cognitive measures were able to differentiate between patients with a more neurodevelopmental and a more reactive profile (chapter 2) and had a direct relationship with functional outcome, cross-sectionally as well as prospectively (chapter 3), but only when premorbid or cognitive measures in patients with a certain illness duration were used. With regard to stress-sensitivity, findings show that it is associated with the illness (criterion 1), that it is presumably heritable (criterion 2), that it is state-independent (criterion 3), that it cosegregates with the illness within families (criterion 4) and is also found in a higher rate in unaffected relatives than in the general population (criterion 5). These findings suggest that stress-sensitivity is indeed a useful endophenotype for schizophrenia, although within-person trait-stability, developmental equivalence and test-retest reliability are concerns that need to be addressed in future research. Furthermore, the findings of this thesis suggest that COMT^{Val158Met} is a viable candidate gene for stress-sensitivity in psychosis, that could be related to the development of psychotic and affective symptoms in subjects with a genetic predisposition. Although available literature has found that pathways of glucoregulation could be relevant for the etiology of schizophrenia, findings from this thesis suggest that its peripheral correlates, ie metabolic abnormalities, can not be considered as stable, 'endophenotypic' traits suited for genetic analyses aiming to investigate etiological mechanisms for schizophrenia, given the large and differential impact of atypical antipsychotics on prevalence and incidence rates of metabolic abnormalities, as was demonstrated in chapters 6 and 7. Furthermore, the increase of metabolic abnormalities with age (developmental unequivalence) and the possibility of familial aggregation caused by non-genetic factors such as social class, lifestyle and dietary habits make the use of metabolic abnormalities as endophenotypic measures unfavorable. The implications of these findings, as well as suggestions for future research are given.

SAMENVATTING

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Schizofrenie is wellicht de meest ernstige psychiatrische stoornis en heeft een hoge mate van erfelijkheid. Schizofrenie wordt gekenmerkt door wanen, hallucinaties, verward gedrag, affectvervlakking, verlies van initiatief en sociale terugtrekking. Ook affectieve problemen komen veelvuldig voor. Hoewel er overeenstemming is over de symptomen die voorkomen bij schizofrenie, is het klinisch beeld van individuele patiënten onderling erg verscheiden, hetgeen het zoeken naar causaal betrokken genen bemoeilijkt. Het gebruik van endofenotypes is een relatief recente benadering voor de genetica van complexe stoornissen zoals schizofrenie. Verschillende kenmerken werden al voorgesteld als kandidaat endofenotypes, hoewel het gebruik van de term endofenotype recent ten onrechte uitgebreid werd naar kenmerken die eerder biologische markers dan echte endofenotypes zijn. Daarnaast werden verschillende goede kandidaat endofenotypes nog onvoldoende onderzocht op essentiële kenmerken van een endofenotype. Deze thesis, *Evaluation of candidate endophenotypes for schizophrenia*, evalueert de toepasbaarheid van cognitie, stressgevoeligheid en metabole stoornissen als endofenotypes voor schizofrenie.

Hoofdstuk 1 beschrijft de fenomenologie van schizofrenie en de tot nu toe relatief weinig succesvolle pogingen om risicogenen voor deze aandoening te vinden. Doordat de klassieke methodes weinig succes kenden werden er alternatieve methodes gezocht, zoals studies die zich richtten op gen-omgevingsinteracties en op continue, endofenotypische maten in plaats van op de aan- of afwezigheid van een bepaalde stoornis. Het concept endofenotype wordt geïntroduceerd, als zijnde quantificeerbare kenmerken die intermediair zijn tussen genen en gedrag. Vijf criteria onderscheiden endofenotypes van gewone biologische markers: 1. ze zijn geassocieerd met de ziekte, 2. ze zijn erfelijk, 3. ze zijn onafhankelijk van de fase van de ziekte, 4. ze segregeren samen met de ziekte binnen families en 5. endofenotypes worden in gezonde familieleden in verhoogde mate gevonden in vergelijking met de algemene bevolking. Gebaseerd op deze criteria en op de beschikbare literatuur voor de kandidaat endofenotypes worden vervolgens een aantal specifieke onderzoeksvragen geformuleerd. *Voor cognitieve stoornissen* was het doel om het verloop van IQ als globale maat voor cognitie te onderzoeken bij eerste episode patiënten, en met name mogelijke verschillen in het verloop van IQ die onderliggend zouden kunnen zijn aan onderliggende fenotypische heterogeniteit. Een tweede doelstelling was om de relatie tussen IQ en outcome te onderzoeken in deze patiëntengroep. *Voor stressgevoeligheid* was het doel om te onderzoeken of een kandidaat genetisch polymorfisme in het COMT gen, COMT^{Val158Met}, de psychotische en affectieve reacties op stress in het dagelijkse leven zou modereren bij patiënten met psychose en bij gezonde proefpersonen, en of deze mogelijke moderatie ook causaal betrokken zou kunnen zijn bij de ontwikkeling van psychose. *Voor metabole stoornissen* waren de doelstellingen om twee verschillende guidelines voor het opsporen van diabetes bij schizofrene patiënten te evalueren. Verder waren doelstellingen om de vroege veranderingen na het opstarten van een atypisch antipsychoticum te belichten en om ook de prevalentie van metabole stoornissen bij bipolaire patiënten te onderzoeken.

Vertrekkende vanuit deze specifieke onderzoeksvragen wordt in **Hoofdstuk 2** het longitudinale verloop van IQ in eerste episode patiënten beschreven. Na tien jaar opvolging was er geen evidentie voor een afname van IQ. De hypothese dat geschat premorbid IQ het verloop van IQ zou modereren werd bevestigd. Dichotomizatie maakte duidelijk dat in de groep met het hoogste IQ, die verondersteld werd om het ‘episodische subtype’ te vertegenwoordigen, IQ niet stabiel bleef gedurende de periode van opvolging. Een significante daling van IQ bij de eerste opname werd gevolgd door een verbetering tot op het premorbide niveau. Bij de groep met het laagste IQ, die verondersteld werd om het ‘neurodevelopmental subtype’ te vertegenwoordigen, werd daarentegen wél een stabiel IQ gemeten. **Hoofdstuk 3** onderzocht of er een verband was tussen cognitie en outcome bij deze patiënten. De aanwezigheid van zowel een prospectief als een cross-sectioneel verband tussen IQ en de outcome na 10 jaar kon worden aangetoond. Daarentegen werd opgemerkt dat er geen verband was tussen IQ gemeten bij de eerste episode en outcome na tien jaar. Deze bevindingen zouden de controverse in de literatuur over een mogelijk prospectief verband tussen cognitie en outcome kunnen verklaren.

In **Hoofdstuk 4** wordt beschreven dat cannabis gebruikende patiënten met psychose sterker op stress reageren dan gezonde cannabis gebruikers. Verder was er ook bewijs voor een interactie tussen stress in het dagelijkse leven en COMT^{Val158Met} op psychotische en affectieve symptomen, waarbij patiënten met het *Met/Met* genotype de grootste toename van symptomatologie vertoonden. In **Hoofdstuk 5** werd de hypothese getest dat het COMT^{Val158Met} *Met* allel causaal verbonden is met de mogelijke ontwikkeling van affectieve en psychotische symptomen bij mensen die een genetisch risico op schizofrenie hadden, namelijk eerstegraads familieleden van patiënten met schizofrenie. Wanneer familieleden een *Met* allel deelden, was er een significante concordantie van subklinische symptomatologie. Dit was niet het geval wanneer familieleden geen *Met* allel deelden, wat een mogelijke betrokkenheid van dit allel in het ontstaan van psychopathologie suggereert, tenminste bij mensen met een genetische predispositie voor psychose.

In **Hoofdstuk 6** worden de diagnostische eigenschappen van twee screenings guidelines voor de opsporing van diabetes bij patiënten met schizofrenie met elkaar vergeleken: 1) het bepalen van een nuchtere glycemie bij alle patiënten, zoals wordt voorgesteld door de American Psychiatric Association/American Diabetes Association (APA/ADA) en 2) een screenings strategie afgeleid van de guidelines van het WHO, namelijk het bepalen van een nuchtere glycemie bij alle patiënten (1^e stap) en het vervolgens doen van een Orale Glucose Tolerantie Test (OGTT) bij patiënten met een verstoorde nuchtere glycemie. (2^e stap). De screening gebaseerd op de guidelines van de APA/ADA detecteerde diabetes in minder dan de helft van de gevallen die werden geïdentificeerd door middel van de OGTT, terwijl de tweestapsstrategie op één na alle gevallen van diabetes detecteerde. Ook werd er een hoge incidentie van diabetes gevonden in deze studie. **Hoofdstuk 7** belicht de vroege veranderingen in glucosemetabolisme bij patiënten bij wie een atypisch antipsychoticum werd opgestart. Een behoorlijk percentage van deze patiënten ontwikkelde diabetes binnen de drie maanden na het opstarten van het antipsychoticum (4.4%). Het opstarten van clozapine gaf een significant hoger risico op het ontwikkelen van diabetes dan aripiprazole. Clozapine, olanzapine en quetiapine hadden ook een significant

slechter effect op glucosespiegels dan aripiprazole. Daarnaast was clozapine ook slechter dan risperidone en amisulpride met betrekking tot de evolutie van nuchtere glycemie. **In Hoofdstuk 8** werd aangetoond dat het metabool syndroom en glucose afwijkingen niet alleen vaak voorkomen bij patiënten met schizofrenie maar ook bij mensen met bipolaire stoornis, wat betekent dat de evaluatie van deze metabole stoornissen ook onderdeel zou moeten zijn van de behandeling van mensen met een bipolaire stoornis.

In Hoofdstuk 9 wordt de evidentie en toepasbaarheid van cognitie, stressgevoeligheid en metabole stoornissen als endofenotypes voor schizofrenie samengevat. De cognitieve instabiliteit rondom de eerste psychotische episode bij patiënten met een hoger premorbid IQ maakt het gebruik van cognitieve stoornissen als endofenotypische markers potentieel problematisch, omdat in tegenstelling tot de vereisten voor een endofenotype, cognitie gemeten in deze periode niet stabiel en betrouwbaar is. Dit terwijl cognitie op langere termijn, namelijk van voor de ziekte tot tenminste tien jaar na aanvang, juist wél stabiliteit vertoont. Dit suggereert dat cognitie wél een goede endofenotypische marker zou kunnen zijn, hetgeen versterkt wordt door de bevinding dat cognitieve maten in staat waren om te differentiëren tussen patiënten met een meer ‘neurodevelopmental’ profiel en patiënten met een meer ‘episodisch’ profiel (Hoofdstuk 2), en ook een direct verband vertoonden met outcome, zowel cross-sectioneel als prospectief (Hoofdstuk 3). De bevindingen met betrekking tot stressgevoeligheid toonden aan dat stressgevoeligheid geassocieerd is met de ziekte (1^e criterium), dat het vermoedelijk genetisch is (2^e criterium), dat het onafhankelijk is van het stadium van de ziekte (3^e criterium), dat het met de ziekte cosegregeert binnen getroffen families (4^e criterium) en dat het in verhoogde mate wordt gevonden in eerstegraads familieleden dan in de algemene bevolking (5^e criterium). Deze bevindingen suggereren inderdaad dat stressgevoeligheid een goed endofenotype zou kunnen zijn voor schizofrenie, hoewel de stabiliteit binnen personen, test - hertest betrouwbaarheid en de invloed van leeftijd nog nader onderzoek behoeven. De bevindingen tonen ook aan dat COMT^{Val158Met} mogelijk betrokken is bij verhoogde gevoeligheid aan stress en het ontwikkelen van symptomatologie. Hoewel er literatuur is die heeft aangetoond dat pathways van glucoregulatie mogelijk relevant zijn voor de etiologie van schizofrenie, tonen de bevindingen van deze thesis dat de perifere correlaten hiervan – metabole afwijkingen – geen stabiele, ‘endofenotypische’ kenmerken zijn die geschikt zijn voor genetische analyses naar schizofrenie, gezien de grote en differentiële impact van atypische antipsychotica op prevalentie- en incidentiecijfers van diabetes en andere metabole stoornissen, zoals werd aangetoond in hoofdstukken 6 en 7. Daarnaast maakt de toename van metabole stoornissen met de leeftijd en de mogelijkheid dat niet-genetische de familiale aggregatie van metabole stoornissen veroorzaken het gebruik van metabole stoornissen als endofenotypische maat onwenselijk. De implicaties van deze bevindingen, alsmede suggesties voor toekomstig onderzoek worden besproken.

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CURRICULUM VITAE

Ruud van Winkel werd geboren op 20 april 1976 in Weert, Nederland. Na de middelbare school in Hamont-Achel (België) startte hij in 1994 de opleiding tot Arts aan de Katholieke Universiteit van Leuven, waarin hij met onderscheiding afstudeerde in 2001. Vanaf 1997 studeerde hij daarnaast ook Familiale en Seksuologische Wetenschappen aan diezelfde Universiteit, waarin hij in 2001 ook met onderscheiding afstudeerde. Nadien startte hij zijn opleiding tot psychiater. Na stages in Munsterbilzen, Maastricht en Kortenberg rondde hij deze opleiding medio 2006 af. De contacten met Maastricht in zijn tweede stagejaar resulteerden in een blijvende samenwerking. Hij coördineerde in nauwe samenwerking met de Universiteit Maastricht het project ‘Geestkracht’ binnen het Universitair Centrum in Kortenberg, wat uiteindelijk uitmondde in een promotietraject aan de Universiteit Maastricht. Inmiddels is hij als Adjunct Kliniekhoofd verbonden aan het Universitair Psychiatrisch Centrum van de Katholieke Universiteit Leuven, waar hij werkzaam is in de psychosoziale zorg op campus Kortenberg, en is hij verantwoordelijk psychiater van een Centrum voor Geestelijke Gezondheidszorg in Aarschot. Daarnaast zal hij als Honorair Docent verbonden blijven aan de Universiteit Maastricht bij de Capgroep Psychiatrie en Neuropsychologie.

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