Studies of the affective and developmental domains of psychopathology in psychosis

Citation for published version (APA):

Kaymaz, N. (2011). *Studies of the affective and developmental domains of psychopathology in psychosis*. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20110622nk>

Document status and date:

Published: 01/01/2011

DOI:

[10.26481/dis.20110622nk](https://doi.org/10.26481/dis.20110622nk)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
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STUDIES OF THE AFFECTIVE AND DEVELOPMENTAL DOMAINS OF PSYCHOPATHOLOGY IN PSYCHOSIS

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ISBN 978 90 75579 529

Cover illustration: 'Mijn hersenspinsels en gedachtecronkels' by Ziad Haider.

Ziad Haider werd in 1954 geboren in Amara, een stad in het zuiden van Irak, gelegen aan de Tigris, zo'n 200 kilometer ten zuiden van Bagdad. In 1972 ging studeren aan de Academie voor Schone Kunsten in Bagdad. In 1992 ontvluchtte hij Irak. Voor vijf jaar verbleef hij achtereenvolgens in Syrië en Jordanië, totdat hij in 1997 als vluchteling aan Nederland werd toegewezen. Vanaf zijn komst naar Nederland in 1997 exposeerde hij ondermeer in België, Finland en Polen.

Het thema van zijn werk is de onzichtbare erfenis. De blijvende erfenis van de ervaring die in mensen besloten ligt.

Ziad schilderde van binnen uit, vertaalde in kleur en beeld dat wat mensen beleven.

Het leven van het individu en een volk. Ziad Haider is in 2006 in Amsterdam overleden.

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STUDIES OF THE AFFECTIVE AND DEVELOPMENTAL DOMAINS OF PSYCHOPATHOLOGY IN PSYCHOSIS

ACADEMIC DISSERTATION

to obtain the degree of Doctor
at Maastricht University,
on the authority of the Rector Magnificus,
Prof. dr. G.P.M.F. Mols,
in accordance
with the decision of the Board of Deans,
to be defended in public on
22nd June 2011 at 14.00 hours

by

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CHAPTER 1

Introduction

Ever since Kraepelin separated the classification of psychotic illnesses into dementia praecox and manic-depressive insanity, there has been controversy over whether these two disorders – now referred to as schizophrenia and bipolar disorder¹ – are really distinct from each other. From a clinical perspective, the disorders may be distinguishable, more specifically in their seldom occurring pure forms, but there are no pathognomonic symptoms to differentiate them. During an exacerbation of bipolar disorder, many patients have *first rank* symptoms of schizophrenia in the form of characteristic delusions and hallucinations, and many patients with schizophrenia have symptoms of depression and mania. Current psychiatric nosology classifies schizophrenia and bipolar disorder as two distinct diagnostic categories with presumed independent aetiologies. There are, however models that challenge the traditional explanations of the aetiology of psychosis. One view is the categorical approach and the conceptualization of these as two distinct disorders in the classification systems of the American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders (DSM) and the World Health Organization: International Statistical Classification of Diseases and Related Health Problems (ICD). The categorical approach is highlighted below for the two main disorders we focused on in this thesis: schizophrenia and bipolar disorder. The alternative view is that the different clinical forms of psychosis represent a continuum, with schizophrenia representing expressions at the most extreme end of the spectrum (Crow TJ, 1986) and schizoaffective disorder embodying the solution for the diagnostic conundrum induced by the considerable overlap between these disorders (Fig. 1). The main assumptions within the continuum theory are: 1) all diagnoses of psychotic disorder share genetic causes and, 2) the disorders show continuity not only with each other, but also with normal mentation in the general population. Thus, the notion of a continuum in this thesis is used to denote a continuum of disorders within the clinical population as well as a continuum of expression of psychosis across clinical and non-clinical populations.

A debate currently persists regards the merit of old diagnostic traditions in psychiatry. It is becoming clear that the strict separation of diagnostic entities set forth by the DSM and ICD classification systems has resulted in major missed opportunities to study the causes and treatments of psychiatric disorders. Most of the symptom domains, whether it is psychosis, mania, depression, cognitive impairment or negative symptoms, are found across the entire psychosis spectrum, which includes all non-affective and affective psychotic disorders. An elegant way of dealing with the discussions of categorical versus dimensional/continuum theory is by simply adding the dimensional indicators mentioned above to the categorical system, as it is depicted in Figure 1. In doing so, the basis for a new cross-diagnostic approach in psychiatry may be laid.

¹ The term *bipolar disorder* replaced name *manic-depressive disorder* in the American Psychiatric Association's DSM-III published in 1980.

Figure 1 Three hypothetical patients diagnosed using a combination of categorical and dimensional representations. The categorical diagnoses of schizophrenia, bipolar disorder and schizoaffective disorder are accompanied by the patients' quantitative scores (connected by red lines) on five main dimensions (psychosis, negative symptoms, cognitive impairment, depression and mania) of psychopathology (Kaymaz et al., 2009 and Van Os & Kapur, 2009).

In this thesis, we approached affective and non-affective psychotic disorders as entities pertaining to a multidimensional syndrome. Most of the studies in this thesis focused on schizophrenia as an example of non-affective psychotic disorder, and bipolar disorder as an example of affective psychotic disorder. We examined the epidemiological and genetic overlap between the two constructs by focusing on developmental and affective domains, and by examining how this is applicable to the ontogenesis of disorder, i.e. in the prodromal stage as well as in the context of prediction. We also investigated how the symptom dimensions found in affective and non-affective psychotic disorders co-vary with and affect each other at the subclinical and clinical level.

General background information on bipolar disorder and schizophrenia Bipolar Disorder (type I and type II)

Bipolar disorder is a chronic disorder associated with episodic extremes in mood, varying from depressive episodes to hypomanic (type II) or manic (type I) episodes. Patients may still experience residual symptoms in the periods between alternations of depressive and manic episodes, or between depressive and hypomanic episodes². The longitudinal outcome of bipolar disorder is defined by recurrent manic and/or depressive mood episodes. These mood episodes have a severe impact on the lives of patients and their families, including job performance, personal relationships and responsibilities. Most of the studies have focused on the syndromal outcome of treatment of patients with bipolar disorder and less on the

² Mania and depression can co-occur in a mixed state.

functional outcome. A study by Strakowski et al. (1998) showed a 61% syndromal recovery for bipolar disorder 12 months after hospitalization, whereas functional recovery was reported to be 36%. In a recent naturalistic study in bipolar I disorder, these numbers were 87.5% and 53.5%, respectively (Montoya et al., 2010).

Restoration of pre-episode quality of life and level of functioning is of primary importance in the treatment of bipolar disorder. In contrast to schizophrenia, very little is known about the basic clinical epidemiology of bipolar disorder. Studies on the incidence rates of bipolar disorder report rates varying from 1.7 to 4.5 for every 100,000 people per year (Lloyd et al., 2005; Ketter TA, 2010). Studies to date may have underestimated true incidence of the disorder. Earlier studies showed little age difference between men and women at onset, but more recent studies, using more strict operational criteria, have tended to show a later onset in women (Arnold LM, 2003; Ketter, 2010). It is also uncertain whether migrants have a higher incidence of bipolar disorder as well as of schizophrenia; although, earlier incidence studies have suggested that this may be so (Der & Bebbington, 1987; Van Os et al., 1996). The prevalence rates vary from 0.5%-5.5% (Angst J, 1998), indicating a broad range possibly due to variances in the populations studied, but also due to the operationalisation and course of the illness (Bebbington & Ramana, 1995) and overlap with other psychiatric disorders (Krishnan, 2005), which all make the diagnosis of bipolar disorder difficult.

Reported rates of bipolar syndromes are highly variable between studies because of age differences, differences in diagnostic criteria or restriction of sampling to clinical contacts. In a study of 1395 adolescents fourteen to seventeen years of age, Tijssen et al. (2010) measured DSM-IV hypomanic and manic episodes (in combination), use of mental health care and five ordinal subcategories representing the underlying continuous score of hypomanic and manic symptoms³ at baseline and approximately at 1.5, 4 and 10 years later. Incidence rates (IR) of mania and hypomania, defined both as DSM-IV episodes and as at least one DSM-IV core symptom were far higher than traditional estimates. In addition, independent of childhood disorders such as attention deficit hyperactivity disorder (ADHD), the risk of developing hypomanic or manic episodes was very low after reaching twenty-one years of age. Most individuals with hypomanic and manic episodes were never in care (87% and 62%, respectively) and did not present with comorbid depressive episodes (69% and 60%, respectively). The probability of mental health care usage increased linearly with the number of symptoms on the mania symptom scale. The incidence of the bipolar categories, in particular at the level of clinical morbidity, was strongly associated with previous childhood disorders and male gender. Therefore, this was the first time a study showed that experiencing hypomanic or manic symptoms is a common adolescent phenomenon that *infrequently* predicts the use of mental health care. The findings suggest that the onset of bipolar disorder can be elucidated by studying the pathway from non-pathological behavioural expression to dysfunction and the need for care (Regeer et al., 2009). This is similar to findings reported in non-affective psychosis, which studies have shown also appears as a distribution in the general population (Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009).

³ Tijssen et al. (2010) used a 'mania symptom scale' based on the CIDI.

Schizophrenia

Schizophrenia is a major mental illness that frequently runs a chronic course, despite the enormous therapeutic advances from the new findings in research, which look not only at the aetiological findings, but also at the protective factors. Schizophrenia manifests itself during late adolescence or early adulthood and has profound effects, not only because of the direct and substantial suffering for the patients but also for their relatives (Sheitman et al., 1997; De Mamani AG, 2010). The symptoms of schizophrenia can be characterized by making a distinction between *positive symptoms* and *negative symptoms*. Positive symptoms refer to the abundance or distortion of normal behaviour. These symptoms are *hallucinations* such as hearing voices, or *delusions*, like believing one's thoughts are controlled by an external force. *Bizarre behaviour* caused by delusions and hallucinations and *formal thought disorder* (incoherence of speech) are also positive symptoms. Negative symptoms refer to the reduction of normal functions. The negative symptoms consist of flat affect expressed with a monotonous voice or immobile facial expression, avolition⁴ or apathy⁵, alogia⁶ and anhedonia⁷ (Andreasen NC, 1985).

The positive symptoms of schizophrenia are potentially responsive to or reversible with antipsychotic medicinal treatment. Negative symptoms, however, are usually stable or even progressive over time and relatively irreversible. The negative symptoms are associated with poor outcome in the long term. The clinical presentation of the disorder is heterogeneous. Either the positive symptoms or the negative symptoms predominate in patients. The onset of negative symptoms tends to occur about five years before the initial psychotic episode, with onset of positive symptoms much closer to the time of first hospitalization (Häfner et al., 1999).

The course of the disorder is also variable. Some patients are left with mild exacerbations of symptoms, while severe cases can involve persistent symptoms that result in hospitalization or even permanent hospitalization.

The estimated life risk varies strongly with the presence or absence of certain risk factors, which are called environmental risk factors, and is on average 1% (Mueser & McGurk, 2004). It seems to occur almost one and a half times more in men than in women (Aleman et al., 2003).

The symptoms of the disorder were first clustered and described by Kraepelin, who called the illness *dementia praecox* in 1919. 'Dementia' refers to the clinical and cognitive deterioration that progresses during the course of the disease, and 'praecox' refers to the early onset of the symptoms of the illness. Bleuler, on the other hand, did not agree with Kraepelin that schizophrenia always had an early onset and that there was an inevitable deterioration in the course of the illness. In turn, he emphasized some core symptoms of the disorder such as the loss of goal-directed behaviour, difficulties in thinking straight and flattening of affect. Bleuler later named the disorder 'schizophrenia' in 1923, referring to the disintegration of personality that could occur in patients. Since then, many attempts have been made to redefine the diagnostic criteria of schizophrenia, resulting in the development of several diagnos-

⁴ lack of desire, drive, or motivation to pursue meaningful goals

⁵ a state of indifference or the suppression of emotions

⁶ poverty of speech

⁷ inability to experience pleasurable emotions

tic classification systems, such as the American Psychiatric Association's Diagnostic and Statistical Manual (DSM) and International Classification of Diseases (ICD; World Health Organization, 1992). Today, we are moving from the DSM-IV-TR definition of schizophrenia as a chronic disorder characterized by psychotic episodes and a decline in social and occupational functioning toward developing the DSM-V, with the possible inclusion of new diagnostic entities such as 'Attenuated Psychotic Symptom Syndrome'. Another major development is that researchers and clinicians in psychiatry are critical about these classification systems. They are posing alternative views about categorical systems and introducing dimensional systems. They are also critical about the term schizophrenia (Van Os J, 2009) and opt to redefine it, as has already been done in Japan in 2006 with '*Integration Dysregulation Syndrome*'. As mentioned earlier, there is evidence that the symptoms of schizophrenia are also expressed at subclinical level in the general population and form part of a continuum (Kaymaz & Van Os, 2010; Linscott & Van Os, 2010; Van Os et al., 2009).

Aetiology of schizophrenia and bipolar disorder; similarities and dissimilarities

For more than a century, it has been uncertain whether schizophrenia and bipolar disorder are distinct disease entities with specific genetic and/or environmental causes and neuro-anatomical substrates. Several studies have published evidence from their particular perspective, challenging this dichotomy between the *categorical view*, which relies on the assumption that both diseases are distinct diagnostic entities, and the *continuum theory* or the *dimensional view*, which points out that there is little evidence for any risk factor, symptom, treatment or course type being specific to any diagnostic category within the functional psychosis (Van Os et al., 1999). It also promotes the idea that different forms of psychosis represent a continuum of disorders with schizophrenia at the most severe end of the spectrum (Crow TJ, 1986).

From a clinical perspective, there are no sharp symptomatic distinctions between the two disorders. Indeed, one piece of evidence for the overlap at the clinical level is the invention of the diagnosis schizoaffective disorder, manic type, which is a diagnosis of a psychopathological state that lies in between bipolar disorder and schizophrenia in terms of clinical symptomatology, showing both psychotic and mania symptoms. Patients with acute mania often display Schneiderian first rank symptoms, such as auditory hallucinations, broadcasting of thoughts, controlled thoughts (delusion of control) and delusional perception (WHO, 1973). Patients with depressive psychosis have delusions and hallucinations (Kendell & Gourlay, 1970; Shergill et al., 1999). Many patients with schizophrenia show symptoms of mania and depression, and in 75% of cases, patients with schizophrenia have depression symptoms during their first schizophrenic episode (Koreen et al., 1993; Häfner et al., 1999). These early affective symptoms are often an early expression of an underlying schizophrenia process, or in some cases, they are viewed as an additional factor that precipitates the onset of psychosis in those who are biologically predisposed (Chadwick & Birchwood, 1994). There are follow-up studies showing that in initially non-psychotic people experiencing auditory hallucinations, those who become depressed have a higher probability of subsequently developing

psychotic disorders needing treatment than do those who do not become depressed (Escher et al., 2002a, 2002b; Krabbendam et al., 2004). Depression precedes the onset of mania in many cases of bipolar disorder. Other overlapping characteristics between bipolar disorder and schizophrenia are at a young age at the time of onset of the disorders, which is slightly earlier in males (Frangou et al., 2002; Kennedy et al., 2002) and they have a frequent occurrence of life events prior to the onset or relapse of illness (Ventura et al., 1989; Bebbington et al., 1993).

As for the question as to whether or not there is *familial co-aggregation* between bipolar disorder and schizophrenia, family studies consistently have shown that the first-degree relatives of *probands* who had schizophrenia are at an increased risk for schizophrenia, schizoaffective disorder and schizotypal personality disorder. Similarly, family studies have also revealed that first-degree relatives of bipolar probands are at an increased risk of developing bipolar disorder, schizoaffective disorder and unipolar depression (Taylor MA, 1992; Faridi et al., 2009). However, whether there is a cross-disorder familial risk for bipolar disorder and schizophrenia has been controversial. Inadequate sample sizes in the studies and low statistical power may have contributed to this lack of evidence. The familial aggregation of schizophrenia with itself is expected to be greater than its co-aggregation with bipolar disorder, however, most studies have examined the co-aggregation of schizophrenia or bipolar disorder with itself and few studies have examined their co-aggregation. One of the largest family studies to date used the Swedish inpatient register and found over 13,000 cases with schizophrenia and 5000 with bipolar disorder. Cross-disorder incidence ratios were clearly increased for both full and half siblings, providing evidence for familial co-aggregation between schizophrenia and bipolar disorder (Osby et al., 2001). The study by Lichtenstein et al. (2009) on the same extended sample shows similar findings. In this study, the question of whether schizophrenia and bipolar disorder are the clinical outcomes of discrete or shared causative processes was investigated by assessing the genetic and environmental contributions to liability for schizophrenia, bipolar disorder and their comorbidity by using data from a multi-generation register. First-degree relatives of probands who had either schizophrenia or bipolar disorder were at increased risk of these disorders. Half siblings had a significantly increased risk, but substantially lower than that of the full siblings. When relatives of probands who had bipolar disorder were analysed, increased risk for schizophrenia existed for all relationships, including adopted children to biological parents with bipolar disorder. Heritability for schizophrenia and bipolar disorder was 64% and 59%, respectively. Shared environmental effects were small but substantial for both disorders. The comorbidity between these two disorders was mainly due to additive genetic effects common for both disorders. This study shows, similar to molecular genetic studies, that schizophrenia and bipolar disorder partly share a common genetic cause. Another meta-analytic study carried out by Van Snellenberg & De Candia (2009) found familial aggregation between these two disorders, which supports the continuum model.

Twin studies show that the siblings of index twins with schizophrenia show a similar prevalence of affective disorder and schizophrenia, while their parents were more likely to suffer affective disorder than schizophrenia (Shields & Slater, 1975). A study by McGuffin et al. (1982) showed that in case of identical triplets, two diagnosed with schizophrenia and the third with bipolar disorder, highlighted how the same genetic makeup could result in diverse forms of psychosis. The study by Cardno et al. (2002) showed substantial cross diagnosis

concordance for monozygotic twins and modest concordance for dizygotic twins. Common genetic contributions as well as diagnosis-specific genetic contributions to the variance in liability to schizophrenia and mania were found using model-fitting techniques. However, diagnosis-specific genetic effects were not found for schizoaffective disorder. The study by Cardno et al. (2002) shows a significant overlap in the genes contributing to schizophrenia, schizoaffective disorder and mania.

Both schizophrenia and bipolar disorder have high *heritability estimates* of around 80%-90% (Cardno et al., 2002; McGuffin et al., 2003). There is evidence for an overlap in familial susceptibility for bipolar disorder and schizophrenia, but there is still a remaining question as to whether the origin of this overlap is due to *genetic overlap*, an *overlap in causal factors (environmental factors)* or to a *genetic and environmental (GxE) interaction*. If the overlap is of genetic origin, molecular genetic studies should report loci in common. Over the past 20 years, numerous genome scans have been carried out to search the susceptibility genes for both schizophrenia and bipolar disorder: their consistent findings have generated some confusion. Due to power limitations, few studies exceed the genome-wide significance levels and attempts to replicate a specific finding require even larger samples. In a study by Badner & Gershon (2002), all the published genome-wide scan studies up until 2002 were identified. The most significant linkage zone for both schizophrenia and bipolar disorder were the two zones on chromosome 13q and 22q.

They concluded that these two regions were likely to harbour susceptibility loci common to these two disorders. A year later, Lewis et al. (2003) published a meta-analysis on the same subject and found a number of candidate regions for either schizophrenia or bipolar disorder, but found no overlap of susceptibility regions between the two disorders. These conflicting results between the two meta-analyses, published only one year apart, may be due to the differences in statistical methodology and in the selection of datasets. However, irrespective of the outcome, the genomic regions covered are large and therefore some overlap in these zones does not necessarily mean that the same genes are involved in both disorders. However, more studies should be carried out that examine evidence for genetic overlap between these two disorders. In a study by Fallin et al. (2005), six genes (DPYSL2, DTNBP1, G30/G72, GRID1, GRM4 and NOS1) showed overlapping suggestive evidence for association in both disorders.

Unfortunately, many of the molecular genetic findings in schizophrenia and bipolar disorder have not been replicated consistently. The allelic association at the ZNF804A locus is now one of the most compelling in schizophrenia to date. In a recent study by Williams et al. (2010), the authors provided additional evidence for association through meta-analysis of a large data set patients with schizophrenia/schizoaffective disorder (N = 18,945), schizophrenia plus bipolar disorder (N = 21,274) and controls (N = 38,675) and their data supports the suggestion of overlapping genetic risk between schizophrenia and bipolar disorder. In a recent study by Grozeva et al., (2010), who investigated the overlap in Copy Number Variations (CNV) between schizophrenia and bipolar disorder, it was found that schizophrenia and bipolar disorder differ with respect to CNV burden in general and association with specific CNVs in particular. Their data are consistent with the possibility that possession of large, rare deletions may modify the phenotype in those at risk of psychosis. They suggested that those possessing such events are more likely to be diagnosed with schizophrenia, i.e. psychotic disorder with a sizeable neurodevelopmental component. Those without them are more

likely to be diagnosed with bipolar disorder, i.e. psychotic disorder without a neurodevelopmental component.

Although the genome-wide association studies (GWAS) are widely used in an attempt to unravel the genetics of psychiatric disorders, in particular schizophrenia, findings are not conclusive and explain only a fraction of the heritability. The number of studies reporting new candidate genes for schizophrenia and for brain structures is expanding; however, there are conflicting results regarding consistency. As linkage analysis and candidate gene hunting have resulted in a new gene almost on a daily basis, all hope was put on GWAS, with inclusion of many thousands of participants, as a result of collaboration of multiple centres across the world. Recent papers on genetic findings in schizophrenia, by Ingason et al. (2010) and by Stefansson et al. (2009) showed associations with several markers; these, however continue to explain only a fraction of the observed heritability. The influence of CNVs also does not necessarily conform to classical nosological disease boundaries in that some CNVs increase risk across a range of neurodevelopmental psychiatric disorders.

As for *brain abnormalities* being considered neurobiological markers of brain dysfunction and seen by many as reflecting the genetic basis to these disorders, i.e. representing endophenotypes; these are presumed to be more proximal to the actions of genes than the clinical syndrome. The endophenotype approach can be used to study the variation among candidate neurobiological markers in subjects with increasing genetic risk. The brain abnormalities have been studied more in schizophrenia than in bipolar disorder and are thought to represent an endophenotype because they are heritable, measurable in both affected and unaffected subjects, manifest whether or not the illness is active, associated with the illness in the general population and found more frequently in the unaffected relatives of patients than controls (Leboyer et al., 1998; Gottesman & Gould, 2003). The research of brain abnormalities in subjects with bipolar disorder and their relatives is less active compared to schizophrenia. Brain imaging studies in schizophrenia have consistently shown reduced whole brain volume as well as enlarged lateral and third ventricles (Wright et al., 2000). In a study by Hoge et al. (1999), seven studies were reviewed which had examined brain size in patients with bipolar disorder and controls and they reported that there were no differences. These findings were similar to those in the study by McDonald et al. (2004). However, in a recent meta-analysis brain changes in bipolar disorder (Arnone et al., 2009) were compared to the brain changes in schizophrenia; the main conclusions were that individuals with bipolar disorder are characterized by significant whole brain and prefrontal lobe reductions and by enlargement of the lateral ventricles and globus pallidus. These findings did not distinguish bipolar disorder from schizophrenia, although schizophrenia was characterized by a greater degree of ventricular enlargement and amygdala volume reduction. The authors concluded that because no such reduction was found in the two previous meta-analyses by Hoge et al. (1999) and McDonald et al. (2004), which encompassed 7 and 11 studies, respectively, the presence of a small effect might require a larger pool of studies to allow detection. The individuals with schizophrenia showed a greater ventricular enlargement compared to those with bipolar disorder. The similarities in the brain changes, but also the differences (greater enlargement of the ventricles in schizophrenia) between bipolar disorder and schizophrenia can be perceived as evidence that they represent the same disorder with a different severity or, less parsimoniously, as two separate processes with a similar outcome.

Objectives and outline of this thesis

In this thesis, several studies are described concerning the *developmental* and *affective* aspects of schizophrenia and bipolar disorder, in terms of where they differ and overlap, and how that potentially overlaps in the *prodrome*. The genetic and environmental factors, shared by these two disorders, were investigated. We also examined evidence for the conceptually different models, from an aetiological perspective, of the categorical (point of rarity, developmental specificity) versus the continuum view (mean differences, no specificity) of bipolar disorder and schizophrenia. In addition, in the search for evidence for aetiological models explaining psychotic disorders, it is necessary to discuss the diagnostic implications of differences in developmental and non-developmental risks across the categories. A literature search of studies concerning these issues was carried out and data was extracted from published work.

One of our publications, the meta-analysis on the maintenance treatment of depression, may be considered an outlier within the global objectives and themes of this thesis. However, our approach to psychosis is one of a multidimensional syndrome, with depression being one of the main symptom dimensions (see Figure 1 above). The presence of affective symptom dimensions increases the probability of early relapse of psychotic disorders and their presence in the prodromal phase may act as a risk factor for transition to psychosis later in life (Strakowski et al., 1995; Bechdolf et al., 2002; Lewandowski et al., 2006). Therefore, the goal of the meta-analysis was to investigate if there is a difference in sensitivity to treatment between first and recurrent episodes of a major depressive disorder. One of our hypotheses was that recurrent depressive patients would have higher relapse rates and would benefit less from the protective effects of antidepressants. If confirmed, the next question is if this can be explained by the behavioural sensitisation model. There is evidence (Post RM, 1992) for behavioural sensitisation in the course of affective illness and Post emphasized the importance of preventing episodes of depression by preventing relapses by prophylactic treatment to inhibit sensitisation. According to the sensitisation model, a subgroup of patients exists, that becomes more vulnerable or sensitised to affective episode precipitants with each recurrent episode. For example, in cases of anticipated stresses or imagined losses, if sufficiently conditioned, the behavioural, physiologic and biochemical alterations usually associated with an affective episode might be produced. It may also explain how stress-induced mood alterations might become so sensitised that they also occur spontaneously. The behavioural sensitisation model may not only be applicable to depression but also to other symptom dimensions, such as psychosis or other psychotic disorders in which depression is a main component, such as bipolar disorder and schizophrenia. Indeed, there is more and more evidence from the literature that behavioural sensitisation plays an important role in relapses of psychoses.

Developmental domains

Developmental impairments, during childhood, preceding the onset in schizophrenia in late adolescence, have been documented extensively for schizophrenia, specifically in the domains of cognition, language, motor performance, social, emotion and behaviour (Jones et al., 1994; David et al., 1997; Cannon et al., 2002; Blanchard et al., 2010). For affective psychosis, broadly defined, there has been some documentation of developmental impairments,

but the effects are not as strong as they are for schizophrenia (David et al., 1997; Van Os et al., 1997; Crow et al., 1995) and they seem to be present only in early onset cases (Van Os et al., 1997). Only a few studies have investigated the childhood development preceding bipolar disorder or mania. In the Dunedin birth cohort (Cannon et al., 2002), one of the larger prospective studies in this area, children who later met criteria for schizophrenia had shown developmental impairment in all domains tested. This was in contrast to children who later developed mania, who showed difficulties in social, behavioural, and emotional development, but not in motor, language or cognition. They even showed better childhood motor performance than the control group (Cannon et al., 2002). It seems that emotional and interpersonal difficulties in childhood reflect a general predisposition to adult psychiatric illnesses, but that early developmental impairments in psychomotor, language and cognitive function show some specificity to schizophrenia outcomes and are not seen in those who later develop bipolar disorder. One explanation is that genes responsible for these developmental impairments are associated with schizophrenia (Jones & Murray, 1991), but not with bipolar disorder, or, that there is a differential occurrence of early environmental insults in those two disorders (Murray et al., 2004).

In **Chapter 2**, the neurodevelopmental component, in relation to genetic factors, was investigated in the disorder most strongly associated with developmental impairment, e.g. schizophrenia. In addition, the degree to which developmental factors discriminate between schizophrenia and bipolar disorder was examined, and to what extent it may be expected that these psychotic phenotypes are distributed categorically or dimensionally.

The *first* article, ***'Heritability of structural brain traits; an endophenotype approach to deconstruct schizophrenia'***, focuses on the heritability of brain structures, using the endophenotype approach to deconstruct schizophrenia. We examined evidence for genetic influence on aberrant neurodevelopment by conducting a literature search on the heritability of brain structures in healthy people, in people with schizophrenia and in pedigrees in order to deconstruct schizophrenia. In addition to this, a search for molecular genetic variation underlying these brain structures was carried out as well.

The *second* article is called: ***'Murray et al. (2004) revisited: is bipolar disorder identical to schizophrenia without developmental impairment?'***. It is a review of literature focusing on work published in the past ten years that examines the actual status of the prediction offered by Murray and colleagues more than five years ago, which said that bipolar disorder may be largely similar to schizophrenia, but without associated developmental impairment. This issue is important to investigate, given the upcoming revisions of diagnostic systems in psychiatry, with the main question of how bipolar disorder and schizophrenia should be discriminated from each other in DSM-V and ICD-11.

In the *third* article, ***'Extended psychosis phenotype-yes: single continuum – unlikely'***, phenotypic continuity in the sense of continuity with normal mentation, as suggested both for schizophrenia and bipolar disorder, is examined from the conceptual point of view. Causation predicts the type of distribution of disease; therefore, given the hypothesized multifactorial aetiology for psychotic disorder, we examined the continuum hypothesis of psychopathology, and why people may shift over the continuum from low values, associated with subclinical psychotic experiences, to higher levels of psychotic disorder.

The affective domain

The paradox of *emotional dysfunction* in psychotic disorder is historic. It was Bleuler who first argued that problems of affect lie at the heart of schizophrenia and that hallucinations and delusions are merely accessory and common to many forms of disorders. This was the view which gave way to the now familiar distinction between affective and non-affective psychosis. However, emotional dysfunction in patients with schizophrenia is common with the core symptoms and disabilities, develops rapidly and aggressively during the prodrome and early phase of the illness into a psychotic episode (Harrison et al., 2001). Following the first episode of psychosis, 50% of patients with schizophrenia report post-psychotic depression (Birchwood et al., 2000) for a period with a high risk for suicide (Westermeyer et al., 1991). One third of the patients report traumatic reactions, fulfilling the criteria of PTSD (McGorry et al., 1991), and 50% report a fear of social interaction, i.e. social anxiety disorder (Cosoff et al., 1998). The most important issue for patients with psychotic disorders is the problem of developing and maintaining intimate relationships, leaving most of the patients in isolated and marginalized positions from social networks. The main question is whether these emotional problems are just a part of the psychotic disorder and should be categorized as negative symptoms such as blunted or flattened affect, or if they should be seen as the (childhood) emotional symptoms of (developing) psychotic disorder. The presence of affective dysregulation may be important, given that the presence of emotional disorders increases the probability of early relapse, and their presence in the prodromal phase may act as a risk factor for transition to psychotic disorder (Strakowski et al., 1995; Bechdolf et al., 2002; Lewandowski et al., 2006). One of the major findings in the study by Debbane et al. (2009) is that the expression of positive schizotypy during adolescence is modulated by emotional factors of depression and anxiety. These affective domains of psychosis, whether it is an affective or a non-affective psychotic disorder, will unfold in a social environment, e.g. the urban environment, social factors influencing the morbidity and outcome of psychotic disorder.

In **Chapter 3**, in the *first* article, '**Evidence that the urban environment specifically impacts on the psychotic but not the affective dimension of bipolar disorder**', the potential overlap of environmental factors on the impact of affective and non-affective symptomatology was examined, specifically focusing on urbanicity and what the impact is of urbanicity on affective and psychotic symptom domains of bipolar disorder. In the first article, the main effect of urbanicity on the rate of the bipolar phenotype, narrowly and broadly defined, was examined in relation to specific symptom dimensions.

In the *second* article, '**The impact of subclinical psychosis on the transition from subclinical mania to bipolar disorder**', the prevalences of subclinical mania and psychotic symptoms in the general population were examined and compared with their clinical counterparts. In addition, we examined how these subclinical population phenotypes, which are more prevalent than the clinical counterparts, co-vary with and impact on each other.

In the *third* article, '**Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials**', we searched for evidence if there is a difference in sensitivity to treatment in depression, given that this is an affective symptom domain that is pertinent to psychotic disorder, including schizophrenia. The aim was to examine the issue of sensitisa-

tion, in terms of progressively greater sensitivity to environmental stress, using a relapse rate paradigm following treatment over short or extended periods of time.

Application to the prodrome

In most cases of schizophrenia or bipolar disorder, the onset of disease is not a sudden event. Before onset, it has been found that in most cases the hospitalization was preceded by a pre-psychotic phase in which attenuated or prodromal psychotic symptoms had been present for about a year, but sometimes as long as five years in the case of non-specific and negative symptoms (Hafner H, 2001). In this study, the onset of social disabilities also pre-dated the first admission to hospital by more than a year and pre-dated even the onset of positive symptoms. As a consequence of these findings, replicated across many studies (Cannon et al., 2008; McGorry et al., 2009; Valmaggia et al., 2009), the issue of prediction of psychosis requires further examination, given that: 1) the prodromal phase is present in the majority of patients with first-episode psychosis (Hafner H, 2001), 2) it is a source of substantial suffering on the part of patients and their families, 3) deficits occur in the prodromal phase, and 4) help-seeking frequently occurs in the prodromal phase (Addington et al., 2002). Early detection and early treatment of psychosis may reduce the psychological, social and possibly biological alterations and deficits (Pantelis et al., 2003) that can lead to poor outcome. However, there is much confusion from different studies about the initial prodrome of psychosis or *at risk mental state* as the high-risk studies are based on the attenuated psychotic symptoms in selected groups of help-seeking individuals. Data are also needed on the prodrome and the risk of transition to psychotic disorder in representative general population samples.

In **Chapter 4**, we discuss in the *first* article, '**DSM-V and the 'Psychosis Risk Syndrome': Babylonian confusion**', the validity of diagnostic entities in the psychosis spectrum and the new paradigm shift in clinical psychiatry to introduce a new category called the *Psychosis Risk Syndrome* in DSM-V, which now likely be relabelled as *Attenuated Psychotic Symptom syndrome*. The introduction of this new category is related to 1) important pioneering work on early intervention in selected high-risk populations and 2) international efforts emphasizing the major impact of early intervention on the course and outcome of psychotic disorders. This paper addresses whether the introduction of another new category in psychosis spectrum is required and whether it is based on valid nosological entities.

The *second* article entitled, '**The case of the missing evidence: what do subclinical psychosis spectrum experiences predict in unselected representative population samples? A systematic review enriched with new results**', is a meta-analysis of existing literature, enriched with new results. We review literature on the risk of developing psychotic disorder given earlier expression of subclinical psychotic experiences in representative, general population samples. We also examine the risk of conversion to non-psychotic, mainly affective disorders, given presence of subclinical psychotic experiences in the general population and investigate which symptom factors moderate risk of conversion to a clinical disorder.

In **Chapter 5**, an English summary of all the studies included in this thesis is given.

In **Chapter 6** the findings and conclusions of all studies described in this thesis are discussed, with recommendations for future research.

In **Chapter 7** a Dutch summary of all the studies included in this thesis is given.

Background information on the data of the two longitudinal studies used in the published studies

Introducing the NEMESIS study

In this thesis, we used the data pertaining to the Netherlands Mental Health Survey and Incidence Study (NEMESIS) in several publications (chapter 3, 4). A more detailed outline of the NEMESIS study is published by Bijl et al., (1998). This is a brief introduction to the NEMESIS study.

The NEMESIS study is a prospective study of prevalence, incidence and course of psychiatric disorders in a representative sample of non-institutionalized Dutch adults. A total of 7146 men and women eighteen to sixty-four years of age, contacted through a multistage sample of municipalities and households, were interviewed at home in 1996. The primary diagnostic interview of the NEMESIS study was the CIDI, which determines the lifetime occurrence of DSM-III-R disorders. The disorders that were included were mood disorders, anxiety disorders, eating disorders, schizophrenia and other non-affective psychotic disorders and dependence, and abuse of psychoactive substances. In this thesis, diagnostic data were used for all disorders with the exception of data regarding eating disorders. Follow-ups of the NEMESIS sample were scheduled at 12 and 36 months. The NEMESIS study had three measurement occasions: 1996, 1997 and 1999. The net response of the first measurement was 69.7%. All respondents, with or without mental disorders at the time of the initial interview in 1996, were monitored for the whole duration of the study. There was no attrition that was differential with regard to mental health.

The objectives of the NEMESIS study are to obtain data on:

- 1) The *prevalence* of psychiatric morbidity amongst adults, eighteen to sixty-four years of age, in terms of subthreshold/subclinical (groups of symptoms that are potentially clinically relevant but that fail to satisfy the DSM criteria for a disorder) or clinical psychiatric disorders and the co-occurrence of psychological and (mainly chronic) somatic ailments. Psychiatric disorders are determined with the aid of DSM-III-R classification (APA, 1987).
- 2) The *consequences* of mental disorders in terms of care use and care needs, quality of life and functional impairments.
- 3) The *incidence* and *course* of disorders. By repeating the measurements, the identification of cases and monitoring of the course of existing disorders over time, in relation to changing life circumstances, was possible. NEMESIS was the first large-scale nationwide population study that was fully prospective.
- 4) *Determinants* of the emergence and the course of mental disorders were identified: in particular, socio-demographic characteristics, distressing recent and early life events (e.g. family history), care received, personality and vulnerability traits (e.g. self-esteem, neuroticism, locus of control) and support from the social environment. Biological and physical examinations are not provided in the NEMESIS study.

Introducing the EDSP study

In one publication, we also used data from the Early Developmental Stages of Psychopathology Study (EDSP). Detailed descriptions of the EDSP study have been published by Lieb et

al., 2000; a brief introduction to the study will be given here. The EDSP study is a prospective longitudinal study investigating substance use and other mental disorders in a representative population sample of 3021 subjects, fourteen to twenty-one years of age (birth cohort 1970-1981) at baseline (T0) living in Munich, Germany. The age range was especially chosen specifically to address the early developmental stages of substance use, abuse and dependence and other mental disorders. Two follow-up investigations were conducted after the baseline investigation covering an overall period of three to four years. In the first follow-up moment (T1) only the younger cohort, fourteen to seventeen years of age at baseline was investigated, in order to be able to focus on the early developmental stages of psychopathology and substance use. In the final follow-up session (T2), the entire baseline sample was assessed again. Special design features are the linkage with a family supplement (EDSP-FS), an independent family survey to investigate familial contributions to the development of substance use and other mental disorders, as well as neurobiological laboratory studies of high-risk subjects. The response rates in the different waves of investigation ranged from 70.9%-88.0% and overall response rate was 84.3%. The interviewers in all assessment stages comprised mainly graduated psychologists. Parental interviewers were in the age range of the targeted mothers and they were blind to the diagnoses of the respondents. All interviewers received training for one week for both the computerized as the paper-pencil version of the M-CIDI.

- 1) The primary goal of the EDSP study is to provide prevalence and incidence estimates of substance use, abuse and dependence among adolescents and young adults.
- 2) Secondly, the EDSP aims to study the natural course of early stages of substance use and substance use disorders (e.g. initiation of use, progression to abuse) over a period of several years and to identify risk factors that are associated with changes from one stage to another.
- 3) Further main goals of the EDSP study are to include the examination of comorbidity of substance use disorders with each other as well as with mental disorders and the investigation of familial vulnerability factors and mechanisms that may be involved in the onset and course of substance use disorders.

Limitations of (epidemiological) studies

One of the limitations of the NEMESIS data is that, although it was set up to reach a broad range of populations, it has not been able to reach certain groups, such as people with no fixed address, those with insufficient proficiency in Dutch and those who are institutionalized for a prolonged time. It is unclear what the impact is of missing data on these populations. For example, it is well known that the prevalence of psychiatric disorders is high in the group of homeless people, about two or three times higher as in the general population (Health Council, 1995), possibly missing out on an estimated 3%-5% of people with schizophrenia among the 20,000 homeless people in the Netherlands. The diagnosis of schizophrenia might not only be limited by this fact, but also because people with a diagnosis of schizophrenia can be presumed to be less willing or able to take part in an interview. Almost 38% of the people who, on the reference date, had been in hospital for over one year were diagnosed with schizophrenia (Mental Health Care Yearbook, 1995/1996). That means the schizophrenia prevalence found by the NEMESIS study is an absolute minimum. One other limitation con-

cerns ethnicity. First generation immigrants were probably not well represented in the NEMESIS study because of language problems (inability to speak Dutch) and/or because of reduced willingness to participate. However, the younger age groups of these ethnic categories (Turkish and Moroccan origin) were reached by NEMESIS.

The advantage of the NEMESIS study is that a response rate above 60% is satisfactory and rare, because there are many scientific, non-scientific and commercial surveys in the Netherlands. The non-response group did not differ significantly from the response group in terms of psychiatric morbidity; they even had a better mental health. Another strength of the study is that the instrument (CIDI) used is widely used internationally. This creates possibilities to compare the NEMESIS data with data from abroad. Moreover, the fact that a computerized interviewing procedure has more advantages in terms of banning partial non-response, which avoids one major source of errors when data is entered manually. However, computerized interviews have their disadvantages, one of which was a technical error that led to missing data of 71 respondents. Another strong feature of the NEMESIS study is the one-step procedure in which all respondents underwent a full psychiatric interview. This is in contrast to other population studies in which a two-step approach is used that results in an indirect estimate. What they entail is a first step when a limited number of people for the interview are selected, and a second step logistic regression analysis has to be performed to compute for every score on the screening instrument the probability that the corresponding subject had a psychiatric disorder. These conversion factors are then applied to the entire sample to estimate the total prevalence of psychiatric cases (Health Council, 1995), leaving us with indirect estimates that may contain substantial error. The NEMESIS prevalence rates are *not* indirect estimates, and have a greater number of respondents, resulting in more accurate estimates and narrower confidence intervals than those in other studies.

As for the EDSP study, the strengths of this study are that it is a combined longitudinal characterization of psychopathology and substance use behaviours and disorders. It is a longitudinal prospective assessment of various risk and protective factors that are involved in the development of substance use and other mental disorders and conducted in a representative sample of adolescents and in young adults with a characterization of family factors. The fact that the EDSP study is conducted in a prospective longitudinal fashion, in a representative population sample, is essential for an unbiased characterization of the psychopathology status of the population and the identification of risk factors, in contrast to clinical samples that are usually influenced by selection bias and in general allow only for retrospective approaches. Therefore, the EDSP study not only provides a description of prevalence and prospectively observed incidence patterns of substance use and mental disorders in a target population on various diagnostic levels such as asymptomatic, symptomatic, subthreshold and full diagnostic level, but it also offers an adequate basis for investigating a variety of familial, cognitive-behavioural and social risk factors, and in particular, their status as causal risk factors. The study also enables one to study various public health related consequences of substance use and other mental disorders prospectively and unaffected by recall bias.

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CHAPTER 2

Developmental studies of psychosis

HERITABILITY OF STRUCTURAL BRAIN TRAITS: AN ENDOPHENOTYPE APPROACH TO DECONSTRUCT SCHIZOPHRENIA

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Structural brain phenotypes are quantitative traits showing considerable variation in human populations. Quantitative structural brain abnormalities are also repeatedly reported in patients with psychiatric disorders such as schizophrenia. Studying the genetic and environmental causes of these differences might therefore highlight biological mechanisms underlying neuroanatomical phenotypes and directly result in the identification of risk factors for schizophrenia. Heritability estimates indicate a strong genetic component contributing to neuroanatomical phenotypes. Brain structure volumes have substantial heritability

rates ranging from high (70–95%) for total brain volume, cerebellar, gray and white matter, and corpus callosum, to moderate (40–70%) determined for the hippocampus, the four lobes (frontal, temporal, occipital, and parietal lobe), temporal horn volume, brain parenchyma, white matter hyperintensity, and planum temporal asymmetry. Middle structures of the brain show high heritability scores for the deeper structures (ontogenetically earlier formed) and moderate heritability scores for the surface structures. Structures formed earlier in development show consistently higher heritability rates than brain structures formed later in development, for example, surface structures, which seem to be influenced by environmental factors. Even higher heritability reaching 0.99 for total brain volume are estimated in nonhuman primate (NHP) models employing inbred extended pedigree and highly uniform rearing conditions, reducing the effects of environmental factors. Applying highly heritable structural brain phenotypes may serve as an endophenotype for gene mapping studies and lead to identification of genes that are involved in the regulation of human brain volume and the biological mechanisms involved in the causal mechanisms of psychiatric disorders.

I. Introduction

A. ENDOPHENOTYPIC APPROACH TO STUDYING SCHIZOPHRENIA

Schizophrenia is a highly heritable disorder (Cannon *et al.*, 1998; Cardno and Gottesman, 2000; Sullivan *et al.*, 2003) characterized by delusions, hallucinations, disorganized speech (frequent derailment or incoherence), grossly disorganized or catatonic behavior, and negative symptoms, that is, affective flattening, alogia (poverty of speech) and avolition (general lack of desire, interest or motivation to pursue meaningful goals) (DSM-IV-Tr, 2000). It is believed that this complex phenotype of schizophrenia is a result of underlying complex genetic architecture involving interactions between multiple loci and environmental factors (van Os *et al.*, 2008). Another source of difficulty is the reliability of phenotypic assessments. Schizophrenia diagnostics employ a patient's self-reports rather than biochemical, electrophysiological, or other reliably measurable biomarkers. The validity of schizophrenia as a diagnostic entity has therefore been criticized by a number of scientists and clinicians as lacking in scientific validity and diagnostic reliability (Bentall *et al.*, 2004; Boyle, 2002; Kendell and Jablensky, 2003; Linscott *et al.*, 2009; van Os, 2009; van Os and Murray, 2008). Due to the diagnostic heterogeneity and the genetic and phenotypic complexity of

schizophrenia, as well as other complex brain-related disorders, identification of a genetic basis of this disease is a very challenging task.

The endophenotypic approach is one of several strategies that have been adopted to deal with the complexities of these disorders and identify underlying genes (Gottesman and Gould, 2003). The principle of this approach is to reduce complex phenotypes into components (neurophysiological, biochemical, endocrine, cognitive, neuropsychological, or neuroanatomical phenotypes) that could be reliably quantified and are under close regulation by genetic variation. The endophenotype (or intermediate phenotype) is therefore a kind of biomarker that, unlike disease diagnosis, has a clearer underlying biological and genetic basis. They are expected to be genetically correlated with disease liability, and can be measured in both affected and unaffected individuals. Since quantitative endophenotypes are generally closer to the action of the gene and are measurable in both unaffected and controls, they exhibit higher genetic signal-to-noise ratios and are anticipated to provide a greater power to localize and identify disease-related quantitative trait loci (QTLs) than affection status alone (Blangero *et al.*, 2003).

Human studies often use endophenotypes that are related to evolutionary conserved traits and therefore can be extended to animal models.

B. NEUROANATOMIC MEASURES AS ENDOPHENOTYPE

Volumes of various brain structures are quantitative phenotypes that can be reliably measured on MRI scans using either automated (voxel-based morphometry method, VBM; deformation-based morphometry; surface-based morphometry) or manual tracing (region and volume of interest, ROI and VOI method) (Ashburner and Friston, 2000; Good *et al.*, 2001a; Thompson and Toga, 1997; Thompson *et al.*, 1996a,b). Brain structure measurements show considerable interindividual variation in general populations and differences between healthy and affected persons, and are therefore considered promising candidate endophenotypes that might facilitate investigations of a genetic basis into the natural variation of brain-related traits in populations and for psychiatric disorders such as schizophrenia. When measuring brain structure and the heritability of these structures, normal neuroanatomical variations in the human brain should be taken into account (Allen *et al.*, 2002). These neuroanatomical variations are under the influence of variables such as gender (Cosgrove *et al.*, 2007; Giedd, 2008) and age (Carne *et al.*, 2006; Good *et al.*, 2001b), or other components of genetic variety such as height (Kappelman, 1993). Intelligence seems to be related to brain volume as well. In humans, brain volume is a quantitative trait with high heritability (Posthuma *et al.*, 2002b; Thompson *et al.*, 2001, 2002). Previous studies have shown that brain volume is also correlated with general intelligence, working memory, perceptual organization, and processing speed, which are also highly

heritable (Posthuma *et al.*, 2003; Roth and Dicke, 2005). In recent years, it has been discovered that the structure of the adult human brain changes when new cognitive or motor skills, including vocabulary, are learned (Lee *et al.*, 2007), and that this structural neuroplasticity (increased gray matter volume), after 3 months of training a visual motor skill, seems to last for at least 3 months without further practicing (Driemeyer *et al.*, 2008; Ilg *et al.*, 2008). Another example is the impact of handedness, which has a significant genetic component (Annett, 1974; McManus and Bryden, 1991) and is strongly related with cerebral asymmetry (Alexander and Annett, 1996; Geschwind and Galaburda, 1985). To what extent the cerebral asymmetry is also heritable remains unclear (Geschwind *et al.*, 2002). The neuroanatomical phenotype and the heritability of brain structures varies among individuals with a neuropsychiatric disorder, meaning that the influence the disease state has on the heritability is such that the morphology of brain structures can be altered by the disease state and these morphologically altered brain structures can be inherited. For example, there are studies showing small hippocampal volumes in adult humans with recurrent major depression (Bremner *et al.*, 2000; Sheline *et al.*, 1999) and posttraumatic stress disorder (Bremner *et al.*, 1995). Hippocampal morphology is also altered by stress in carefully controlled studies with rodents (Gould and Tanapat, 1999; Magarinos *et al.*, 1995; Sapolsky, 2000). These smaller hippocampi have been taken as evidence that stress-related disorders induce hippocampal volume loss (Sapolsky, 2000; Sheline *et al.*, 1999). One possible pathway by which altered brain morphology changes might be inherited is that small hippocampal volumes are inherited and act as predisposing factors toward the development of psychiatric disorders that are triggered by stress (Gurvits *et al.*, 1996; Sapolsky, 2000).

When measuring brain structure volumes and calculating heritability estimates, these variables, having a strong genetic component themselves, should be taken into account.

C. HERITABILITY ESTIMATES TO DETERMINE CONTRIBUTION OF GENETIC FACTORS TO STRUCTURAL BRAIN TRAITS

(to study genetics of both natural and disease-related variation)

Twin and adoption studies have shown substantial genetic influences are involved in the risk of developing schizophrenia (Cannon *et al.*, 1998; Cardno *et al.*, 2002; Kendler and Diehl, 1993; McGuffin *et al.*, 1984). The identification of predisposing genes has been hampered by difficulties in detecting nonpenetrant carriers and by uncertainties concerning the extent of locus of heterogeneity (McDonald and Murphy, 2003). By studying the inheritance of endophenotypes, we can increase the power to detect the genes involved in clarifying the pathways leading from genetic predisposition to clinical disorder

(Gottesman and Gould, 2003). One of the most extensively studied endophenotypes in schizophrenia research is the study of structural brain abnormalities. These structural changes are well established in schizophrenia. The most robust findings from meta-analyses of these structural brain abnormalities is increased total ventricular volume, reduction of whole brain and intracranial volume, reduced hippocampal and amygdalar volume (Lawrie and Abukmeil, 1998; Ward *et al.*, 1996; Wright *et al.*, 2000). These brain abnormalities are also present in unaffected family members of patients with schizophrenia, to a less degree, but significantly more than in controls according to a meta-analysis reporting on brain changes in unaffected family members of patients with schizophrenia (Boos *et al.*, 2007; van Haren *et al.*, 2004).

One hypothesis in using these structural abnormalities as endophenotypes, in order to get closer to the action of the genes, suggests that there might be an overlap in the neurodevelopmental genes responsible for both the volume change and the development of the illness, that is, the existence of a genetic correlation. Schizophrenia may involve genetically determined pathological processes of early brain development which continue to unfold as the brain matures through neuronal loss and synaptic pruning during adolescence. Neurodevelopmental abnormalities then lead to the activation of pathological neural circuits, which respond to environmental stressors, leading to the emergence of symptoms (Deutch, 1993). This hypothesis is supported by the finding that MRI abnormalities are present at the onset of the illness, and progress very slowly if at all (Weinberger, 1995). A contrasting view on the etiology of schizophrenia is that the relationship between schizophrenia and brain volumes might be environmental in nature. For example, perinatal trauma has been shown to be an important determinant of some brain structure abnormalities in schizophrenia (Cannon *et al.*, 2003; McNeil, 2000; Verdoux *et al.*, 1997).

Defining to what degree the development of these brain structures is of genetic origin, that is, the heritability of brain structures, and using these brain structures as an endophenotype may be helpful in better identifying the action of these neurodevelopmental genes. Heritability estimates for brain structures in healthy persons and persons with schizophrenia will help to differentiate between disease related alterations in brain morphology and genetic influences (heritability).

Twin studies are considered important in investigating genetic influences on variation in human brain morphology in healthy individuals and those with schizophrenia. The twin model is particularly helpful in determining the relative contribution of genetic, common, and unique environmental influences on variation in brain structures (Posthuma and Boomsma, 2000). Heritability estimates of brain structure are usually based on data from monozygotic twins (MZ, who are nearly genetically identical) and dizygotic twins (DZ, who share on average 50% of their segregating genes). If heritability estimates are based on the assumption that for a certain brain measure, MZ twin pairs will resemble each other more closely than DZ twin pairs, it can be inferred that variation of the brain measure is

heritable. However, in addition to genetic influences, common (or shared) environmental influences may play a role in explaining resemblances. The effects of shared environmental factors may be suggested when correlations in DZ twins are larger than half of the MZ correlation (Boomsma *et al.*, 2002). The effects of unique environmental factors are obtained from the extent to which MZ twins do not resemble each other. However, the twin method has been criticized for its nongeneralizability due to differences in intrauterine and family environment differences between the twins and compared with singletons (Price, 1950).

Heritability estimates and the search for genes in diseased and nondiseased humans are difficult due to the impact of environmental factors. Studies in nonhuman primates (NHPs) might be helpful in elucidating the impact of environmental factors.

D. NONHUMAN PRIMATE MODEL FOR STUDYING BRAIN NEUROSTRUCTURAL STUDIES

Obstacles in investigating complex traits in human subjects involve the hard-to-control and extensive effects of environment, personal development, and medical history including administrated medications. To a large extent, these problems can be overcome by applying an animal model. Particularly useful are NHPs due to the high conservation of anatomical, neurophysiological and cognitive traits as well genetic sequence with humans. NHP pedigrees have helped studies of various complex traits including the neuroanatomical due mostly to the availability of pedigree facilitating genetic studies, established genetic relationships among pedigree animals, well-documented medical and developmental history and uniform rearing conditions reducing the influence of environmental factors.

To disentangle the possible mechanisms by which genetic and environmental factors contribute to the morphological abnormalities in the brain animal models may be used, specifically NHPs, for example, monkey brains, in which the influence of environment is reduced. The evolution of cognitive function in hominoids, for example, depends largely on our understanding of the organization of the frontal lobes in extant humans and apes (Semendeferi *et al.*, 1997). There are studies with findings showing similarities to human brains, such as the possibility of microstructural plasticity in the NHP hippocampus (Sapolsky *et al.*, 1990; Siegel *et al.*, 1993; Uno *et al.*, 1989). Other studies show the impact of environmental factors on the volumes of different brain structures, such as the affect of differential rearing on the corpus callosum size in rhesus monkeys (Sánchez *et al.*, 1998). Studies on brain characteristics and the genetic variation of regional brain morphologies of NHPs will help us understand the meaning of the brain characteristics in humans as well. They will also help us determine whether certain assumptions, such as those about certain brain characteristics

being strictly unique to humans, are correct. For example, it is often claimed that the frontal lobe is disproportionately larger in humans than in other species, but conflicting reports exist on this issue. Results of a study by Semendeferi *et al.* (1997) indicate that although the absolute volume of the brain and the frontal lobe is the largest in humans, the relative size of the frontal lobe is similar across hominoids and humans do not have a larger frontal lobe than expected from a primate brain of human size. Other important functional parts of the brain, like area 10 in cortical areas of the frontal lobe, which is involved in higher cognitive functions, also seem to form the frontal pole in chimpanzee, bonobo, orangutan, macaque, and gibbon brains. Area 10 has similar cytoarchitectonic features in the hominoid brain, but aspects of its organization vary slightly across species, including relative width of its cortical layers and the space available for connections (Semendeferi *et al.*, 2001). Although some features of the human brain, like the asymmetric Broca's area and the planum temporal in Wernicke's posterior receptive language area in the left hemisphere, were thought to be unique to humans, studies in great apes (Cantalupo and Hopkins, 2001) and chimpanzees (Gannon *et al.*, 1998) show the same anatomic hemispheric asymmetry in the Broca's area and planum temporal, respectively.

II. Heritability of Brain Structure Phenotypes

Heritability estimates allow for determining which neuroanatomical measures are traits with marked genetic components and could therefore be interesting both from the perspective of natural variation in brain related processes in population and as an attractive endophenotype for schizophrenia studies. Investigating heritability in various aspects in healthy individuals, in relation to schizophrenia and in the NHP model, may answer two essential questions: (1) to what degree are brain volumes genetically determined? and, (2) which brain volumes are mostly heritable and therefore useful as endophenotypes for genetic studies?

A. HERITABILITY OF BRAIN STRUCTURES IN HEALTHY PERSONS

There are 24 studies reporting on heritability of brain structures in healthy persons. These studies are listed in Tables I and II, where the measured brain structures, the heritability rates of these brain structures or regions (denoted as h^2 or as ICC or as Risch's λ), and the method of calculating heritability (in superscript) is given, besides the sample size/mean age of the persons (twins, singletons, family members)/sex ratio/other variables, whenever available and mentioned in the articles are reported in the table as well, with the study ID and

TABLE I
STRUCTURAL BRAIN PHENOTYPES IN HEALTHY PERSONS WITH HIGH HERITABILITY
(h^2 BETWEEN 0.70 AND 0.99)

Brain structure	Heritability of brain structure (h^2 , ICC or λ)	Sample size and age, gender, whenever different	Study ID
Cranial, intracranial volume	0.91	74 MZ, 71 DZ twin pairs (all M, 68–79 years)	Carnelli <i>et al.</i> (1998) ^a
	0.88	54 MZ, 58 DZ twin pairs, 34 siblings	Baaré <i>et al.</i> (2001a) ^a
	0.80	44 MZ, 40 DZ twin pairs (all M, 68–78 years)	Sullivan <i>et al.</i> (2001) ^a
	0.938	1881 individuals: 1330 genetically related (± 60 years)	Atwood <i>et al.</i> (2004) ^a
Total brain volume	0.94	10 MZ (± 34 years), 9 DZ (± 23 years) twin pairs	Bartley <i>et al.</i> (1997) ^a
	0.97	23 MZ (12 M), 23 DZ (16 M) twin pairs, all reading disability, C (NRD) = 9 MZ (4 M), 9 DZ (4 M) twin pairs	Pennington <i>et al.</i> (2000) ^b
	0.90	54 MZ, 58 DZ twin pairs, 34 siblings	Baaré <i>et al.</i> (2001a) ^a
	0.99	12 MZ, 12 controls (all M)	White <i>et al.</i> (2002) ^b
	0.89	90 MZ (52 M, 38 F), 37 DZ (22 M, 15 F) twin pairs, 158 unrelated singletons (± 11.5 years)	Wallace <i>et al.</i> (2006) ^a
	0.91	107 MZ and DZ twin pairs (± 9 years)	Peper <i>et al.</i> (2009) ^a
Gray matter volume	0.82	54 MZ, 58 DZ twin pairs, 34 siblings	Baaré <i>et al.</i> (2001a) ^a
	0.99	12 MZ, 12 controls (all M)	White <i>et al.</i> (2002) ^b
	0.82	54 MZ, 58 DZ twin pairs, 34 siblings	Posthuma <i>et al.</i> (2002b) ^b
	0.82	90 MZ (52 M, 38 F), 37 DZ (22 M, 15 F) twin pairs, 158 unrelated singletons (± 11.5 years)	Wallace <i>et al.</i> (2006) ^a
	0.91	107 MZ and DZ twin pairs (± 9 years)	Peper <i>et al.</i> (2009) ^a
	0.55–0.85	49 MZ, 65 DZ twin pairs (± 28 years)	Hulshoff Pol <i>et al.</i> (2006) ^a

White matter volume/hyper-intensity		0.71	74 MZ, 71 DZ twin pairs (all M, 68–79 years)	Carnelli <i>et al.</i> (1998) ^a
		0.88	54 MZ, 58 DZ twin pairs, 34 siblings	Baaré <i>et al.</i> (2001a) ^a
		0.98	12 MZ, 12 controls (all M)	White <i>et al.</i> (2002) ^b
		0.97	54 MZ, 58 DZ twin pairs, 34 siblings	Posthuma <i>et al.</i> (2002b) ^b
		0.85	90 MZ (52 M, 38 F), 37 DZ (22 M, 15 F) twin pairs, 158 unrelated singletons (± 11.5 years)	Wallace <i>et al.</i> (2006) ^a
		0.91	107 MZ and DZ twin pairs (± 9 years)	Peper <i>et al.</i> (2009) ^a
		0.69–0.82	49 MZ, 65 DZ twin pairs (± 28 years)	Hulshoff Pol <i>et al.</i> (2006) ^a
		0.73, 0.90	5 MZ twin pairs, 10 unrelated controls	Oppenheim <i>et al.</i> (1989) ^b
		0.89,	7 MZ twin pairs	Biondi <i>et al.</i> (1998) ^a
	AC-PC distance	0.906, 0.705		
<i>Callosal vol.</i>	Area	$p = 0.02$	10 MZ twin pairs	Tramo <i>et al.</i> (1998) ^b
	CC	0.79	44 MZ, 40 DZ twin pairs (all M, ± 68 –78 years)	Sullivan <i>et al.</i> (2001) ^a
	CC	0.94	14 MZ, 12 DZ twin pairs (± 27 years)	Scamvougras <i>et al.</i> (2003) ^b
	CC	0.90	34 MZ, 37 DZ (all M, ± 76 years)	Pfefferbaum <i>et al.</i> (2004) ^a
	CC	0.85	90 MZ, 37 DZ twin pairs, 158 unrelated singletons (± 11.5 years)	Wallace <i>et al.</i> (2006) ^a
	CC	0.93	107 MZ and DZ twin pairs (± 9 years)	Peper <i>et al.</i> (2009) ^a
	Midline structures	0.83	107 MZ and DZ twin pairs (± 9 years)	Peper <i>et al.</i> (2009) ^a
	Cau, put, thal	0.84, 0.75, 0.75	12 MZ, 12 controls (all M)	White <i>et al.</i> (2002) ^b
	Cau	0.80	90 MZ, 37 DZ twin pairs, 158 unrelated singletons (± 11.5 years)	Wallace <i>et al.</i> (2006) ^a
	Middle frontal volume	0.90–0.95	10 MZ, 10 DZ twin pairs (50–70 years)	Thompson <i>et al.</i> (2001) ^b
FL, TL, PL		0.84, 0.88, 0.86	90 MZ, 37 DZ twin pairs, 158 unrelated singletons (± 11.5 years)	Wallace <i>et al.</i> (2006) ^a

(continued)

TABLE I (continued)

Brain structure	Heritability of brain structure (h^2 , ICC or λ)	Sample size and age, gender, whenever different	Study ID
Cerebellum	0.88	43 MZ, 37 DZ twin pairs, 34 siblings	Posthuma <i>et al.</i> (2000) ^a
	0.99	12 MZ, 12 controls (all M)	White <i>et al.</i> (2002) ^b
Subcortex	0.70	23 MZ (12 M), 23 DZ (16 M) twin pairs, all reading disability, C (NRD) = 9 MZ (4 M), 9 DZ (4 M) twin pairs	Pennington <i>et al.</i> (2000) ^b
Lateral ventricle	0.83	34 MZ, 37 DZ (all M, $\pm$ 76 years)	Pfefferbaum <i>et al.</i> (2004) ^a
Cerebral ventricle	0.83	18 MZ, 21 DZ twin pairs ($\pm$ 37 years)	Reveley <i>et al.</i> (1984) ^{a,b,c}

Summary of published studies by August 2009 (PubMed and Medline citations) on the heritability of brain structural phenotypes including study results from healthy monozygotic (MZ) and dizygotic (DZ) twins, singletons (sibs), and in some studies healthy controls (C). Heritability is denoted as h^2 or as intraclass correlation factor (ICC) or as Risch's λ . A higher ICC for MZ twins then for DZ twins indicates a genetic component to these structures, but large confidence intervals indicate that the similarities measured are a rough estimates of the degree to which a brain structure is genetically controlled. Another way of denoting the heritability is by $\lambda_s = \text{Risch's } \lambda = \text{a measure of heritability}$. For Risch's λ , $\lambda_s = 1$ is the expected value for nonfamilial traits, whereas $\lambda_s > 2.0$ is considered evidence for familiarity. h^2 or ICC or Risch's $\lambda = \text{heritability rate}$.

TB, total brain volume; WM, total white matter volume; GM, total gray matter volume; WM, white matter volume; GM, gray matter volume; CC, corpus callosum; AC-PC distance, the distance between anterior and posterior commissure; CB, cerebellar volume; FL, frontal lobe; TL, temporal lobe; PL, parietal lobe; OL, occipital lobe; OC, occipital cortex; TH, temporal horn volume; LV, lateral ventricle volume; TV, third ventricle; HC, hippocampal volume; Parahip, parahippocampal gyrus; Cau, caudate nucleus; Thal, thalamus; SS or SL, sulcus shape or sulcus length; put, putamen; Hpt, hypothalamus; PHC gyrus, parahippocampal gyrus; MZ, monozygote; DZ, dizygote; M, male, F, female; Sibs, siblings; n.a., not available; n.s., not significant.

^aSEM, structural equation modeling., ^bFalconer method., ^cAnalysis of variance estimate of heritability.

TABLE II

STRUCTURAL BRAIN PHENOTYPES IN HEALTHY PERSONS WITH MODERATE HERITABILITY (h^2 BETWEEN 0.40 AND 0.70), LOW HERITABILITY (h^2 BETWEEN 0.00 AND 0.40) AND NO SIGNIFICANT HERITABILITY ($h^2 = 0$ AND DENOTED AS N.S.)

Brain structure	Heritability of brain structure (h^2 , ICC or λ)	Sample size	Study ID
Frontal lobe (L, R), Temporal lobe (L, R), Parietal lobe (L, R) Occipital lobe (L, R)	0.66, 0.56 0.59, 0.41 (n.s.) 0.41 (n.s.), 0.47 0.28 (n.s.), 0.69	72 MZ, 67 DZ twin pairs (± 71 years)	Geschwind <i>et al.</i> (2002) ^{a,b,c}
Total brain volume	0.66 0.61	9 MZ, 10 DZ twin pairs (± 23 years) 72 MZ, 67 DZ twin pairs (± 71 years)	Wright <i>et al.</i> (2002) ^b Geschwind <i>et al.</i> (2002) ^{a,b,c}
Hippocampus	0.40	44 MZ, 40 DZ twin pairs (all M, 68–78 years)	Sullivan <i>et al.</i> (2001) ^b
Neocortex	0.56	23 MZ (12 M), 23 DZ (16 M) twin pairs, all reading disability, C (NRD) = 9 MZ (4 M), 9 DZ (4 M) twin pairs	Pennington <i>et al.</i> (2000) ^a
Cerebral Cortex	0.30–0.57	107 MZ, 47 DZ twin pairs, siblings of twins 64, singletons 228	Schmitt <i>et al.</i> (2008) ^b
WM hyperintensity	0.553	1881 individuals: 1330 genetically related (± 60 years)	Atwood <i>et al.</i> (2004) ^b
Planum Temporale asymmetry	0.612 MZ cc:0.21, MZ disc: 0.41	27 MZ, 12 DZ win pairs (± 27 years) 10 MZ concordant and 10 MZ discordant twin pairs for handedness (± 26 and 22 years)	1) Eckert <i>et al.</i> (2002) ^a 2) Steinmetz <i>et al.</i> (1995) ^a
Brain Parenchyma	0.62	74 MZ, 71 DZ twin pairs (all M, ± 68 –79 years)	Carmelli <i>et al.</i> (1998) ^b
Temporal Horn	0.60	44 MZ, 40 DZ twin pairs (all M, 68–78 years)	Sullivan <i>et al.</i> (2001) ^b
CC perimeter	0.620	7 MZ twin pairs	Biondi <i>et al.</i> (1998) ^d
Cerebellum	0.49	90 MZ, 37 DZ twin pairs, 158 unrelated singletons (± 11.5 years)	Wallace <i>et al.</i> (2006) ^b

(continued)

TABLE II (continued)

Brain structure	Heritability of brain structure (h^2 , ICC or λ)	Sample size	Study ID
Other (n.s. or low h^2); SS or SL	0.377 (n.s.)	27 MZ, 12 DZ twin pairs (± 6 –16 years)	Eckert <i>et al.</i> (2002) ^a
LV	0.31	90 MZ, 37 DZ twin pairs, 158 unrelated singletons (± 11.5 years)	Wallace <i>et al.</i> (2006) ^b

Summary of published studies by August 2009 (PubMed and Medline citations) on the heritability of brain structural phenotypes including study results from healthy monozygotic (MZ) and dizygotic (DZ) twins, singletons (sibs), and in some studies healthy controls (C). Heritability is denoted as h^2 or as intraclass correlation factor (ICC) or Risch's λ . A higher ICC for MZ twins than for DZ twins indicates a genetic component to these structures, but large confidence intervals indicate that the similarities measured are a rough estimates of the degree to which a brain structure is genetically controlled. Another way of denoting the heritability is by $\lambda_s = \text{Risch's } \lambda = \text{a measure of heritability}$. For Risch's λ , $\lambda_s = 1$ is the expected value for nonfamilial traits, whereas $\lambda_s > 2.0$ is considered evidence for familiarity. h^2 or ICC or Risch's $\lambda = \text{heritability rate}$.

TB, total brain volume; WM, total white matter volume; GM, total gray matter volume; WM, white matter volume; GM, gray matter volume; CC, corpus callosum; AC-PC distance, the distance between anterior and posterior commissure; CB, cerebellar volume; FL, frontal lobe; TL, temporal lobe; PL, parietal lobe; OL, occipital lobe; OC, occipital cortex; TH, temporal horn volume; LV, lateral ventricle volume; TV, third ventricle; HC, hippocampal volume; Parahip, parahippocampal gyrus; Cau, caudate nucleus; Thal, thalamus; SS or SL, sulcus shape or sulcus length; put, putamen; Hpt, hypothalamus; PHC gyrus, parahippocampal gyrus; MZ, monozygote; DZ, dizygote; M, male, F, female; Sibs, siblings; n.a., not available; n.s., not significant.

^aFalconer method, ^bSEM, structural equation modeling, ^cAnalysis of variance estimate of heritability, ^dVisual comparison of the 3D surface rendering models of the brains and manual measurements of the AC-PC distance by six blinded observers.

year of publication. Magnetic resonance imaging (MRI scans) brain scans were obtained from MZ and dizygotic (DZ) healthy twin pairs. The inclusion of monozygotic, dizygotic, singletons, and family members, but also unrelated controls is done to assess the extent of genetic control over these structures. Within pair similarities for certain brain structures can be compared for each group, for example within pair similarity for brain structures with high heritability rates such as the total brain volume increases as pair members are more closely related genetically (monozygotic > siblings (included dizygotic) > unrelated controls). In one study healthy controls were also included (Oppenheim *et al.*, 1989). In five studies, unrelated and related singletons were included as well (Baaré *et al.*, 2001a; Posthuma *et al.*, 2000, 2002b; Schmitt *et al.*, 2008; Wallace *et al.*, 2006), and in one study (Atwood *et al.*, 2004) family members were also included. In three studies the heritability rates were investigated only in a male population (Carmelli *et al.*, 1998; Eckert *et al.*, 2002; Sullivan *et al.*, 2001), and the remaining studies consisted of a mixed population. The age range for most of the studies was between 23 and 80 years, except for one study (Peper *et al.*, 2009) in which 9-year-old children were included.

There were 37 structures measured in total. Some structures were measured in multiple studies, such as the total brain volume (six studies), total cranial/intracranial volume (four studies), white matter (seven studies), white matter hyperintensity (two studies), gray matter (six studies), corpus callosum (eight studies), cerebellar volume (three studies), frontal/temporal/parietal lobe (two studies), lateral ventricle (two studies), amygdalar and caudate (two studies), sulcus shape/length (two studies), planum temporal asymmetry (two studies), and ventricular volume (three studies). The rest of the structures were measured in a single study. In one study (Hulshoff Pol *et al.*, 2006) gray matter and white matter volume was measured for different brain parts such as superior frontal, medial frontal, postcentral gyrus, posterior cingulate, and Heschl's gyrus for the left and the right part. In Table I, the heritability rates ranging from 0.55 to 0.85 for gray matter and 0.69–0.82 for white matter volume are given. In another study (Schmitt *et al.*, 2008) various parts of the cerebral cortex were investigated and in Table II heritability rates between 0.30 and 0.57 for the cerebral cortex are recorded.

1. *Results on the Heritability of the Reviewed Studies*

Gross brain structures show higher heritability rates than specific structures. High heritability rates ranging from 0.70 to 0.99 are characteristic to intracranial volume, whole brain volume, total gray matter volume, total white matter volume, calosal volume, middle frontal volume, midline structures, and the volumes of both the right and left hemispheres (Table I). Studies including DZ, resulting in a full twin study (Bartley *et al.*, 1997; Carmelli *et al.*, 1998; Pennington *et al.*, 2000), reported heritability of >0.90 for total brain volume. A moderate heritability rate was found on the four lobes investigated, such as frontal, temporal, occipital, and

parietal lobe, ranging from 0.41 to 0.70 (Geschwind *et al.*, 2002), but conflicting results were reported on the lobes by Wallace *et al.* (2006) for the frontal, temporal and parietal lobe, resulting in high h^2 scores between 0.84 and 0.88. Moderate heritability rates are also reported for temporal horn volume, brain parenchyma, hippocampus, neocortex, white matter hyperintensity, and planum temporal asymmetry ranging from 0.60 to 0.63. Studies showing a moderate or a low heritability of brain structures are listed in Table II.

2. *Effects of Gender, Age, Handedness, and Development in Time*

Some studies have investigated variables that could have an influence on heritability rates. In a study by Steinmetz *et al.* (1995), the effect of gender on measuring the midsagittal area of the corpus callosum and total brain volume in 120 healthy young adults was shown, finding that the forebrain volume-adjusted size of the corpus callosum was larger in women than in men and that handedness had no effect on this measurement. However, an effect of handedness on cerebral asymmetry was found in two studies (Eckert *et al.*, 2002; Steinmetz *et al.*, 1995) reporting a lack of cerebral asymmetry in persons who were left handed. This might be explained by the hypothesis that early “epigenetic” events that take place during embryogenesis may contribute to a significant variability in the development of the anatomofunctional laterality of the cerebral hemispheres. In a study by Peper *et al.* (2009), children ($n = 47$) with signs of secondary sexual characteristics (based on Tanner stages) were compared to children without these signs and the heritability of brain structures was estimated using MRI scans. They found high heritability for most gross brain structures (see Table I) and regional brain structures. They also found that the onset of secondary sexual characteristics of puberty were associated with decreased frontal and parietal gray matter densities that accompany the transition of our brains from childhood into adulthood, still showing high heritability for brain structures such as global brain volumes, white matter density in fronto-occipital and superior longitudinal fascicles and gray matter density of (pre)frontal and temporal areas. Only one study (Pfefferbaum *et al.*, 2004) investigated the heritability rates examined over time and found no evidence for new genetic variance on the h^2 scores of corpus callosum and lateral ventricles recalculated after 4 years. The heritability of surface morphology, which is formed later in development and assumed to be under more environmental influence than the deeper structures (formed earlier in life and under more genetic control) indicate that sulcal depth effect was stronger for related twins. These results show that the shape of the deeper sulci is more strongly predetermined than that of superficial sulci, for example, sulcal depth having an influence on sulcal similarity. Also, subjects with similar brain shape have more similar patterns of their sulci, suggesting both features are the result of ontogenetically related processes (Bartley *et al.*, 1997; Biondi *et al.*, 1998;

Lohmann *et al.*, 1999; White *et al.*, 2002). This anatomical similarity was also found for the corpus callosum shape and size (Oppenheim *et al.*, 1989).

3. *Conflicting Results on Some Brain Structures*

Two studies (Posthuma *et al.*, 2000; White *et al.*, 2002) report high h^2 rates for cerebellar volume and one study (Wallace *et al.*, 2006) reports a moderate h^2 rate. This might be due to the age difference of the participants, and thus, the ongoing development of the brain. In the first two studies, adults were included, whereas the latter study, included adolescents (mean age of 11.5 years). A low heritability rate for lateral ventricle volume was found in one study (Wallace *et al.*, 2006), but a high h^2 score was reported in another (Pfefferbaum *et al.*, 2004), and an h^2 of 0.00 is recorded by Wright *et al.* (2002). The differences in these studies might be due to the differences in age of the participants, but could also be due to the differences in sample size. The mean age of the participants in the study by Wallace *et al.* (2006) was 11.5 years, reflecting results of brains in development. Additionally, the sample size in the study by Wright *et al.* (2002) is small compared to the bigger sample sizes of the other two studies. Conflicting results also exist on the heritability of sulcus shape and length, with one study indicating moderate heritability rate (Bartley *et al.*, 1997) and not reaching significance in another (Eckert *et al.*, 2002). There is a difference in the mean age between the studies, resulting in an older mean age (23 years) in the study by Bartley *et al.* (1997) and younger (6–16 years) in the study by Eckert *et al.* (2002). However, it is unclear what might be of influence in the differences between these studies, because different statistical heritability estimates were used in both. Other conflicting results are found for the ventricle volume, having a high h^2 rate in one study (Reveley *et al.*, 1984) and not being significant in other studies (Baaré *et al.*, 2001a; White *et al.*, 2002). In the study by Reveley *et al.* (1984), three statistical ways of calculating heritability rates were used, whereas the other two studies used one of the methods (both different from each other).

The differences between the studies with conflicting results might be a result of the differences in sample size, age, gender of the population (only male participants vs. mixed group), statistical method applied to calculate the heritability rates and the way measurements of the brain structures is done. As for the latter, some studies used the manual measurement of brain structures (region or VOI) and others automated (VBM, deformation based morphometry).

Seven studies used the Falconer method of heritability calculation and 15 studies used the structural equation modeling (SEM), in which the unique environmental factors are also included. Two studies (Geschwind *et al.*, 2002; Reveley *et al.*, 1984) used all three methods of heritability calculation, reaching significance in both studies for the three methods.

Heritability estimates show considerable differences between gross and specific brain structures. High heritability is characteristic for gross brain structures, such as intracranial volume, whole brain volume, cerebellar volume, total gray

matter and white matter volume, and calosal volume, with effect sizes in the high range. Moderate effect sizes have been found for structures such as the heritability of the different lobes, sulcus shape or length, white matter hyperintensity, hippocampal volume, and other brain structures like brain parenchyma, middle frontal regions, temporal horn and planum temporal asymmetry. The highly heritable gross brain structures are also the brain structures that are examined in multiple studies. The volume measurements of these brain structures and thus, the heritability rates, are easier to calculate than the specific, middle brain, deeper or small brain structures in both the manual and automated quantitative measurement techniques. From the reviewed literature, these brain structures with high and moderate heritability rates seem to be useful as endophenotypes.

B. HERITABILITY OF BRAIN STRUCTURES IN PATIENTS WITH SCHIZOPHRENIA COMPARED TO HEALTHY CONTROLS

Heritability calculations of the brain structures of patients with schizophrenia compared to healthy controls is very complicated, due to the impact of disease related factors on brain changes, together with the effect of medication intake and the use of drugs (Kanaan *et al.*, 2009; Rais *et al.*, 2008; van Haren *et al.*, 2007). Some studies show an increase in brain structure volumes and others a decrease. However, use of medication does not account for the total changes in the brain structures of patients with schizophrenia, since there are also studies showing brain changes in medication naïve patients (Cahn *et al.*, 2001; Okugawa *et al.*, 2007; Weinberger, 1995). Using twins concordant and discordant for schizophrenia in these studies would help elaborate the disease's effect on the brain changes to a certain degree.

Until now, there have been nine studies published on the heritability of brain structures in patients with schizophrenia compared to healthy controls. These studies are listed in Table III. The studies report on the heritability rates of brain structures in twins concordant and discordant for schizophrenia, monozygotic, and DZ, compared to healthy twins. These studies included adult patients, females, and males. Some brain structures have been studied in multiple studies, such as the total brain volume (four studies), gray matter volume (two studies), hippocampal volume (four studies), and the rest of the brain structures listed on the table in single studies.

High heritability for the intracranial volume, total gray and white matter volume, ranging from 0.72 to 0.89 was found (Table III). The overall gray matter volume was also found to be highly heritable in monozygote twins, both in the control and in the group of patients with schizophrenia. The heritability of total brain volume was found to be high in two studies (Hulshoff Pol *et al.*, 2004; Rijdsdijk *et al.*, 2005) and high in patients with schizophrenia, but moderate in healthy controls in another study (Narr *et al.*, 2002). In one study (Rijdsdijk *et al.*, 2005), a low heritability rate was found for the hippocampus, third and lateral ventricle.

TABLE III
HERITABILITY OF STRUCTURAL BRAIN PHENOTYPES IN PERSONS WITH SCHIZOPHRENIA COMPARED TO HEALTHY CONTROLS

Brain structure	Heritability of brain structure (h^2 , ICC or λ)	Sample size	Study ID
Intracranial or cranial volume	(1) SCZ: MZ:0.93, DZ:0.45 C: MZ:0.86, DZ: 0.35 (2) 0.89	(1) 15 MZ, 15 same sex DZ disc for SCZ, 29 healthy twin pairs (2) 11 MZ, 11 DZ disc for SCZ, 11 MZ and 11 DZ C twin pairs	(1) Baare <i>et al.</i> (2001b) ^a (2) Hulshoff Pol <i>et al.</i> (2004) ^a
TB volume	(1) SCZ: MZ: 0.86, DZ: 0.06 C: MZ: 0.93, DZ: 0.36 (2) 0.86 (3) 0.88 (4) 0.66	(1) 15 MZ, 15 same sex DZ disc for SCZ, 29 healthy twin pairs (2) 11 MZ, 11 DZ disc for SCZ, 11 MZ and 11 DZ C twin pairs (3) 14 MZ cc for SCZ and 10 MZ disc for SCZ, 17 MZ C pairs, 22 disc sibling pairs, 3 cc sibling pairs, 114 healthy C (4) 9 MZ, 9 DZ disc for SCZ, 14 MZ and 13 DZ healthy twin pairs	(1) Baare <i>et al.</i> (2001b) ^a (2) Hulshoff Pol <i>et al.</i> (2004) ^a (3) Rijdsdijk <i>et al.</i> (2005) ^a (4) Brans <i>et al.</i> (2008) ^a
GM volume	(1) SCZ: MZ: 0.73, DZ:0.05 C: MZ: 0.83, DZ = 0.32 (2) 0.72	(1) 20 MZ, 20 DZ twin pairs with SCZ, 20 MZ and 20 DZ healthy twin pairs ($\pm$ 48 years) (2) 11 MZ, 11 DZ disc for SCZ, 11 MZ and 11 DZ C twin pairs	(1) Cannon <i>et al.</i> (2002) ^b (2) Hulshoff Pol <i>et al.</i> (2004) ^a
WM volume	0.72	11 MZ, 11 DZ disc for SCZ, 11 MZ and 11 DZ C twin pairs	Hulshoff Pol <i>et al.</i> (2004) ^a
Frontal lobe	(1) FL; SCZ: MZ:0.84, DZ: 0.26 C: MZ: 0.93, DZ: 0.00	(1) 15 MZ, 15 same sex DZ disc for SCZ, 29 healthy twin pairs	(1) Baare <i>et al.</i> (2001b) ^a
Parietal lobe	(2) FL: 0.76, TL: 0.79	(2) 9 MZ, 9 DZ disc for SCZ, 14 MZ and 13 DZ healthy twin pairs	(2) Brans <i>et al.</i> (2008) ^a

(continued)

TABLE III (continued)

Brain structure	Heritability of brain structure (h^2 , ICC or λ)	Sample size	Study ID
Hippocampus	(1) SCZ: MZ: 0.68, DZ: 0.00 C: MZ: 0.73, DZ: 0.00 (2) SCZ: 0.42, C: 0.71 (3) 0.36 (4) L: 3.10, R: 2.33 (λ_s)	(1) 15 MZ, 15 same sex DZ disc for SCZ, 29 healthy twin pairs (2) 7 MZ cc and 16 MZ disc and 28 DZ disc twin pairs for SCZ, 28 MZ and 26 DZ healthy control twin pairs (3) 14 MZ cc and 10 MZ disc for SCZ (4) SCZ: 169 patients, unaffected siblings: 183, controls: 221	(1) Baare <i>et al.</i> (2001b) ^a (2) van Erp <i>et al.</i> (2004) ^a (3) Rijsdijk <i>et al.</i> (2005) ^a (4) Goldman <i>et al.</i> (2007)
Corpus callosum	(1) SCZ: MZ: 0.91, DZ: 0.33 C: MZ: 0.54, DZ: 0.74 (2) L: 4.93, R: 8.50 (λ_s)	(1) 10 MZ, 10 DZ twin pairs disc for SCZ and 10 MZ, 10 DZ unaffected co twin pairs (2) SCZ: 169 patients, unaffected siblings: 183, controls: 221	(1) Narr <i>et al.</i> (2002) ^b (2) Goldman <i>et al.</i> (2007)
Third ventricle	(1) SCZ: MZ: 0.36, DZ: 0.17 C: MZ: 0.71, DZ: 0.27 (2) 0.33	(1) 15 MZ, 15 same sex DZ disc for SCZ, 29 healthy twin pairs (2) 14 MZ cc for SCZ and 10 MZ disc for SCZ, 17 MZ C pairs, 22 disc sibling pairs, 3 cc sibling pairs, 114 healthy C pairs	(1) Baare <i>et al.</i> (2001b) ^a (2) Rijsdijk <i>et al.</i> (2005) ^a
Lateral ventricle	(1) SCZ: MZ: 0.67, DZ: 0.18 C: MZ: 0.73, DZ: 0.00 (2) 0.05 (3) L: 0, R: 0 (λ_s)	(1) 15 MZ, 15 same sex DZ disc for SCZ, 29 healthy twin pairs (2) 14 MZ cc for SCZ and 10 MZ disc for SCZ, 17 MZ C pairs, 22 disc sibling pairs, 3 cc sibling pairs, 114 healthy C pairs (3) SCZ: 169 patients, unaffected siblings: 183, controls: 221	(1) Baare <i>et al.</i> (2001b) ^a (2) Rijsdijk <i>et al.</i> (2005) ^a (3) Goldman <i>et al.</i> (2007)

Hypothalamus	MZ: ICC = 0.58, $p < 0.05$, DZ: 0.07. Correction for TB→n.s.	11 MZ, 11 DZ same sex twin pairs, disc for SCZ and 11 MZ, 11 DZ same sex healthy twin pairs	Koolschijn <i>et al.</i> (2007) ^a
PHC gyrus	SCZ: MZ: 0.34m DZ: 0.37 C: MZ: 0.70, DZ: 0.10	15 MZ, 15 same sex DZ disc for SCZ, 29 healthy twin pairs	Baare <i>et al.</i> (2001b) ^a
Dorsal striatum	L: 0, R: 0.87 (λ_s)	SCZ: 169 patients, unaffected siblings: 183, controls: 221	Goldman <i>et al.</i> (2007)

Summary of published studies by August 2009 (PubMed and Medline citations) on the heritability of brain structural phenotypes with study results from twins concordant (cc) and discordant (disc) for schizophrenia (SCZ), singletons, and healthy controls (C). Heritability is denoted as h^2 or as intraclass correlation factor (ICC). A higher ICC for monozygotic (MZ) twins than for dizygotic (DZ) twins indicates a genetic component to these structures, but large confidence intervals indicate that the similarities measured are a rough estimates of the degree to which a brain structure is genetically controlled.

Another way of denoting the heritability is by $\lambda_s = \text{Risch's } \lambda$ as a measure of heritability. For Risch's λ , $\lambda_s = 1$ is the expected value for nonfamilial traits, whereas $\lambda_s > 2.0$ is considered evidence for familiarity. h^2 or ICC or Risch's λ = heritability rate.

TB, total brain volume; WM, total white matter volume; GM, total gray matter volume; WM, white matter volume; GM, gray matter volume; CC, corpus callosum; AC-PC distance, the distance between anterior and posterior commissure; CB, cerebellar volume; FL, frontal lobe; TL, temporal lobe; PL, parietal lobe; OL, occipital lobe; OC, occipital cortex; TH, temporal horn volume; LV, lateral ventricle volume; TV, third ventricle; HC, hippocampal volume; Parahip, parahippocampal gyrus; Cau, caudate nucleus; Thal, thalamus; SS or SL, sulcus shape or sulcus length; put, putamen; Hpt, hypothalamus; PHC gyrus, parahippocampal gyrus; MZ, monozygotic; DZ, dizygotic; M, male; F, female; Sibs, siblings; n.a., not available; n.s., not significant.

^aSEM, structural equation modeling.

^bFalconer method.

Low heritability rates were also found in the group of DZ twins discordant for schizophrenia (Narr *et al.*, 2002), for the overall gray matter volume in control DZ twins and in DZ twins with schizophrenia. There was no significant heritability found for the parahippocampal gyrus, third and lateral ventricle (Baaré *et al.*, 2001b) or for the hypothalamus (Koolschijn *et al.*, 2007). The study by Brans *et al.* (2008) reports on whether genetic (heritability) and/or environmental factors are associated with progressive brain volume changes in schizophrenia. They found that significant decreases over time in whole brain, frontal, and temporal lobe volume in patients with schizophrenia and in their unaffected co-twins compared with control twins revealed significant additive influences on the correlations between schizophrenia liability and progressive whole brain (0.66), temporal (0.79), and frontal (0.76) lobe changes.

The samples in these studies consist of both healthy MZ and DZ twins and twins concordant and discordant for schizophrenia, with the exception of three studies (Baaré *et al.*, 2001b; Hulshoff Pol *et al.*, 2004; Koolschijn *et al.*, 2007) where twins concordant for schizophrenia were not included, resulting in a sample group where environmental factors played a more important role in the development of the disorder and a genotypic estimation of the true population genetic variance was not possible.

Three studies (Cannon *et al.*, 2002; Narr *et al.*, 2002) used the Falconer method of heritability estimates and four studies used the SEM method (Brans *et al.*, 2008; Hulshoff Pol *et al.*, 2004; Rijdsdijk *et al.*, 2005; Van Erp *et al.*, 2004). The study by Koolschijn *et al.* (2007) used the intraclass correlation factor (ICC) to estimate the heritability rates of the hypothalamus. One study, by Goldman *et al.* (2007), used ICC and also Risch's relative risk for siblings (λ_s) for heritability measurements of each region. Risch's relative risk for siblings (λ_s), was calculated to quantitatively measure the likelihood that siblings of patients with volumetric reductions or increases would express the phenotype themselves. Because this parameter depends on the presence or absence of the phenotype, cutoffs were defined on the basis of the distribution of the volumes in patients.

One complicating factor in the heritability estimates of brain structures in twin studies is that the twin discordant for schizophrenia also shows, to a milder degree, brain changes seen in their co-twins with schizophrenia. The unaffected twins show lower brain volume, lower hemispheric volumes and/or frontal lobe gray matter volume decrease. These observations may suggest the involvement of genetic factors in cortical gray matter deficits in patients with schizophrenia (Baaré *et al.*, 2001b; Reveley *et al.*, 1984; Suddath *et al.*, 1990). As suggested by Cannon *et al.* (2002), it is important that these studies include an evaluation of the regional cortical variation and that individual differences in gyral/sulcal patterning and shape are taken into account. It is not clear to what extent these changes are similar to the changes in their co-twins who have schizophrenia. A distinction between these possibly genetic differences and the disease related changes in the

brain should be done by isolating the topography of nongenetic, disease related differences in cortical gray matter volume, as suggested by Cannon *et al.* (2002).

C. HERITABILITY OF BRAIN STRUCTURES IN NONHUMAN PRIMATES (MONKEYS)

Studies in pedigrees, where there is an extensive control of the environmental factors, are particularly useful in heritability calculations. Studies in NHPs are therefore a good model for genetic control and could be useful in heritability calculations as mentioned previously.

There are five studies published on the heritability of brain structures in NHPs (e.g., monkeys). These studies are listed in Table IV. Results of these studies strongly support findings from human studies showing the heritability of gross brain structures in the high effect size range, such as whole brain volume, cerebral volume, and cranial size. The moderate effect size range for heritability was reported for cranial capacity, sulcus length, brain weight, hippocampus and surface area, and gray matter. The number of studies reporting on heritability of brain structures in NHPs is limited and the sample sizes of monkeys included in these studies is small. There are only two studies (Mahaney *et al.*, 1993; Rogers *et al.*, 2007) in which the same monkey type was included, but these studies did not look at the same brain structure, which makes comparison difficult. Only the study by Fears *et al.* (2009) used a big sample size of vervet monkeys and calculated heritability estimates using manual tracings as well as automated tracings of brain structures. In this study, high heritability rates are found for gross brain structures, such as total brain volume, cerebral volume and corpus callosum. In contrast to other NHP heritability estimations of the hippocampus, this study showed a high heritability rate for the hippocampus. The findings from the NHP studies support the findings in human twin studies.

Table IV shows that samples consist of different types of monkeys, making it difficult to compare the conflicting results between studies on the same brain structure, such as the hippocampus, where Lyons *et al.* (2001) find moderate heritability rates and Fears *et al.* (2009) find a high heritability rate. There is also a big difference in the sample sizes.

One other complicating factor is the method of measuring the volume of brain structures (manual vs. automated or both), particularly, the calculation of heritability of brain structures across the different studies. The method used by Lyons *et al.* (2001) consists of obtaining MRI scans of Guyanese monkeys and quantitative estimates of the heritability rates were generated by using the one-way ANOVA as used to evaluate paternal half siblings effect. Rogers *et al.* (2007) used the VBM approach to look at the regional differences in the genetic effects on brain structure and calculated the heritability estimates. The study by Cheverud *et al.* (1990) shows that brain size was defined as endocranial capacity

TABLE IV
HERITABILITY OF STRUCTURAL BRAIN PHENOTYPES IN NONHUMAN PRIMATES

Brain structure	Heritability of brain structure (h^2 , ICC or λ)	Sample size and monkey type	Study ID
<i>Brain</i>			
(1) Weight	(1) 0.409, $p < 0.005$	(1) Baboons: 601; 307 assigned to 25 pedigrees (2–49 members), 294 individual animals	(1) Mahaney <i>et al.</i> (1993)
(2) Size Cranial capacity	(2) 0.75, $p < 0.005$ 0.60, $p = 0.02$	(2) Rhesus Macaques; 179 skeletons, measuring endocranial capacity and using mother offspring regression and SDS method	(2) Cheverud <i>et al.</i> (1990)
Total brain volume	(1) 0.82 ($p = 0.00022$) (2) 0.99 (SE = 0.06)	(1) Baboons (papio hamadryas): 109 MRI Scans (VBM approach) (2) Vervet research colony: 357 (>2 years of age)	(1) Rogers <i>et al.</i> (2007) (2) Fears <i>et al.</i> (2009)
Gray matter volume	0.67, $p = 0.01$	Baboons (papio hamadryas): 109 MRI Scans (VBM approach)	Rogers <i>et al.</i> (2007)
Cerebral volume	(1) 0.86, $p = 0.0006$ (2) 0.98 (SE = 0.09)	(1) Baboons (papio hamadryas): 109 MRI Scans (VBM approach) (2) Vervet research colony: 357 (>2 years of age)	(1) Rogers <i>et al.</i> (2007) (2) Fears <i>et al.</i> (2009)
Surface area of the cerebrum	0.673, $p = 0.0069$	Baboons (papio hamadryas): 109 MRI Scans (VBM approach)	Rogers <i>et al.</i> (2007)
Corpus callosum	0.87 (SE = 0.07)	Vervet research colony: 357 (>2 years of age)	Fears <i>et al.</i> (2009)
Hippocampus	(1) 0.54 ($F = 2.58$, $p = 0.02$) (2) 0.95 (SE = 0.07)	(1) Guyanese (saimiri sciures): 39 MRI scans (1 way ANOVA) (2) Vervet research colony: 357 (>2 years of age)	(1) Lyons <i>et al.</i> (2001) (2) Fears <i>et al.</i> (2009)
Sulcus length	0.31, $p < 0.05$	Rhesus Macaques; 179 skeletons, measuring endocranial capacity and using mother offspring regression and SDS method	Cheverud <i>et al.</i> (1990)

Summary of published studies by August 2009 (PubMed and Medline citations) on the heritability results of brain structural phenotypes in nonhuman primates. Heritability is denoted as h^2 .

SDS, symmetric differences squared method, SE, standard error, MRI, magnetic resonance imaging; VBM, voxel based morphometry method.

and was measured by filling the cranium with mustard seed, then pouring the enclosed seed into a graduated cylinder. The cube root of cranial capacity was used in statistical analysis to better fit the data with statistical models. The heritability was estimated by standard mother–offspring regression (Falconer and Mackay, 1996; Falconer *et al.*, 1981) and a slight modification of the symmetric-differences-squared (SDS) method (Bruckner and Slanger, 1986). In the study by Mahaney *et al.* (1993), the heritability estimates, specifically of the brain weight, were measured by quantitative genetic analyses on available loge-transformed organ weights. Fears *et al.* (2009) used both manual and deformation based volume measurements (automated) to measure volumes of brain structures.

Despite the difference in heritability rates of brain structures between the few studies published on this topic, the results are nonetheless comparable to the human studies. The newest publications on this subject in NHP (Fears *et al.*, 2009; Rogers *et al.*, 2007) have used big sample sizes and also comparable volume measurements on the MRI scans as seen in human studies. More research on heritability in NHPs will help us get more insight into the genetic control on brain structures and will create the potential for future genetic mapping of QTLs underlying the variance in the heritability of these brain structures.

III. Genes for Brain Structures in Healthy and Persons with Schizophrenia

The dramatically increased brain volume plays an important role in the origin of our species. In humans, brain volume is a quantitative trait with high heritability (Posthuma *et al.*, 2002b; Thompson *et al.*, 2001). Disturbances in brain development is one of the explanations for neuropsychiatric disorders such as schizophrenia (Weinberger, 1995), suggesting that developmental genes involved in the development of the brain may overlap with the causal genes, for example, potential candidate genes, for schizophrenia (Murray, 1994). However, no susceptibility genes with high effect sizes have been found for schizophrenia. Therefore, most studies have focused on the testing of specific genetic markers in a known candidate gene for association with the different endophenotypes. In this study, research using brain structures as neuroanatomical endophenotypes in healthy and patients with schizophrenia are reviewed. Studies on the association between specific genes and brain structures and between genes and brain morphological changes in schizophrenia will be reviewed.

A. GENES FOR BRAIN STRUCTURES IN HEALTHY PERSONS

There are eight studies published on the genes for brain structures in healthy persons. These studies are listed in Table V. These studies looked at brain structures and specific genes (and alleles or SNPs, single nucleotide polymorphisms) for these brain structures and at the interaction between these genes.

TABLE V
GENES FOR STRUCTURAL BRAIN PHENOTYPES IN HEALTHY PERSONS

Genes (alleles)	Association with brain structures	Sample size	Study ID
BDNF (both Val66 Met allele)	(1) Hippocampal gray matter: Left HC GM: $p = 0.013$, $t = 2.24$, Right: $p < 0.001$, $t = 3.41$ (2) Hippocampal volume: $\downarrow$ 12.5%, $df = 33.1$, $F = 4.24$, $P = 0.048$	(1) 111 Persons (2) 36 persons	(1) Pezawas <i>et al.</i> (2004) (2) Bueller <i>et al.</i> (2006)
MCHP1 ASPM	(1) Brain volume: MCHP1: n.s. ($df = 2$, 112, $P = 0.20$), ASPM: n.s. ($df = 2$, 114, $p = 0.49$) (2) Cranial volume: MCHP1: $\uparrow$ volume in males with allele rs 1057090 ($R = 0.126$, $P = 0.016$)	(1) 120 persons (2) 867 (387 M, 480 F)	(1) Woods <i>et al.</i> (2006) (2) Wang <i>et al.</i> (2008)
COMT	Gray matter density in anterior cingulate cortex: $\downarrow$ Gray Matter density	75 persons (persons at risk for SCZ) 87 persons	McIntosh <i>et al.</i> (2007) McIntosh <i>et al.</i> (2008)
Neuroglin 1 (rs69994992)	White matter density: $\downarrow$ White Matter density ant limb of the internal capsule ($t = 4.41$, $p = 0.0028$ (T allele). $\downarrow$ Fractional anisotropy in C allele homozygotes		
APOE ϵ 4	ϵ 4 allele: $\downarrow$ Hippocampal volume	10 MZ twin pairs (± 62.5 years) 106 persons	Plassman <i>et al.</i> (1997) Buckholtz <i>et al.</i> (2007)
RGS4 (A alleles)	Gray matter: RST gyrus: $Z = 3.49$, $p = 0.000$, Thalamus: $Z = 3.21$, $p = 0.001$, RVLPFC: $Z = 3.14$, $p = 0.001$, LIPL: $Z = 3.08$, $p = 0.001$ White matter: RVLPFC: $Z = 3.68$, $p = 0.000$, LVLPFC: $Z = 4.17$, $p = 0.000$, LHC: $Z = 3.77$, $p = 0.000$		

Summary of published studies by August 2009 (PubMed and Medline citations) on genes for brain structural phenotypes in healthy persons. The studies report on the brain structures that is investigated, the sample size, the results of the interaction between genes (alleles) and brain morphological changes (significant or nonsignificant association (n.s.), a decrease ($\downarrow$) or increase ($\uparrow$) in brain volume/density in interaction with a gene or an allele) and on the (candidate) genes/alleles.

BDNF, brain derived neurotrophic factor; COMT, catechol-*o*-methyl transferase; NRG, neuroglin 1; MCPH1, microcephalin 1; ASPM, abnormal spindle-like microcephaly associated; RGS4, regulator of G protein signaling; C, controls; SCZ, schizophrenia; MZ, monozygotic; DZ, dizygotic; RVLPFC, right ventrolateral prefrontal cortex; LVLPFC, left ventrolateral prefrontal cortex; LIPL, left inferior parietal lobule; RST gyrus, right superior temporal gyrus.

In some of the studies the interaction of the specific genes with the variance in brain morphology is expressed in quantitative measures.

As presented in Table V, the genetics of heritability of brain structures indicate that in one study (Wang *et al.*, 2008) there is a significant association ($p = 0.016$) between the MCPH1 gene and intracranial volume, reaching bigger intracranial volume in patients with the rs1057090 allele and not reaching a significant association in another study (Woods *et al.*, 2006), not for the MCPH1 gene ($p = 0.20$) nor for the ASPM gene ($p = 0.49$). The heritability of gray matter density has been investigated in three studies. In the first study, there was a significant association for the right ($p < 0.001$) and left hippocampus ($p = 0.013$) for the *BDNF* gene for the Val66met allele carriers (Pezawas *et al.*, 2004). In the second study, there was a significant association in the right superior gyrus, temporal lobe, right prefrontal cortex, and left inferior parietal lobe ($p = 0.001$) (Buckholtz *et al.*, 2007) for the *RGS4* gene and specifically persons carrying the A allele. In the third study, there was a significant association in the anterior cingulate cortex for the *COMT* gene, specifically for persons carrying the Val gene (McIntosh *et al.*, 2007). The white matter density shows a significant association with two genes, namely, the *RGS4* gene (A allele carriers, $p = 0.000$) in the right and left ventral prefrontal cortex and left hippocampus in one study (Buckholtz *et al.*, 2007) and neuroglin 1 (rs699994992 allele carriers, $p = 0.00028$) with a white matter density decrease in anterior limb of the internal capsula in another study (McIntosh *et al.*, 2007). The hippocampal volume and the association with the APOE ϵ 4 gene shows HC volume decrease in one study (Plassman *et al.*, 1997) and of 11.2% reduction in volume in another study ($p = 0.048$) (Bueller *et al.*, 2006) for the *BDNF* gene Val66met allele carriers.

The samples consist of healthy individuals, not related, except for one study in which 10 MZ twin pairs were compared (Plassman *et al.*, 1997) and in another study, persons at risk for schizophrenia were included (McIntosh *et al.*, 2007). In the study by Woods *et al.* (2006), individuals from different ethnic backgrounds were included, but correcting the data for race, ethnicity or sex did not change the results. The sample in the study by Wang *et al.* (2008) consisted of 90% Chinese and 10% other ethnic minorities. The study by Buckholtz *et al.* (2007) consisted of Caucasian subjects of European descent. The sample in the study by McIntosh *et al.* (2007) consisted of persons at risk for schizophrenia.

The method used by the studies in Table III varies from one study to the other. In the study by Woods *et al.* (2006), heritability of brain volume related to genotype was estimated by using the coefficient of the genetic terms in the full fitted ANOVA model to compute the variance attributable to genotype. This variance was then divided by the total variance to estimate heritability. This method was also used by Bueller *et al.* (2006) and Pezawas *et al.* (2004). The study by Wang *et al.* (2008) used the linear regression model to do the single SNP association analysis. Buckholtz *et al.* (2007) used multimodal neuroimaging to

investigate the impact on brain structure and function and looking at allelic variation. The study by McIntosh *et al.* (2007) imported the data into SAS (version 9.1, SAS Institute, Cary, North Carolina) and the effects of group status by COMT group interactions were investigated by analysis of variance.

B. GENES FOR BRAIN STRUCTURES IN PATIENTS WITH SCHIZOPHRENIA

There are 23 studies where the genetics of variation on heritability of brain structures was investigated in patients with schizophrenia compared to healthy controls. These studies report on the association between specific genes and brain morphological changes in schizophrenia. Several candidate genes for schizophrenia have been studied and the association with specific brain morphological changes has been examined. There are multiple studies on the Brain Derived Neurotrophic Factor gene (*BDNF* gene) (five studies), Catechol-*O*-Methyl Transferase gene (*COMT* gene) (three studies), Disrupted in Schizophrenia 1 (*DISC1*) (two studies), APOE $\epsilon 4$ gene (two studies) and Interleukin-1 receptor antagonist gene (*IL 1*) (two studies). These studies are listed in Table VI. There are single studies on the Neuroglin 1 (*NRG1*), prion protein (*PP* gene), tumor necrosis factor receptor-II gene (*TNF-RII* gene), *NOTCH4* gene, *PCMI* gene, *Plexin B3* gene, *GAD1* gene, *PROHD* gene, regulation of G protein signaling (*RGS4*) and *neurotrophin* gene. These studies are listed in Table VII. The brain structures that are looked at in multiple studies include: the brain lobes (six studies), hippocampal volume (eight studies), ventricles (three studies), gray matter volume (seven studies), white matter volume (seven studies) and cerebrospinal fluid (CSF) volume (three studies). The following structures have been studied in a single study: cerebral asymmetry, intracranial volume, regional gray matter volume/density, prefrontal cortex, caudate, putamen, and cerebellum.

One of the most investigated genes is the *BDNF* gene. BDNF is a neurotrophic factor involved in the development and maintenance of the nervous system. It is neuroprotective and prevents cell loss in the cerebral cortex, the striatum, and the hippocampus (Angelucci *et al.*, 2005). The *BDNF* gene consists of several polymorphisms that affect the amino acid sequence and possibly the function of the protein. In patients with schizophrenia, lower concentrations of BDNF have been found in cortical areas and the hippocampus as well as in the blood serum. The *COMT* gene is thought to be involved in the degradation of dopamine. The BDNF allele, in particular the Met allele, was found to be associated with a decrease in hippocampal volume (Bueller *et al.*, 2006) and with frontal lobe and occipital lobe gray matter in two other studies (Ho *et al.*, 2006; Pezawas *et al.*, 2004). Szeszko *et al.* (2005) found an association in a post hoc analysis between hippocampal volume decrease for schizophrenia patients only and no association with the intracranial volume. Wassink *et al.* (1999) studied the BDNF alleles in 48 trios and found an association with the parietal lobe, but not with the temporal or

TABLE VI
MOST STUDIED GENES FOR STRUCTURAL BRAIN PHENOTYPES IN PATIENTS WITH SCHIZOPHRENIA COMPARED TO HEALTHY PERSONS

Genes (alleles)	Association of genes/alleles with brain structures	Sample size	Study ID
<i>BDNF</i>			
(1) BDNF	(1) Parietal lobe: $\chi = 7.90, p = 0.0049$, n.s. with FL, TL, OL, ventricles	(1) 48 trios	(1) Wassink <i>et al.</i> (1999)
(2) Val66Met vs val/val	(2) Hippocampus: $F = -3.22, df = 42, p = 0.002$ (SCZ + C); $F = 11.72, df = 15, p = 0.004$ (SCZ), Intracranial volume: $t = -1.24, df = 42, p = 0.221$ (SCZ + C)	(2) 19 SCZ, 25 C	(2) Szeszko <i>et al.</i> (2005)
(3) Met carriers	(3) GM volume in 2 cognitive domains: $\downarrow$ GM vol in TL: $F = 5.44, p = 0.02$ and OL: $F = 5.73, p = 0.02$	(3) 183 SCZ, 80 C	(3) Ho <i>et al.</i> (2006)
(4) Polymorphisms	(4) All brain structures in literature identified abnormal in SCZ: 111757G/C: larger frontal GM ($p < 0.001$) (SCZ), 270 C/T: totale caudate volume ($p = 0.006$) and GM in caudate ($p = 0.022$), 111757G/C + 270 C/T + 633T/A + Val66Met = n.s. for HC, n.s. for controls either with any brain structure except putamen ($p = 0.006$)	(4) 30 SCZ, 104 C	(4) Agartz <i>et al.</i> (2006)
(5) Val66Met	(5) $\downarrow$ Frontal GM in Met allele carriers ($F = 4.20, df = 1, 113, p = 0.05$), $\uparrow$ lateral ventricles and sulcal CSF ($\geq 3.95, df = 44, p \leq 0.0003$), $\uparrow$ CSF in FL and TL ($F \geq 6.71, df = 1, 113, p \leq 0.01$), n.s. in PL and OL ($F \leq 1.84, df = 1, 113, p \geq 0.18$)	(5) 119 SCZ	(5) Ho <i>et al.</i> (2007)
<i>COMT</i>			
(1) Val158Met	(1) FL, GM, WM, CSF: n.s. ($F = < 1.43, df = 2, 148, P > 0.24$)	(1) 100 SCZ, 49 C	(1) Ho <i>et al.</i> (2005)
(2) Polymorphisms	(2) Val COMT: ACC (bilateral) $p = 0.007$, MTG (R) = 0.016, Amygdala-uncus (L) $p = 0.01$, thalamus (left) $p = 0.014$	(2) 30 SCZ, 104 C	(2) Ohnishi <i>et al.</i> (2006)
(3) Val allele, PRODH (rs20086720)	(3) $\uparrow$ GM density in right superior temporal gyrus (AA genotype of COMT), $p = 0.039$, $\downarrow$ WM density bilateral frontal lobes (GG genotype of PRODH), $p < 0.05$, COMT val allele epistasis with PRODH alleles: $\uparrow$ WM left anterior lobe	(3) 51 SCZ (M)	(3) Zinkstok <i>et al.</i> (2007)

(continued)

TABLE VI (continued)

Genes (alleles)	Association of genes/alleles with brain structures	Sample size	Study ID
<i>DISC1</i>			
(1) Rare DISC1/TRAX haplotypes	(1) HEP1 allele: ↓focal GM density sup + inf frontal gyri ($p < 0.05$) ($p < 8.61 \times 10^{-31}$ and $P < 1.21 \times 10^{-8}$) ↓HC volume ($\chi^2 = 3.42$, $p = 0.06$, trend), HEP2/HEP3 allele: n.s. HC volume change ($p = 0.58$), AATG Haplotype: ↓focal GM density in superior + middle frontal gyri and superior temporal gyrus and superior parietal cortex (2) ↓HC gray matter volume (Serine allele) ($d = 0.36$, $p < 0.05$)	(1) 6 MZ + 1 DZ twins pairs cc for SCZ, 28 MZ and 31 DZ C twin pairs (2) 86 SCZ (Serine), 72 C (Cysteine)	(1) Cannon <i>et al.</i> (2005) (2) Callicott <i>et al.</i> (2005)
(2) Serine/Cysteine allele			
APOE $\epsilon 4$	(1) HC: $t = 0.23$, $df = 33$, $p = 0.82$, TL volume: $t = 0.27$, $df = 33$, $p = 0.79$ (2) HC: n.s. ($T = 1.9$, $df = 19$, $p < 0.10$), Cerebral Asymmetry: n.s. ($T1.9$, $df = 19$, $P < 0.10$)	(1) 40 SCZ COS, 57 C (2) 21 SCZ	(1) Fernandez <i>et al.</i> (1999) (2) Hata <i>et al.</i> (2002)
IL 1	(1) GM volume: Frontal: $F = 6.06$, $df = 1$, $p < 0.02$, Temporal: $F = 11.62$, $df = 1$, $p = 0.001$, WM volume whole brain: $F = 5.54$, $df = 1$, $p < 0.03$ (2) ↑ Ventricles: Left: $t = 3.504$, $df = 21$, $p = 0.002$, Right: $t = 2.784$, $df = 21$, $p = 0.01$, HC: $t < 1.6$, $df = 21$, $p =$ n.s., DLPFC GM: $T < 1.5$, $df = 21$, $p =$ n.s. ($p = 0.06$)	(1) 44 SCZ, 48 C (2) 23 SCZ, 45 C	(1) Meisenzahl <i>et al.</i> (2001) (2) Papiol <i>et al.</i> (2005)

Summary of published studies by August 2009 (PubMed and Medline citations) on genes for brain structural phenotypes including study results from patients with schizophrenia (SCZ) compared to healthy controls (C) in most studies. The studies report on the brain structure that is investigated, the sample size, the results of the interaction between genes (alleles/SNPs, single nucleotide polymorphisms) and brain morphological changes (significant or nonsignificant association (n.s.), a decrease (↓) or increase (↑) in brain volume/density in interaction with a gene or an allele or a SNP).

SCZ, schizophrenia; SCZ COS, schizophrenia childhood onset (before age 12); C, controls; cc, concordant and disc, discordant; HC, hippocampus; GM volume, gray matter volume; WM volume, white matter volume; CSF volume, cerebrospinal fluid spaces volume; DLPFC GM, dorsolateral prefrontal cortex gray matter; ACC, anterior cingulate cortex; MTG, middle temporal gyrus; TL volume, Temporal lobe volume; BDNF, brain derived neurotrophic factor; COMT, catechol-*o*-methyl transferase; RGS4, regulators of G protein signalling; NRG1, neuregulin 1; PP, prion protein gene; NT3 gene, neurotrophin 3 gene; APOE, apolipoprotein E; PRNP, prion protein; DISC1, disrupted in schizophrenia 1; IL-1RN, interleukin -1 receptor antagonist; TNF, tumor necrosis factor; NOTCH4 gene; PCMI gene; PLXN B3, plexin B3 gene; GAD1 gene; ph, polymorphism; L, left; R, right; n.s., not significant; trios, both parents and a child; vol, volume; ant, anterior; sup, superior; inf, inferior.

GENES FOR STRUCTURAL BRAIN PHENOTYPES IN PATIENTS WITH SCHIZOPHRENIA COMPARED TO HEALTHY CONTROLS, GENES STUDIED IN SINGLE STUDIES

TABLE VII

Genes (alleles)	Association of genes/alleles with brain structures	Sample size	Study ID
NT gene (A3 allele)	HC volume: Mean Left HC: $t = 1.87$, $df = 10$, $p = 0.091$, Mean Right HC: $t = 2.72$, $df = 10$, $p = 0.022$	12 SCZ	Kunugi <i>et al.</i> (1999)
TNF-RII (homozygous allele 1)	Allele 1: $\uparrow$ ventricle volume, $\downarrow$ Frontal lobe volume	140 probands with SCZ, 197 parents of probands, 46 C	Wassink <i>et al.</i> (2000)
PRNP gene (Met codon 129 allele)	WM volume: $F = 5.285$, $df = 1/84$, $p = 0/024$, CSF volume: $F = 4.400$, $df = 1/84$, $p = 0.039$, GM volume: $F = 1.843$, $df = 1/84$, $p = 0.178$ (n.s.)	43 SCZ and 47 C	Rujescu <i>et al.</i> (2002)
NOTCH4 (CTG) _n	Frontal lobe (GM, WM, CSF); n.s. ($\chi = 7.09$, $df = 6$, $p = 0.31$)	158 SCZ, 48 C	Wassink <i>et al.</i> (2003)
GADI	GM volume: $\downarrow$ GM volume in 6 out of 10 SNPs ($p = 0.04-0.003$)	72 SCZ COS, 25 C	Addington <i>et al.</i> (2005)
RGS4 (non G allele)	DLPFC: $\downarrow$ Left DLPFC GM volume, SNP4 ($p = 0.0072$), SNP18 ($p = 0.012$), $\downarrow$ Right DLPFC GM volume, SNP1 ($p = 0.0024$), SNP4 ($p = 0.012$), SNP7 ($p = 0.022$)	30 SCZ, 27 C	Prasad <i>et al.</i> (2005)
PCMI (allele + or - on chromosome 8)	Gray matter bilateral orbitofrontal: $\downarrow$ GM volume, $F = 4.6$, $p < 0.05$ Gray matter in temporal lobe, HC, inferior temporal cortex: $\downarrow$ GM, $F = 12.7$, $p < 0.01$	14 SCZ (allele +), 14 C 13 SCZ (allele -), 14 C	Gurling <i>et al.</i> (2006)
NRG1 (risk allele 420M9-1395)	GM trajectories, volumes: $\uparrow$ ($p = 0.001$) WM trajectories, volumes: $\uparrow$ ($p = 0.04$)	78 SCZ COS, 165 C	Addington <i>et al.</i> (2007)
PLXNB3 (haplotype A+)	WM: $F = 4.275$, $df = 1/85$, $p = 0.042$, GM: $F = 2.362$, $df = 1/85$, $p = 0.128$, CSF: $F = 5.302$, $df = 1/85$, $p = 0.024$	48 SCZ, 48 C	Rujescu <i>et al.</i> (2007)

Summary of published studies by August 2009 (PubMed and Medline citations) on genes for brain structural phenotypes including study results from patients with schizophrenia (SCZ) compared to healthy controls (C) in most studies. The studies report on the brain structure that is investigated, the sample size, the results of the interaction between genes (alleles/SNPs, single nucleotide polymorphisms) and brain morphological changes (significant or nonsignificant association (n.s.), a decrease ($\downarrow$) or increase ($\uparrow$) in brain volume/density in interaction with a gene or an allele or a SNP).

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frontal lobe. Ho *et al.* (2007) found an association between Met allele and a decrease in frontal gray matter and with an increase in lateral ventricles and in CSF sulcal volume and an increase in CSF volume in the frontal and temporal lobe, but not in the parietal and occipital lobe. Agartz *et al.* (2006) found a significant association of the 11757 G/C polymorphism with larger frontal gray matter and a 270C/T polymorphism with caudate volume and gray matter volume in caudate and no association with hippocampus, nor with brain volumes in controls except for the association between the -633 T/A polymorphisms and putamen. This *COMT* gene is the second most investigated gene and is located in a region of chromosome 22q11, which is deleted in patients with the velocardio-facial syndrome. In 25% of these patients, schizophrenia is diagnosed as well. In a recent meta-analysis the *COMT* gene has not been strongly associated with schizophrenia (Williams *et al.*, 2007). *DISC1* gene is one of the genes found to be associated with several psychiatric disorders, such as schizophrenia, bipolar disorder, and depression (Hennah *et al.*, 2006). This gene was studied in a large Scottish family study, where a translocation was found to be inherited with different psychiatric disorders (Porteous, 2008). In persons with schizophrenia, there was a disruption of a gene of unknown function on one of the chromosomal breakpoints, and was therefore named disrupted in schizophrenia 1. This gene and the enzymes it codes for are of influence to neuronal migration and memory. In the study by Cannon *et al.* (2005), logistic regression was used to evaluate associations of *DISC1* and *TRAX* haplotypes with diagnostic status, entering age, sex, substance use disorder, and parental social class as covariates and controlling for the dependency of observations within twin pairs using generalized estimation equations. The data of this study show that one of the three haplotypes (HEP 1) was associated with schizophrenia. The HEP1 haplotype (i.e., TCG) defines a 3-SNP segment located near the translocation break point of *DISC1*. The HEP1 haplotype was more often associated with individuals with schizophrenia (61.0%; $\chi^2 = 6.8$ [$p = 0.02$]; OR = 2.6; 95% CI = 1.2–5.6) when a recessive mode of transmission was assumed, but not among their nonschizophrenic co-twins (49.1%; $\chi^2 = 0.8$ [$p = 0.38$]). This haplotype was also significantly associated with small, focal reductions of gray matter in the superior and inferior frontal gyri. The HEP1 haplotype also shows evidence of an association with hippocampal volume reduction ($\chi^2 = 3.42$, $p = 0.06$). The regions affected by *DISC1* and *TRAX* haplotypes identified in these maps have previously been shown to be highly heritable in normal twins (Thompson *et al.*, 2001). These regions are also sensitive to the degree of genetic relationship to an affected individual in twins discordant for schizophrenia (Cannon *et al.*, 2002; Van Erp *et al.*, 2004).

The APOE $\epsilon 4$ allele is a major risk allele for late-onset Alzheimer's disease (Mahaney *et al.*, 1993). The study by Hata *et al.* (2002) shows similar findings to studies carried out in patients with Alzheimer's disease (Soininen and Riekkinen, 1996; Tohgi *et al.*, 1997) in that there is a decrease in hippocampal volume of the

ε4 allele carriers compared to noncarriers. The IL-RII gene has been studied twice until now, one showing an association between a high activity allele in the interleukin-1b (IL-1b) gene and orbitofrontotemporal volume reductions of gray and white matter in schizophrenia subjects but not in controls (Meisenzahl *et al.*, 2001) and the other study showing variability at the *IL-1RN* gene contributing to the ventricular volumetric variation in patients with schizophrenia. The PP gene, with a Val/Met polymorphism at position 129 in the prion protein gene (*PRNP*), is known as a risk factor for Creutzfeldt-Jakob disease, which is accompanied by psychosis in the early stages. It is unclear whether this *PP* gene is also associated with schizophrenia (Martorell *et al.*, 2007), but in the study by Rujescu *et al.* (2002), there was a decrease in white matter volume and larger CSF volume in both the controls as well as the patients with the Met homozygotes. The other genes are studied in just one study. These studies have all been analyzed in detail in previous reviews (Pearlson and Calhoun, 2007; Van Haren *et al.*, 2008).

While the reviewed studies suggest high heritability rates for some brain structures, limitations on the neuroimaging, twin studies and NHP studies make the interpretation and the generalizability of their findings difficult.

IV. Limitations and Clinical Relevance of the Studies

A. LIMITATIONS OF NEUROIMAGING STUDIES

A number of limitations in imaging studies need to be acknowledged, such as the validity and reliability of measures (e.g., using measurements that rely on a representative slice vs. whole volume or do not correct for total brain volume). Measurements of brain volumes reveal differences between affected subjects and healthy controls, but the magnitude of these differences is moderate and there is always a substantial overlap in the distributions of the comparison groups. However, looking at the heritability of brain volumes and shapes in healthy twin studies shows high heritability rates of these brain measurements. One solution to this problem might be to shape analysis to quantify subtle differences in brain structures, in order to enhance the identification of structural brain abnormalities that might be associated with neurological and psychiatric disorders such as schizophrenia. Another limitation of the reported studies is the sample size, which is a major issue since imaging techniques and genetic studies require considerable statistical power. Although the gross differences in size or symmetry of brain structures might be quantified, the individual cells and cell layers cannot yet be visualized. This means that, although the volume and shape of brain structures may be determined, the underlying cause of any differences cannot. Another limitation in imaging studies is the method applied to measure

the volumes of brain structures. Some studies use the ROI analyses, where specific brain areas are manually traced. This method does not accommodate changes at sites distant to the ROI, and thus may be inherently biased in spatial terms. Investigating covariation between structures is important, for it may suggest that different brain structures are being influenced by the same gene or sets of genes. This approach may also be less sensitive to small variations in brain structure or tissue type distribution than more modern modeling methods (Good *et al.*, 2001a, 2002). There is also a wide intra- and inter-rater variability, and ROI measurement errors are likely to be greater for smaller structures with complex architectures, particularly if anatomical borders are defined by arbitrary criteria. Other studies used the VBM method to measure volumes of brain structures, a fully automated whole brain technique. The VBM method avoids many of the constraints of ROI analyses, but it incorporates a series of preprocessing steps that may complicate the simple interpretation of regional changes of gray matter loss. One new method used in the heritability estimates is the elastic deformation procedure, used by Thompson *et al.* (2001), in which researchers modeled the genetic influences on neuroanatomic variation between healthy MZ and DZ twin pairs at each voxel on the surface of the cortex. Findings from these analyses showed a significant influence of the genetic factors on the gray matter density in subregions of prefrontal and temporal lobes, particularly in Broca's and Wernicke's language areas. Other areas within these structures were found less heritable, suggesting that heritability estimates based on gross lobular regions of interest blur more subtle local differences.

B. LIMITATIONS OF TWIN STUDIES

Twin studies cannot solve the problem of sources of variance, such as the gene-environment interactions, nonrandom assortative mating, and the possibility of differential interactions of environment in MZ and DZ twin pairs and the chorion type in MZ twins. Reliable detection of differences in correlations may therefore require hundreds of twin pairs. Interpretation of all the data in the reported studies is based on three assumptions in the classical twin designs: (1) MZ twins share 100% and DZ twins share on average 50% of their polymorphic genetic material and current methods adequately identify zygosity, (2) the environment shared among MZ and DZ twins is similar, and (3) twins are similar to singletons such that findings in twins can be generalized to nontwin populations. Conflicting results exist on the first assumption in schizophrenia, specifically that MZ twins discordant for schizophrenia share the same genetic material. Some studies (Guidry *et al.*, 1999; Petronis and Kennedy, 1995; Petronis *et al.*, 2003; Singh *et al.*, 2002) suggest that twins discordant for schizophrenia share less of their polymorphic material than concordant and healthy twins in contrast to

other studies claiming there is no empirical evidence for this (Nguyen *et al.*, 2003; Tsujita *et al.*, 1998; Vincent *et al.*, 1998). The second assumption, that twins share the same environmental factors, has been criticized because of the physical maternal stress, which may be higher for twins than for singletons. There may also be more competition between the twins regarding nutrition. Although classic twin studies attempt to estimate unique environmental effects (events occurring to one twin but not to the other), as well as genetic (heritability) and environmental effects, one limitation of the model is that the gene–environment correlation and interaction is not discernible as a distinct effect. Another limitation is that there is no opportunity in the classic twin design to consider both shared environment and nonadditive genetic effects simultaneously. This limitation can be addressed by including additional siblings to the design, which was done by some studies in the healthy twin studies (Tables I and II). None of the studies reported in this review indicate the impact of possible prenatal and perinatal obstetric complications, except for the study by Van Erp *et al.* (2004) in which the obstetric records of half of the studied twin pairs did not differ between discordant MZ and DZ twin pairs, and the study by Wallace *et al.* (2006) in which data were corrected for the 29 weeks postgestational weight of the individuals included in the study. The third assumption on the generalizability of twin data to singletons is not possible according to some, because twins are not a random sample of the population and they differ in their developmental environment; in this sense they are not representative (Kempthorne and Osborne, 1961). Other studies claim that twins differ very little from their non-twin siblings and that measured studies on personality and intelligence of twins suggests that they have scores on these traits very similar to those of nontwins (Deary *et al.*, 2005). Only one study, by Hulshoff Pol *et al.* (2002), addresses this question and suggests that the data from twin studies can be generalized to singletons, when correcting for the intracranial volume for the second born twin compared to the first born, since second born twins have lower intracranial volume. All other volumes are comparable as well, suggesting that twin studies provide reliable estimates of heritability and can be generalized to singletons.

C. LIMITATIONS OF NONHUMAN PRIMATE STUDIES

Due to the close anatomical, physiological, biochemical, and genetic similarity to humans, NHPs play an important role as model in many aspects of research, specifically for genetic analysis of individual variation in brain structure. The most used species are the baboons, belonging to the old-world monkeys the rhesus macaques, cynomolgus macaques, and vervet monkeys, and being very closely related to the humans. Other primate species that are more similar to humans are the chimpanzees and gorillas. These species would represent a better model for the human neuroanatomy, but they present only minimal opportunities

for intraspecies genetic analyses due to the lack of extensive multigeneration pedigrees (Rogers *et al.*, 2007). Due to the use of large colonies, the analysis of complex phenotypes in the old world monkey can help us understand more about the genetic basis of individual variation in important traits.

One of the limitations of the NHP studies is that the heritability estimates in monkeys are specific to the population and circumstances in which they are assessed. Genetically diverse populations in homogeneous environments demonstrate larger heritability than do inbred populations in diverse environments (Falconer and Mackay, 1996).

Very few parents in the monkey colonies that make up study cohorts share a common mother or father, and extended family pedigrees cannot be determined from monkey breeding colony records. The generality of the NHP studies should therefore be tested in studies of other populations (Lyons *et al.*, 2001).

It may be clear that the human brain is more than simply a large monkey brain. On the one hand, the monkey and the human brains share a common plan of organization, but on the other hand, striking species differences and specific regional differences exist. In the course of evolution, besides an increase in mean size, the brain of the newborn human is exposed to the physical, social, and cultural environmental factors for an extended period compared to the monkey, resulting in “cultural imprints,” such as learning the spoken and written language (Deheane *et al.*, 2005).

D. CLINICAL RELEVANCE OF THE HERITABILITY ESTIMATIONS

Study of the influence of genetic factors on brain structures will help us to understand normal development and age, gender, and other variable associated changes, and will moreover help us understand the meaning of morphological changes found in schizophrenia.

One of the functional relevancies of the heritability of brain volumes is demonstrated best by the association between brain volumes and intelligence. In a study by Posthuma *et al.* (2002b), the association between brain volumes and intelligence was found to be of genetic origin. In two other studies (Thompson *et al.*, 2001; Thompson *et al.*, 2002), the association between frontal gray matter volume and intelligence was shown to be due to genetic factors. In a recent study by Hulshoff Pol *et al.* (2006), an association between intelligence and gray matter of the frontal and occipital lobe, the parahippocampus and the connecting white matter was found. While these findings suggest a common set of genes and intelligence, a study by Carmelli *et al.* (1998), shows that in elderly twins, the association between frontotemporal brain volumes, and executive function were found to be associated with common environmental influences shared by twins from the same family. Whether there is a gene–environment interaction, for example, persons with high level of cognitive functioning leading to select an

environment that also increases brain size, or the possibility of overlapping sets of genes or common environmental influences causing variation in two distinct phenotypes, the cause of the findings between intelligence, and these brain structures, remains unknown. The heritability estimates are necessary to estimate the degree to which genetic factors and environmental factors have influence on the phenotype. Estimation of the impact of environmental factors is much more complicated and generally the effect size of environmental factors are considered to be the remaining part of the total heritability of a disease once the heritability due to genetic factors is known. In addition to the heritability measurements, genes involved in brain structures that are under the influence of genetic factors would be more easily investigated than looking at genes for brain structures in patients with schizophrenia, without knowing the origin (e.g., genetic vs. environmental, a gene–environment interaction or disease related) of these brain changes. This is where the studies in NHPs might be useful, specifically since the impact of the environmental factors can be controlled and questions regarding the evolution of different brain parts and of human cognition only can be addressed adequately if the differences and similarities in the underlying neural circuitry of humans and all extant apes can be identified. Some data from older studies have been used by investigators to address these issues, but problems regarding the methodology used in the measurements, the incomplete representation of hominoid species and the small samples included makes the interpretation of these data difficult.

E. IMPLICATIONS OF THESE OF BRAIN VOLUMES AS ENDOPHENOTYPES FOR GENETICS OF PSYCHIATRIC DISORDERS

Despite the limitations of the twin studies and neuroimaging studies, it is fair to say that these studies only represent a subset of the possible genetic and environmental relationship and that the heritability estimates from these studies represent a first step in understanding the genetics of brain structures.

Using the brain structures with high heritability scores as endophenotypes and looking at the gene action for these endophenotypes, might solve problems in neuroimaging and genetic studies. In this study we found that global structures, with high heritability rates, such as total brain volume, hemispheres, cerebrum, cerebellum, gray and white matter, the four lobes (frontal, temporal, occipital and parietal), and corpus callosum seem to be more useful as endophenotype markers than specific structures with lower heritability rates. These structures are indeed formed earlier in development and the high heritability rates are suggestive of more genetic influences on early developed structures. Lower heritability rates for the specific structures might be due to lower sample sizes found in most of the studies, due to differences in methods measuring the volumes or due to difference in age in participating persons. The studies in NHPs show the same results on the

heritability of gross brain structures, although there are few studies on the heritability of brain structures in NHPs. Looking at the genes for brain structures in healthy persons and persons with schizophrenia shows us that gene approach studies do not show a causal pathway for the brain morphological changes in patients with schizophrenia, and no susceptibility gene with a high effect size has yet been found for schizophrenia.

To summarize, the findings of the reviewed studies suggest that the overall brain volume is highly heritable, comparable with twin based estimates for the most highly genetically determined human traits, including fingerprint ridge count ($h^2 = 0.98$) (Spence *et al.*, 1977), height ($h^2 = 0.66$) (Lettre, 2009; Silventoinen, 2003), and systolic blood pressure ($h^2 = 0.57$) (Williams *et al.*, 1990). The structures that are formed earlier in development (Rubenstein and Rakic, 1999; Rubenstein *et al.*, 1999) and located deeper in the brain may be more genetically influenced thus, they show higher heritability scores than the structures which are formed later in development (Rakic, 1988) or are located on surface areas (Nadarajah and Parnavelas, 2002; Rakic, 1972). These structures are also under more environmental influence. Heritability studies on the genetic control of the human brain structure and how much individual genotype accounts for the wide variations among individual brains using neuranatomically defined endophenotypes will make it easier to look for the actions of genes on brain structures. However, a critical look at the genetic and or disease related changes in the brains of patients with complex disorders such as schizophrenia is necessary, as is suggested by Cannon *et al.* (2002). Further research on the influences of genetic, common, and unique environmental factors is necessary with advanced quantitative genetic methods. Genotyping studies in search of genes for brain structures in healthy subjects and for brain morphological changes in diseased need to be replicated; however, until now individual studies have been generally underpowered in replicating the small number of promising susceptibility genes (Ross *et al.*, 2006) with small effect sizes ($OR < 1.5$). Looking for an association between brain morphological changes with genes, in particular the search for rare variants for overall genetic risk, with a more advanced method like the Genome Wide Association studies in combination with brain morphological changes, could bring new findings in causal pathways wherein genes interact with brain morphology. This may also shed light on understanding the relationship between schizophrenia and other major psychiatric disorders.

Acknowledgments

This research was supported by the Netherlands Organization for Scientific Research (NWO) under project number 017.002.048. We also thank A. Jasinska, Ph.D., UCLA/Los Angeles/USA, for her advices.

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Editorial

Murray et al. (2004) revisited: is bipolar disorder identical to schizophrenia without developmental impairment?

In 2004, Murray et al. (1) suggested that the main difference between bipolar disorder (BPD) and schizophrenia (Sz) was a larger prevalence of developmental impairments in the latter. A number of recent articles in *Acta Psychiatrica Scandinavica* suggest that categories of affective and non-affective psychosis may be similar in their pattern of associations with measures as diverse as social cognition (2), brain volumes (3) and metabolic dysregulation (4), begging the question what the actual status is of the prediction offered by Murray et al. more than 5 years ago. These issues are particularly important given the upcoming revisions of diagnostic systems in psychiatry: how should bipolar disorder and schizophrenia be classified in DSM-V and ICD-11?

A review was conducted of studies focussing on this issue, with a special focus on work published in the last 10 years; results are displayed in Table 1 below.

Both Sz and BPD have onset in adolescence and young adulthood, with an earlier onset in men. The incidence of both disorders is low and associated with a high prevalence:incidence ratio, indicative of a high rate of chronicity. Schizophrenia patients

have high rates of affective symptoms, although lower than in BPD, and bipolar patients have negative symptoms and cognitive impairment, although lower than in Sz. The diagnostic contrast between Sz and BPD is high for affective symptoms, but this is mostly due to artificial diagnostic exclusion criteria.

Sz and BPD have correlated genetic liabilities, some of which is becoming substantiated in recent genome-wide molecular genetic association studies. Of interest, however, is the fact that genetic risk for Sz is strongly expressed as neurocognitive impairment whereas genetic risk for BPD is only weakly expressed in the neurocognitive domain. Danish studies have shown that BPD and Sz have a high population comorbidity index; general population studies have shown that both BPD and Sz phenotypes are associated with psychometric risk states in healthy individuals, and that BPD and Sz psychometric risk states are similarly highly comorbid with each other. Risk factors representing social stress and defeat as well as early emotional alterations are associated with both BPD and Sz whereas risk factors reflecting early motor and cognitive alterations appear specific for schizo-

Fig. 1. A combined dimensional and categorical system of diagnosis of psychotic disorders. Categorical diagnoses of schizophrenia (yellow), bipolar disorder (brown), and schizoaffective disorder (pink) are accompanied by a patient's quantitative scores (connected by red lines) on five main dimensions of psychopathology.

Table 1. Review of critical contrasts and similarities in schizophrenia and bipolar disorder

Type of variable	Variable	Schizophrenia (Sz)	Bipolar disorder (BPD)	Comment
Psychometric risk states in general population	Subclinical psychometric risk states in representative population samples	Subclinical psychosis prevalence around 5–10% (6)	Subclinical bipolarity prevalence around 10–20% (7)	Strong comorbidity between psychosis and bipolar psychometric risk states in population (8), similar to the comorbidity seen in clinical disorders (9)
	Transition from subclinical psychometric risk states to clinical disorder in epidemiological studies	At a rate of around 4% over 1 year follow-up (10)	At a rate of around 3% over 1 year (11)	
Psychopathology	Positive symptoms	Present	Present	Sz>BPD, diagnostic contrast low(12)
	Negative symptoms	Present	Present	
Epidemiology	Disorganisation	Present	Present	Sz>BPD, diagnostic contrast low(12)
	Mania symptoms	Present	Present	
Risk factors	Depression symptoms	Present	Present	BPD>Sz, diagnostic contrast high(12, 13)
	Lifetime prevalence	≈1%	≈1%	
Genetics	Prevalence:incidence ratio	≈100	≈100	BPD>Sz, diagnostic contrast high(12, 13)
	Age of onset	Developmental pattern(14)	Developmental pattern(15)	
Cognition	Sex differences onset	Earlier in men(16)	Earlier in men(17)	High P1 ratio indicates high proportion chronic course; Onset and sex differences shifted to later ages in BPD compared to Sz
	Cannabis	Positive association(18)	Positive association(19)	
Intermediate phenotypes	Urban upbringing	Positive association(20)	No association(21, 22)	Generally much fewer studies in BPD; meta-analyses largely in Sz only.
	Ethnic group	Positive association(23)	Positive association(24, 25)	
Developmental alterations	Parental age	Positive association(26)	Positive association(27, 28)	Molecular genetic studies (GWAS) suggest genetic variation common to Sz and BPD e.g. ZNF804A and CACNA1C(36)
	Prenatal famine	Positive association (early)(29)	Positive association (late) (30)	
Neurocognitive impairment	Pregnancy complications	Reviews suggest association with Sz(31) but not BPD(32); However, reviews largely based on retrospective studies; suggestion of increased risk for BPD in rare prospective studies(30, 33, 34)	Positive association(35)	Sz>BPD; may be mediated by neurocognitive alterations(2, 39)
	Relative with BPD	Positive association(35)	Positive association(35)	
Neurocognitive impairment	Relative with Sz	Positive association(35)	Positive association(35)	Other measures, e.g. neurophysiology, too few comparative data, some reports suggest similarities(43)
	Neurocognition	Impaired(37, 38)	Impaired(37, 38)	
Developmental alterations	Mentalizing ability	Impaired(2)	Impaired(2)	Molecular genetic studies (GWAS) suggest genetic variation common to Sz and BPD e.g. ZNF804A and CACNA1C(36)
	Neurocognitive impairment	Generalised alterations associated with familial/genetic risk for Sz(40, 41)	Very few and specific alterations associated with familial risk for BPD(37, 42)	
Neurobiological findings and other biological markers	Child cognitive ability	Alterations (44–46)	No alterations(47–49)	Suggest similarities(43)
	Child motor development	Alterations(44–46)	No alterations(47–49)	
Neurocognitive impairment	Child emotional development	Alterations(44–46)	Alterations(47–49)	Suggest similarities(43)
	Many individual studies but to date no systematic quantitative integration of findings of Sz vs. BPD. Uncertain whether this will ever be possible given heterogeneity of measures; methodologies, patient selection, unmeasured confounding and differential neurotrophic effects of medications(50). Fronto-temporal systems may be most affected in both Sz and BPD. Ventricular enlargement, cortical gray matter reductions and abnormal gyral folding (51) reported in both Sz and BPD, data suggest Sz>BPD, suggestion of qualitative differences in hippocampal and amygdalar volumes in Sz and BPD.	Alterations(44–46)	Alterations(47–49)	

phrenia. Interesting is the differential association with growing up in an urban environment (not associated with bipolar disorder), suggesting that this exposure impacts on specific developmental alterations associated with schizophrenia.

The literature on neuroimaging, biological variables and prenatal life suggests differences and similarities as regards their prevalences in Sz and BPD; firm conclusions, however, cannot be drawn because of many methodological constraints and the lack of direct comparisons.

In conclusion, science is catching up with century-old diagnostic traditions in psychiatry. It is becoming apparent that due to the strict separation imposed by DSM and ICD on the domains of affective and non-affective psychotic disorder, major opportunities have been missed to study the causes and treatment of psychiatric disorders. Psychotic disorders appear to be originating from (partly) overlapping areas of risk, one more developmental associated with cognitive impairment, and one more associated with affective dysregulation. It has been suggested that where these areas of risk overlap and interact with environmental risks, delusions and hallucinations may ensue through a final common pathway of dopamine dysregulation and affective cognitive biases (5). Therefore an elegant way of adapting the revisions of DSM and ICD diagnostic manuals to the scientific reality is to keep diagnostic categories more or less as they were and add cross-disorder dimensions of psychopathology, as depicted in Fig. 1. The simple addition of dimensions would finally clear the way for an official cross-diagnostic approach in psychiatry, ending a dysfunctional and rigid system of artificial partitioning.

Acta Psychiatrica Scandinavica
Nil Kaymaz and Jim van Os
Invited Guest Editors

Acknowledgement

Nil Kaymaz is supported by the Netherlands Organisation for Scientific Research (NWO) under project number: 017.002.048.

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Extended psychosis phenotype – yes: single continuum – unlikely

A commentary on 'Why we need more debate on whether psychotic symptoms lie on a continuum with normality' by David (2010)

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Received 7 February 2010; Accepted 8 February 2010

Key words: Diagnosis, psychosis, risk factors.

The accepted dogma is that psychotic disorders come as diagnosable 'things', categories, the carriers of which form a diagnostic boundary, below which reside the healthy non-carriers who do not display the mental phenomena observed in patients. This model has come under some pressure, as population research has shown high rates of psychotic experiences in people who are not readily diagnosable according to International Classification of Diseases (ICD) criteria, Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria and Research Diagnostic Criteria (RDC) – suggesting an extended psychosis phenotype. Research on psychotic experiences in the general population is in its early stages. A recent meta-analysis showed that half of the heterogeneity in rates of sub-clinical psychotic experiences across studies is due to study cohort and design factors (Linscott & Van Os, 2010). Furthermore, systematic review of the literature shows that there is evidence not only for a psychometric 'continuum' (in the sense of an extended psychosis phenotype blending gradually into clinical syndromes) (Van Os *et al.* 2009), but also for an underlying latent categorical structure of the population (in the sense that regardless of the presence of a psychometric continuum, the population may still be composed of two different types of people) (Linscott & Van Os, 2010).

Therefore, more, and more detailed and fine-grained work is necessary. Nevertheless, research on psychotic experiences suggesting an extended psychosis phenotype already is producing certain 'side

effects', essentially to do with perceived blurring or undermining of diagnostic boundaries, expressed from a statistical (type I and type II continuum), philosophical (continuity in risk or essence) or moral (madness is rare or common) perspective (David, 2010). However, the notion that high rates of psychotic experiences undermine diagnostic categories only has relevance if (ICD, DSM, RDC) diagnoses like 'schizophrenia' represent valid nosological entities, i.e. 'exist'. As the evidence for the hypothesis of valid nosological entities is weak, it may be necessary to formulate an alternative, but scientifically productive, approach. In this context, it may be helpful to not use the word 'continuum', as it carries the implication of a specific theory, but instead refer to the more agnostic psychosis 'extended phenotype' (coined by Howes & Kapur, 2009).

Extended psychosis phenotype and need for care

Psychotic disorders, spread over a myriad of diagnostic categories in the different classification systems, in reality represent highly variable syndromal clusters of continuous psychotic and affective symptom dimensions, in combination with variable degrees of motivational and neurocognitive impairments (van Os & Kapur, 2009). Until recently, research on syndromal clustering of these psychosis dimensions was carried out almost exclusively in the population of people attending mental health services. The implicit assumption was that symptoms observed in patients with psychotic disorder naturally did not exist outside the mental health service. However, now that general population research is showing that similar clusters of psychotic, affective, motivational and neurocognitive phenomena are also expressed as extended

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Table 1. Factors influencing transition to clinical disorder in representative general population studies of extended psychosis phenotype

Factors	References
1 Number of psychotic experiences	Poulton <i>et al.</i> (2000); Hanssen <i>et al.</i> (2005); Welham <i>et al.</i> (2008)
2 'Definite' versus 'likely' psychotic experience	Poulton <i>et al.</i> (2000)
3 Degree of persistence of psychotic experience over time	Dominguez <i>et al.</i> (2009)
4 Presence of affective dysregulation	van Rossum <i>et al.</i> (2009)
5 Pre-morbid social dysfunction	Werbeloff <i>et al.</i> (2009)
6 Presence of negative symptoms	Dominguez <i>et al.</i> (in press)
7 Functional versus 'symptomatic' coping	Bak <i>et al.</i> (2003)

Fig. 1. Simulation of psychosis continuum model (a) versus latent categorical structure model of psychosis (b). On the left side (a) is depicted the apparent psychosis continuum, greater load of subclinical psychotic experiences predicting greater probability of clinical outcome. On the right side (b) is depicted a latent categorical structure representing two different groups: one with psychotic experiences in the context of cognitive and motivational impairments, associated with high probability of need for care (●) and one group with psychotic experiences of a different origin, associated with low likelihood of need for care (◐).

phenotypes in the general population (Stip & Letourneau, 2009), a conceptual switch is required: it may not be productive to consider populations inside and outside mental health services qualitatively different at the level of symptoms *per se*, but at the level of whether or not need for care has developed. One person with hallucinatory experiences may experience distress to such a degree that he will visit his GP; another may not. The first person may become a patient with a diagnosis of schizophrenia; the second may never receive a diagnosis.

Need for care and the psychopathological, neurodevelopmental and psychological context of psychotic experiences

To date, very little research has been carried out in trying to determine which persons, given a certain level of expression of the extended psychosis phenotype, will develop need for care and help-seeking behaviour. Several longitudinal studies in

representative non-help-seeking general population samples, following individuals with subclinical psychotic experiences over time to determine the likelihood of transition to a clinical outcome, have produced a number of variables predicting transition (Table 1). These suggest that not only the 'load' of psychotic experiences is important, and what type of coping the person develops, but also the degree of persistence over time. Another important observation is that admixture with affective dysregulation, negative symptoms and pre-morbid social dysfunction also increases the likelihood of transition to a clinical psychotic outcome. In other words, not just the presence of psychotic experiences *per se*, but the psychopathological, developmental and psychological context determines the outcome.

A model for future research

It is generally accepted that the risk for psychotic disorder treated in mental health services is much more

prevalent than the rate of psychotic disorder itself; more people have risk than there are people with the disease. Research has demonstrated that (genetic and non-genetic) risk for psychotic disorder is not behaviourally silent: it is expressed in the area of cognition, subtle psychotic experiences and sensitivity to stress (reviewed by van Os & Kapur, 2009). Therefore, the fact that psychotic experiences are encountered in non-diagnosed individuals in the general population is not surprising: psychotic experiences probably represent the behavioural expression of distributed risk for psychotic disorder. There is also evidence, however, that the causes of positive psychotic symptoms may only partly overlap with the causes of developmental and cognitive impairment seen in psychotic disorder (Murray *et al.* 2004; Kaymaz & van Os, 2009b). Therefore, the hypothesis of a single psychosis continuum lacks explanatory power, and also is not in agreement with the observation that motivational and developmental impairments, possibly of genetic origin (Kaymaz & van Os, 2009a; Picchioni *et al.* 2009), moderate the probability of clinical outcome in those with subclinical psychotic experiences. Instead, we suggest that the model depicted in Fig. 1 (simulated data) may apply. On the one hand, there is an observed apparent continuum (Fig. 1a), indicating that the greater the load of subclinical psychotic experiences, the greater the probability of clinical outcome. This concept is heuristically useful, as it allows for examination, for example, of how coping and the degree of distress associated with psychotic experiences may affect development of need for care. On the other hand, the apparent continuum model may be 'confounded', at least to a degree, as underneath the continuum, a latent categorical structure may exist, representing two different groups: one with psychotic experiences in the context of cognitive and motivational impairments, associated with high probability of need for care (Fig. 1b; black dots) and one group with psychotic experiences of a different origin, associated with lower likelihood of need for care (Fig. 1b; grey dots). Future research will examine to what degree the continuum model, the latent categorical structure model, or both (a distinct possibility), apply.

Acknowledgements

N.K. was supported by The Netherlands Organization for Scientific Research (NWO), project no. 017.002.048.

Declaration of Interest

None.

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CHAPTER 3

Affective studies of psychosis

ORIGINAL PAPER

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Evidence that the urban environment specifically impacts on the psychotic but not the affective dimension of bipolar disorder

Accepted: 10 May 2006 / Published online: 3 July 2006

Abstract *Objectives* High rates of psychotic disorders and psychotic symptoms have been found in urban environments but reports for bipolar affective illness have been inconsistent, possibly due to failure to stratify for comorbid psychotic symptoms. It was hypothesised, therefore, that any effect of urbanicity on the bipolar phenotype would be moderated by comorbid psychotic symptoms. *Methods* In a random, representative population cohort of 7049 adults with no history of non-affective psychotic disorder, the cumulative incidence of bipolar and psychotic symptoms and syndromes, assessed with the CIDI, was examined over five levels of population density of place of residence. Similarly, the degree of comorbidity between broadly and narrowly defined bipolar phenotypes on the one hand, and the dichotomous presence of broadly (17.2%) and narrowly defined (3.8%) psychotic symptoms on the other, was examined as a function of population density of place of

residence. *Results* The rate of bipolar disorder, however defined, was progressively higher in more urbanised areas. However, in models of bipolar phenotypes, a strong interaction between comorbid psychosis and level of urbanicity was apparent, indicating that the greater the degree of psychotic comorbidity, the greater the effect size of the urban environmental factor. For bipolar disorder without psychosis, no effect of urbanicity was apparent. *Conclusions* The results suggest differential environmental causal effects on affective and cognitive dimensions of bipolar psychopathology that are nevertheless strongly comorbid within the same categorically defined disorder, possibly due to the effect of shared genetic risk factors.

Key words bipolar disorder – urbanisation – psychosis

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Introduction

There is remarkably consistent evidence that the rate of psychotic disorder and subclinical psychotic experiences is higher in urban environments, which is thought to reflect the impact of an as yet unidentified environmental causal risk factor [1]. Similar risks, albeit of lower effect size, have been reported for affective disorder in some studies [2, 3], but not in others [4]. One likely reason for the inconsistent results is failure to stratify for comorbid psychotic symptoms. It is attractive to speculate that the urban environment will affect the rate of affective disorder in those who also have a propensity to develop psychosis, but not in those without this propensity. The importance of such stratification has been shown in family and high risk studies, where inconsistent results on the familial association between bipolar disorder and non-affective psychotic disorder could be retraced in part by failure to

stratify for the presence of psychotic symptoms in bipolar probands [5–7]. In the current study, we examined main effects of urbanicity on the rate of the bipolar phenotype narrowly and broadly defined [8, 9], and hypothesised that any effect of urbanicity would be modified synergistically by comorbid psychotic symptoms.

Patients and methods

The Netherlands Mental Health Survey and Incidence Study (NEMESIS), is a prospective study with three measurement points over a period of 3 years [10–12]. All procedures were approved by the local Ethical Committee, and were in accordance with the Helsinki Declaration of 1975. The current report is based on the baseline data. A multistage, stratified, random sampling procedure was used to first select 90 municipalities, then a sample of private households, and finally a Dutch-speaking individual aged 18–64 years within each household. Selected households were sent an introductory letter by the Minister of Health, inviting them to participate. A total of 7076 individuals provided informed consent and were interviewed at baseline, representing a response rate of 69.7%. The sample was found to be representative of the Dutch population in terms of gender, marital status and level of urbanisation [11], with the exception of a slight underrepresentation of individuals in the age group 18–24 years.

■ Instruments

Subjects were interviewed at home. The Composite International Diagnostic Interview (CIDI) version 1.1 [13–15] was used, yielding DSM-III-R diagnoses. The CIDI was designed for trained interviewers who are not clinicians and has been found to have high inter-rater reliability [16, 17], and high test–retest reliability [18–20]. A total of 90 interviewers, experienced in systematic data collection, collected the data, having received a 3-day training course in recruiting and interviewing, followed by a 4-day course at the WHO-CIDI training centre in Amsterdam. Extensive monitoring and quality checks took place throughout the entire data collection period [11].

■ Psychosis ratings

Baseline CIDI lifetime ratings, yielding cumulative incidence figures, from the 17 CIDI core psychosis items on delusions (13 items) and hallucinations (4 items) were used (items G1–G13, G15, G16, G20, G21). These concern classic psychotic symptoms involving, for example, persecution, thought interference, auditory hallucinations and passivity phenomena. All these items can be rated in six ways: “1”—No symptom, “2”—Symptom present but not clinically relevant (not bothered by it and not seeking help for it), “3”—Symptom result of ingestion of drugs, “4”—Symptom result of somatic disease, “5”—True psychiatric symptom, “6”—Symptom may not really be a symptom because there appears to be some plausible explanation for it. Since psychotic symptoms are difficult to diagnose in a structured interview [21–23], clinical re-interviews were conducted over the telephone by an experienced trainee psychiatrist for all individuals who had at least one rating of “5” or “6”, using questions from the Structured Clinical Interview for DSM-III-R (SCID), an instrument with proven reliability and validity in diagnosing schizophrenia [24]. The proportion of eligible individuals that was successfully re-interviewed by the clinician was 47.2%. Whether or not eligible individuals were re-interviewed was not associated with level of urbanicity (OR = 0.9, 95% CI: 0.8, 1.02, $P = 0.10$; proportions in lowest and highest levels of urbanicity, respectively, re-interviewed: 13.9% and 15.4%; not re-

interviewed: 15.5% and 19.8%). CIDI ratings were corrected on the basis of these clinical interviews, and the NEMESIS DSM-III-R diagnoses of psychotic disorder are based on the data from these clinical re-interviews.

Non-affective psychotic disorder was defined as any DSM-III-R non-affective psychotic diagnosis ($n = 26$, 0.4%). A broad measure of psychosis was defined as any CIDI rating of 2,3,4,5 or 6 on any of the 17 CIDI core psychosis items. In a previous study, it was shown that all these 6 different ratings on the CIDI psychosis items were strongly associated with each other, including the clinical re-interview ratings of psychotic symptom (i.e. a rating of “5” on any of the CIDI psychosis items). In addition, the 6 different ratings independently showed a similar pattern of associations with known risk factors for psychosis [25, 26]. As they, therefore, appear to reflect the same underlying latent dimension of “psychosis” they were joined together into a single broad rating of psychotic experience for the purpose of the current study (hereafter: “psychosis broadly defined”). In order to check on the validity of this procedure, associations were also examined with clinical psychotic symptoms, more narrowly defined as a clinical re-interview rating of psychosis (i.e. a rating of “5” on any of the CIDI psychosis items, hereafter: “psychosis narrowly defined”).

■ Bipolar phenotypes

At baseline, a CIDI lifetime diagnosis of bipolar disorder, reflecting cumulative incidence, was made in 132 individuals (1.9%). A mania symptom score was constructed using ratings from the 11 items of the CIDI core mania section (section F; see [27]). The mania symptom score consisted of the sum score of these 11 items. The range of this score was 0–10 symptoms, and the minimum positive score was 3 symptoms (absence of score of 1 or 2 due to cut-off stem questions in the CIDI). Apart from the CIDI bipolar diagnosis, two broader bipolar outcomes, in line with current conceptualisation of the bipolar phenotype [8, 9] were used, derived from this score: a score of at least 3 symptoms (hereafter: mania 3-symptoms) and a score of at least 5 symptoms (hereafter: mania 5-symptoms). For the two broader phenotypes, manic rather than depressive symptoms were used, given the fact that mania is the distinguishing feature between unipolar and bipolar affective phenotypes and no accepted method exists for defining subclinical bipolar disorder using both depressive and manic symptoms.

Level of urbanicity

Five levels of urbanisation were defined, following the standard classification of urbanisation of place of residence according to the Dutch Central Bureau of Statistics. These are based on the density of addresses per km² in an area and are classified as <500, 500–999, 1000–1499, 1500–2499 and ≥ 2500 . This density is calculated by assessing, for each address, the density of addresses in a circle of 1 km around that address. The density of addresses in an area is then calculated as the mean address density of all the addresses in that area [28].

■ Data analyses

Main effect of urbanicity

The cumulative incidences of bipolar disorder, 3-symptom mania and 5-symptom mania were examined in relation to level of urbanicity of place of residence, adjusted for the a priori selected possible confounding effects of age in years, sex, level of education (4-levels) and cannabis use [26, 29, 30].

Logistic regression yielding odds ratios and 95% confidence intervals [31] was used to examine associations between bipolar outcomes and level of urbanicity.

Interactions

The classic problem with regard to possible co-participation between causes in nature (biological synergism) is how such synergism can be inferred from statistical manipulations with research data (statistical interaction), in particular with regard to the choice of additive (change in risk occurs by adding a quantity) or multiplicative (change in risk occurs by multiplying with a quantity) models. Recent progress in the study of interactions indicates that the most frequently used statistical models of interaction are not suitable to identify biological synergism. For example, the commonly used statistical models in which two causes multiply each other's effects (multiplicative models) assume that individuals who are exposed to both risk factor A and risk factor B could not have become ill because the effect of A alone or B alone [32]. It has recently been shown that the true degree of biological synergism can be better estimated from (but is not the same as) the additive statistical interaction (see [32]). This method was recently applied to schizophrenia showing synergy between traumatic head injury and familial liability [33], between cannabis and psychosis liability [34] and between urbanicity and familial morbid risk for psychosis [35].

In order to calculate the statistical interaction under an additive model, the BINREG procedure in the STATA statistical programme [36], which fits generalised linear models for the binomial family estimating risk differences, was used to model interactions.

Risk set

The risk set consisted of all individuals who had participated in the baseline CIDI interview, with the exception of the 26 individuals with a lifetime diagnosis of non-affective psychotic disorder ($n = 26$), resulting in a sample for analysis of 7049 individuals.

Results

Sample description

The sample included 3287 men (47%) and 3762 women (53%) and the mean age was 41.2 years ($SD = 12.2$). The cumulative incidence of psychosis broadly defined was 17.2% ($n = 1211$) and the cumulative incidence of psychosis narrowly defined was 3.8% ($n = 267$). The cumulative incidence of mania 3-symptoms was 4.0% ($n = 283$), of mania 5-symptoms was 2.3% ($n = 161$) and of DSM-III-R bipolar disorder 1.9% ($n = 132$).

Main effects urbanicity and psychosis comorbidity

The five level urbanicity rating was strongly associated with the rate of mania, however defined. Both the CIDI bipolar diagnosis, as the two broader bipolar outcomes were all progressively more common in more urbanised areas (Table 1). Adjustment for the a priori selected possible confounding effects of age, sex, level of education (4-level) only changed the parameters by a small amount (Table 1).

Table 1 Cumulative incidences of mania 3-symptom, mania 5-symptom and bipolar disorder by 5 levels of population density

Population density	M3 ^a (%)	M5 ^a (%)	bip ^a (%)
1	2.8	1.4	1.3
2	2.7	0.9	1.2
3	3.8	2.1	2.2
4	5.0	2.9	2.1
5	6.1	4.0	2.8
Total	4.0	2.2	1.9
OR linear trend ^b	1.27	1.43	1.24
(95% CI)	(1.16, 1.39)	(1.26, 1.62)	(1.09, 1.42)
P	<0.001	<0.001	0.001
Adjusted ^c OR	1.22	1.34	1.18
linear trend			
(95% CI)	(1.11, 1.34)	(1.18, 1.53)	(1.03, 1.35)
P	<0.001	<0.001	0.016

^a "M3" is broad mania phenotype of at least 3 manic symptoms, "M5" is broad mania phenotype of at least 5 manic symptoms, "bip" is DSM-III-R bipolar disorder

^b The summary increase in risk, expressed as odds ratio, associated with one unit change in the five-level exposure

^c Adjusted for age in years, sex, level of education (4-levels) and cannabis use

Table 2 Cumulative incidences of mania 3-symptom, mania 5-symptom and bipolar disorder by 5 levels of population density, stratified by presence of psychosis broadly defined

Population density	M3 ^a (%)	M5 ^a (%)	bip ^a (%)
<i>No psychotic symptom</i>			
1	1.7	0.8	0.8
2	1.4	0.4	0.7
3	2.1	0.9	1.2
4	2.0	0.8	0.9
5	2.5	1.6	1.5
Total	1.9	0.9	1.0
RD linear trend ^b (%)	0.22	0.16	0.16
(95% CI)	(0.00, 0.48)	(0.00, 0.33)	(0.00, 0.34)
P	0.095	0.076	0.10
<i>At least one psychotic symptom</i>			
1	9.9	4.9	4.3
2	10.6	4.2	4.6
3	12.2	7.9	7.1
4	16.7	11.3	6.7
5	18.3	12.2	7.2
Total	14.1	8.7	6.2
RD linear trend ^b (%)	2.3	2.1	0.78
(95% CI)	(0.92, 3.7)	(1.1, 3.2)	(0.00, 1.8)
P	0.001	<0.001	0.12
Interaction ^c (χ^2 , P, df = 1)	8.4, 0.004	13.0, 0.0003	1.5, 0.21

^a "M3" is broad mania phenotype of at least 3 manic symptoms, "M5" is broad mania phenotype of at least 5 manic symptoms, "bip" is DSM-III-R bipolar disorder

^b The summary increase in risk, expressed as risk difference, associated with one unit change in the five-level exposure

^c Tests whether RD linear trend for mania with psychosis is significantly different from RD linear trend for mania without psychosis

Urbanicity and psychosis interaction effects

There was a directionally positive interaction on the additive scale between urbanicity and broadly defined psychosis in the models of mania, reaching statistical significance for 2 of the 3 mania outcomes (mania 3-

Table 3 Cumulative incidences of mania 3-symptom, mania 5-symptom and bipolar disorder by 5 levels of population density, stratified by presence of psychosis narrowly defined

Population density	M3 ^a (%)	M5 ^a (%)	bip ^a (%)
<i>No psychotic symptom</i>			
1	2.6	1.1	1.2
2	2.0	0.6	0.8
3	3.3	1.7	1.7
4	3.5	1.8	1.6
5	4.4	2.7	2.2
Total	3.1	1.5	1.5
RD linear trend ^b (%)	0.50	0.39	0.27
(95% CI)	(0.19, 0.81)	(0.18, 0.60)	(0.00, 0.48)
P	0.001	<0.001	0.012
<i>At least one psychotic symptom</i>			
1	11.1	11.1	3.7
2	28.2	15.4	15.4
3	14.8	11.5	13.1
4	30.4	22.8	10.1
5	36.5	27.0	12.7
Total	26.0	19.0	11.5
RD linear trend ^b (%)	5.4	3.9	0.82
(95% CI)	(0.69, 9.6)	(0.63, 7.4)	(-0.02, 3.8)
P	0.024	0.020	0.59
Interaction ^c	6.3, 0.01	4.4, 0.04	0.13, 0.72
(χ^2 , P, df = 1)			

^a "M3" is broad mania phenotype of at least 3 manic symptoms, "M5" is broad mania phenotype of at least 5 manic symptoms, "bip" is DSM-III-R bipolar disorder

^b The summary increase in risk, expressed as risk difference, associated with one unit change in the five-level exposure

^c Tests whether RD linear trend for mania with psychosis is significantly different from RD linear trend for mania without psychosis

symptoms: $\chi^2 = 8.4$, $P = 0.004$, mania 5-symptoms: $\chi^2 = 13.0$, $P = 0.0003$; DSM-III-R bipolar disorder: $\chi^2 = 1.5$, $P = 0.21$) (Table 2). Similar results were apparent for interactions between urbanicity and psychosis narrowly defined (mania 3-symptoms: $\chi^2 = 6.3$, $P = 0.01$, mania 5-symptoms: $\chi^2 = 4.4$, $P = 0.04$; DSM-III-R bipolar disorder: $\chi^2 = 0.13$, $P = 0.72$) (Table 3). Stratified analyses revealed that in mania outcomes without comorbid psychosis narrowly defined, only a weak effect of urbanicity remained (Table 3), whereas in mania outcomes without comorbid psychosis broadly defined the effect of urbanicity disappeared altogether (Table 2).

Discussion

The main finding of this study was that in models of bipolar phenotypes, a strong interaction between psychosis and level of urbanicity was apparent, indicating that the greater the degree of psychotic comorbidity, the greater the effect size of the urban environmental factor. Although the interaction term was not significant for DSM-III-R bipolar disorder, the difference in urbanicity effect size in the groups with and without comorbid psychosis was equally large so that lack of power is the likely explanation for the inconclusive interaction.

For bipolar disorder without psychosis, no strong or clear effect of urbanicity was apparent. Thus, in the analyses of bipolar disorder where only narrowly defined comorbid psychosis had been excluded, a weak effect of urbanicity was still apparent. However, for bipolar disorder outcomes where all psychosis had been excluded, an (inconclusive) effect of urbanicity was only possibly apparent for the highest category of urbanicity and the broadest definition of mania. Thus, the conservative conclusion is that although a weak association between mania without psychosis and urbanicity cannot be excluded, by far the greatest part of the apparent association between bipolar phenotypes and urbanicity is due to comorbid psychosis. Indeed, although the incidence of other psychiatric disorders may also be higher in urban areas [3, 4], the effect size for psychotic disorders appears to be much larger, possibly explaining around 30% of all schizophrenia incidence [1, 4, 44]. Given the fact that associations with urbanicity are thought to reflect the impact of an environmental exposure that interacts with genetic liability to produce illness [1, 35, 37], these results should be interpreted in the light of previous work in the field of both molecular genetics and genetic epidemiology that has shown that there is substantial sharing of genetic risk between bipolar disorder and non-affective psychosis [38–40]. Thus, if two individuals have a similar amount of shared genetic liability for both bipolar disorder and schizophrenia, the one that becomes subsequently exposed to an urban environment may develop a more "psychotic" illness, whereas the one not exposed to an urban environment may develop a more "pure" manic illness, suggesting that within the bipolar spectrum, the impact of the urban environment on the occurrence of more "psychotic" illness may be mediated by a different pathway than the rate of more "pure" manic illness. Research suggests that this type of gene-environment interactions may not be uncommon. For example, a similar scenario has been described for anxiety and depression, two conditions that have been shown to share genes that, however, produce differential outcomes depending on subsequent exposure to divergent environmental risk factors, some resulting in anxiety outcomes, and others in depression [41–43].

Possible mechanisms

Recent studies have shown that the impact of the environmental factors that are thought to mediate the effect of urbanicity is conditional on pre-existing indicators of genetic risk for psychosis [35, 37, 45]. However, a plausible mechanism explaining the pathway from impact of the exposure to onset of psychotic symptoms is lacking, as it is unclear which underlying factors in urban areas are responsible for the causation of psychotic symptoms in genetically

pre-disposed individuals [46]. Recent studies, focusing on within-city neighbourhood contrasts, have demonstrated that the impact of environmental factors in the urban area varies across neighbourhoods in such a way that the increase in the incidence of psychosis or psychosis-like phenomena is likely not associated with indicators of material deprivation, but with indicators of social isolation and social cohesion [47]. These studies have focused on the developmental effects of variables referred to as “social capital” and suggest that in particular cognitive social capital, or the degree of perceived mutual trust, bonding, safety and social control in neighbourhoods, exerts a developmental impact on the mental health of the children growing up in these environments [48–51]. The hypothesised effects of cognitive social capital can be readily integrated in current hypotheses of cognitive neuropsychiatric models of psychotic symptoms [52, 53].

■ Methodological issues

These results should be considered in the light of several limitations: Psychotic symptom ratings were assessed by lay interviewers (CIDI ratings of 1–4), whereas the other CIDI ratings [5, 6] were assessed by clinicians through telephone interviews in approximately 50% of eligible cases. It is likely that with lay interviewer ratings a degree of misclassification did occur. However, the findings with both broad (only lay interviewer based) and narrow (also clinical re-interview based) psychosis concurred, suggesting that lay interviews were reasonably accurate, something which was previously reported [54].

Bias could also have been introduced by differential rating of psychosis due to incomplete clinical re-interview rates at baseline. This is unlikely, however, as the probability of re-interview was not associated with the exposure, urbanicity, which would have been required for bias to occur [55]. In order to examine the possibility of bias further, sensitivity analyses were conducted to examine whether differential re-interview rates could have biased the findings. This was done by setting values of psychosis narrowly defined to missing if individuals had been eligible for re-interview by clinicians but had not been re-interviewed ($n = 253$). Subsequently, multiple imputation of missing values [56, 57] of psychosis narrowly defined was applied using the HOTDECK command in STATA. The HOTDECK procedure is used several times within a multiple imputation sequence since missing data are imputed stochastically rather than deterministically. Five imputation sequences were run, yielding 5 data sets in which the average coefficient of the urbanicity $\times$ psychosis narrowly defined interaction term in the model of the two mania outcomes, which had shown significant interactions (mania 3-symptom and mania 5-symptom) was estimated within the

HOTDECK procedure. This revealed that the interaction term effect size decreased only slightly for the mania 5-symptom model (12% reduction effect size) whereas it increased substantially for the mania 3-symptom model (47% increase effect size). These results therefore, suggest that bias due to differential re-interview rate did not occur.

Another bias could be the examination of lifetime rates of psychotic disorder in relation to current urban residence. For example, symptomatic subjects could have ‘drifted’ to urban areas. However, in a previous study in the Netherlands we found that there was a high degree of lifetime stability of urban exposure status, indicating that current exposure is likely to reflect stable lifetime exposure in most cases. Furthermore, work from Denmark has suggested drift is an unlikely explanation for the urbanicity effect, since changing exposure status in childhood changes adult risk for schizophrenia, indicating causality rather than drift [58].

■ **Acknowledgement** Funded by the Dutch Department of Health.

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Research report

The impact of subclinical psychosis on the transition from subclinical mania to bipolar disorder

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Received 25 April 2006; received in revised form 29 June 2006; accepted 30 June 2006

Available online 28 August 2006

Abstract

Background: In the general population, symptoms of mania and psychosis are more broadly distributed than their associated clinical syndromes. Little is known, however, about how these subclinical population phenotypes co-vary with and impact on each other.

Method: In a representative population cohort of 7076 adults, prevalence of mania and psychosis symptoms and syndromes were assessed with the CIDI at baseline, at one (T1) and two years later (T2). The degree of comorbidity between subclinical mania and subclinical psychosis was examined, as well as the impact of subclinical comorbidity on social impairment and transition from subclinical mania to onset of bipolar disorder.

Results: The lifetime prevalence of at least one manic and one psychotic symptom was 4.1% and 4.2% respectively. Excluding individuals with any lifetime DSM-III-R bipolar or psychotic disorder ($n=218$), these prevalences were 2.3% (subclinical mania) and 2.8% (subclinical psychosis). Individuals with subclinical mania had a 17% risk of subclinical psychosis, compared with 2.3% in those without ($P<0.000$). Comorbid subclinical psychosis in individuals with subclinical mania was much more predictive of a future diagnosis of bipolar disorder (positive predictive values of 3% versus 10% respectively).

Conclusion: Subclinical phenotypes of mania and psychosis are more prevalent than their clinical counterparts and cluster together. The risk factors for psychosis may facilitate the formation of more “toxic” combinations of subclinical mania and subclinical psychosis with a higher probability of transition to bipolar disorder. A better understanding of this pathway is crucial for the development of early interventions.

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Keywords: Mania; Psychosis; Genetics; Environment; Prevention; Comorbidity

1. Introduction

It is increasingly recognised that in the general population, the expression of mania and psychosis is more broadly distributed than the associated clinical syndromes (Akiskal et al., 2000; Angst, 2002; Johns and van Os, 2001; Judd et al., 2003; Peters et al., 1999; Stefanis et

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al., 2002; van Os et al., 2001). Thus, even though the prevalence of a clinical disorder may be low, the prevalence of isolated symptoms can be much higher. In addition to phenomenological correspondence, continuity between the clinical and subclinical phenotypes is suggested by similar associations with demographic factors (Johns and van Os, 2001; van Os et al., 2000a; Verdoux et al., 1998), transitions over time from the subclinical to the clinical phenotype (Chapman et al., 1994; Hanssen et al., 2005; Poulton et al., 2000), familial co-clustering of the clinical and the subclinical phenotype (Kendler et al., 1993), sharing of cognitive and motor deficits (Lenzenweger, 1994; Matsui et al., 2004; Neumann and Walker, 2003; Voglmaier et al., 2000), and sharing of risk genes (Stefanis et al., 2004a).

There is substantial overlap between dimensions of mania and psychosis in clinical samples, which may be due to the sharing of genetic and non-genetic aetiological influences. Familial co-aggregation suggests that psychosis shares common genetic risk factors with mania (Bailer et al., 2002; Cardno et al., 2002; Kendler and Gardner, 1997; Potash et al., 2001; Valles et al., 2000) and recent studies have indeed implied shared susceptibility genes (Bramon and Sham, 2001; Green et al., 2005; Maier et al., 2005; Walss-Bass et al., 2005). Although there are quantitative differences in effect size (Van Os et al., 1998), risk factors such as life events, ethnic group, prenatal famine and urban birth also tend to overlap to a degree between psychotic and mood disorders (Bebbington et al., 1993; Brown et al., 2000; Marcelis et al., 1998; van Os, 1996) as do cognitive impairments and high levels of neuroticism prior to the onset of disorder (Goodwin et al., 2003; Jones et al., 1994; Myin-Germeys et al., 2002; Van Os and Jones, 2001b).

Given the continuity between clinical and subclinical levels of psychopathology within a particular symptom domain, it can be surmised that the overlap between mania and psychosis should also be detectable at lower levels of the continuum. However, little is known about how subclinical population phenotypes of mania and psychosis co-vary with and have impact on each other and which variables affect observed comorbidity between subclinical phenotypes. It was hypothesised that the demographic, familial, psychological, and social risk factors for clinical psychotic disorder (Van Os, 2000; Van Os et al., 2000b; Van Os et al., 2005) would also predict the presence of subclinical psychosis in individuals with subclinical mania. It was further hypothesised that since the presence of psychosis in clinical bipolar disorder predicts poorer outcome (Coryell et al., 2001), the coexistence of psychotic features with sub-

clinical mania would similarly have a negative impact on social impairment and be predictive of a future diagnosis of bipolar disorder.

2. Methods

The Netherlands Mental Health Survey and Incidence Study (NEMESIS), is a prospective study with three measurement points over a period of 3 years (Alegria et al., 2000; Bijl et al., 1998a,b). The current report is based on the baseline data, with the exception of the predictive analysis of the post-baseline diagnosis of bipolar disorder. A multistage, stratified, random sampling procedure was used to first select 90 municipalities, then a sample of private households, and finally a Dutch-speaking individual aged 18–64 years within each household. Selected households were sent an introductory letter by the Minister of Health, inviting them to participate. A total of 7076 individuals provided informed consent and was interviewed at baseline, representing a response rate of 69.7%. Nearly 44% of non-responders agreed to fill in a postal questionnaire, including a General Health Questionnaire (Goldberg and Williams, 1988), and were found to have the same mean GHQ score (responders: 1.19; non-responders: 1.16). At T₁, 5618 subjects participated for the second time; at T₂, 4848 subjects participated. The sample was found to be representative of the Dutch population in terms of sex, marital status and level of urbanisation (Bijl et al., 1998b), with the exception of a slight underrepresentation of individuals in the age group 18–24 years. As this was a study of relative rather than absolute risk, no poststratification weightings were applied to the data.

2.1. Instruments

Subjects were interviewed at home. The Composite International Diagnostic Interview (CIDI; <http://www3.who.int/cidi/>) version 1.1 (Robins et al., 1988; Smeets and Dingemans, 1993) was used, yielding DSM-III-R diagnoses. The CIDI was designed for trained interviewers who are not clinicians and has been found to have high inter-rater reliability (Cottler, 1991; Wittchen et al., 1991), and high test–retest reliability (Semler et al., 1987; Wacker et al., 1990; Wittchen, 1994). Ninety interviewers experienced in systematic data collection collected the data, having received a 3-day training course in recruiting and interviewing, followed by a 4-day course at the WHO-CIDI training centre in Amsterdam. Extensive monitoring and quality checks took place throughout the entire data collection period (Bijl et al., 1998a).

2.2. Psychosis ratings

Lifetime ratings from the 17 items of the CIDI core psychosis sections, assessed at baseline, on delusions (13 items) and hallucinations (4 items) were used (items G1–G13, G15, G16, G20, G21). These concern classic psychotic symptoms involving, for example, persecution, thought interference, auditory hallucinations and passivity phenomena. All these items can be rated in six ways: “1”—no symptom, “2”—symptom present but not clinically relevant (not bothered by it and not seeking help for it), “3”—symptom result of ingestion of drugs, “4”—symptom result of somatic disease, “5”—true psychiatric symptom, “6”—symptom may not really be a symptom because there appears to be some plausible explanation for it. Because psychotic symptoms are difficult to diagnose in a structured interview (Anthony et al., 1985; Cooper and Collacott, 1994; Helzer et al., 1985), clinical reinterviews were conducted over the telephone by an experienced trainee psychiatrist at the level of senior registrar for all individuals who had at least one rating of “5” or “6”, using questions from the Structured Clinical Interview for DSM-III-R (SCID), an instrument with proven reliability and validity in diagnosing schizophrenia (Spitzer et al., 1992). CIDI ratings were corrected on the basis of these clinical interviews, and the NEMESIS DSM-III-R diagnoses of psychotic disorder are based on the data from these clinical reinterviews; approximately 50% of eligible people were reinterviewed. Of a possible $226 \times 17 = 3842$ CIDI ratings of psychotic symptoms in the 226 individuals who were reinterviewed, changes after clinical reinterview were introduced in 266 ratings (6.9%).

Psychotic disorder was defined as any DSM-III-R affective or non-affective psychotic diagnosis. Subclinical psychosis was defined as a CIDI rating of 5 on any of the 17 CIDI core psychosis items.

2.3. Bipolar diagnoses and mania symptom scores

Lifetime manic symptoms were assessed using ratings from the 11 items of the CIDI core mania section (F) at baseline. All these items can be rated either “yes”(1) or “no”(0). The manic symptom has to be present for at least 2 days. The mania section starts with assessing the presence of abnormally and persistently elevated, expansive or irritable mood, which, if positive, results in further questioning about other symptoms. Subclinical mania was defined as at least one manic symptom thus assessed.

The diagnosis of bipolar disorder was defined as DSM-III-R diagnosis on the basis of the CIDI. In order

to assess social impairment, item 6 of the Short Form Health Survey, i.e. SF-36 (Van der Zee et al., 1993; Ware et al., 1994) was used. The SF-36 measures the health-related quality of life and item 6 of the SF-36 inquires about the interference of physical and emotional problems with normal social activities in the past 4 weeks (in the analyses used as: none, a little, more than a little).

2.4. Predictors of comorbidity

Guided by previous research as described above, the following predictors of psychotic symptoms occurring in the context of subclinical mania were examined: age (two groups around median split), sex, marital status (living alone or not), education (4 levels), unemployment (present or absent), urbanisation (three levels), family history of depression (present or absent), family history of delusions and hallucinations (present or absent), lifetime use of cannabis (present or absent), lifetime use of other drugs (present or absent), childhood trauma (present or absent), discrimination (present or absent) and neuroticism (two groups around median split of continuous score). Urbanisation was defined following the standard classification of urbanisation of place of residence according to the Dutch Central Bureau of Statistics, based on the density of addresses per km² in an area (van Os et al., 2001). The three levels of urbanicity represented respectively 0–499, 500–1499 and 1500 and more persons per km².

Family history of delusions and hallucinations as well as a family history of depression were assessed at T1 by asking the subjects, for each first-degree relative, whether any ever had presented with delusions or hallucinations (Van Os et al., 2003) or depression respectively, describing the symptoms associated with these disorders. Lifetime use of cannabis and lifetime use of other drugs (stimulant drug, cocaine, PCP and psychedelics) were assessed at baseline using the CIDI section on alcohol and drugs (van Os et al., 2002). All these items were classified dichotomously as either “no”(0) or “yes”(1).

At baseline, subjects were asked using a semi-structured interview whether they had experienced any kind of emotional, physical, psychological or sexual trauma before age of 16 years. Subjects answered “yes” or “no” to each of the questions and were able to give an indication about the frequency on a 6-point scale, “1” never, “2” once, “3” sometimes, “4” regular, “5” often and “6” very often. In the analyses, trauma was *a priori* dichotomised as follows; “no trauma” if the score on any item ≤ 3 and “trauma” if the score on any item > 3 (Janssen et al., 2004). Given a specific finding of early trauma

predicting hallucinations in bipolar disorder (Hammersley et al., 2003), prediction was also tested using hallucinations only as the outcome. In order to assess exposure to discrimination, subjects were asked if they had experienced discrimination over the past year because of their skin colour or ethnicity, their sex, age, appearance, disability or sexual orientation (Janssen et al., 2003). Level of neuroticism was assessed with the 14-item Groningen Neuroticism Scale (Krabbendam et al., 2002; Ormel, 1980; Ormel et al., 2001).

2.5. Data analyses

All analyses were carried out using the software package STATA, version 9 (StataCorp, 2005). The risk for psychosis was calculated in individuals with and without subclinical mania, and at different levels of the predictor variables. In order to examine whether the risk for psychosis comorbidity was statistically different between different levels of the predictor variables, a STATA risk regression model of subclinical psychosis was used in which the interaction between subclinical mania and the predictor variable was estimated.

In order to assess whether the effect of any predictor was additive to that of others, a variable representing the sum score of significant predictor variables was constructed in order to assess whether comorbidity would increase in a dose–response fashion with higher levels of the predictor sum score.

In the predictive analyses, post-baseline onset of bipolar disorder was the outcome variable and the presence or absence of one or more manic symptoms at baseline (T0), outside any lifetime diagnosis of bipolar or psychotic disorder, was the predictor variable. Predictive power of the predictor variable was expressed as the post-test probability (PPs) calculated with the DIAGTEST procedure in the STATA statistical program, and calculated separately for i) those with subclinical psychosis at baseline and ii) those without subclinical psychosis at baseline. The PP is the likelihood of disease (post-baseline bipolar disorder) given a positive test result (baseline mania symptoms) (Sackett and Wennberg, 1997).

2.6. Risk set

The risk set consisted of all individuals who had participated in the baseline CIDI interview, with the exception of the 218 individuals with a lifetime diagnosis of psychotic disorder ($n=107$) or bipolar disorder ($n=132$, of whom 21 also had a diagnosis of psychotic disorder) resulting in a sample for analysis of 6857

individuals. For the predictive analysis, the risk set consisted of all individuals who had i) participated in the baseline CIDI interview with the exception of the 218 individuals with a lifetime diagnosis of psychotic disorder or bipolar disorder and ii) who had had at least one post-baseline CIDI interview (T1 or T2). After applying these criteria, the risk set for the predictive analysis consisted of 5501 individuals.

3. Results

3.1. Sample description

In the entire baseline sample of 7076 individuals, the lifetime population prevalence of at least one manic and one psychotic symptom were 4.1% and 4.2% respectively. The mean age of the risk set of 6857 individuals, in which persons with any lifetime DSM-III-R bipolar or psychotic disorder diagnosis ($n=218$) had been excluded, was 41.2 years ($SD=12.2$) and 47% was male (Table 1). In the risk set of 6857, the prevalence of subclinical mania was 2.3% (mean symptom sum score: 0.1, $SD=0.65$) and of subclinical psychosis was 2.8%.

Table 1
Risk set demographics, mania outcome and moderator variable distributions

Variable	Frequencies (%) or mean (SD)
Age	41.2 (12.2%)
Male	3214 (47%)
Female	3643 (53%)
No partner	1837 (27%)
Unemployment	451 (7%)
Education	
Highest	1865 (28%)
High	508 (8%)
Low	2485 (37%)
Lowest	1911 (28%)
At least one subclinical manic symptom	156 (2.3%)
At least one subclinical psychotic symptom	192 (2.8%)
Psychological problems interfere with functioning	
A little	16%
More than a little	7%
Cannabis use	629 (9%)
Use of other drugs	134 (2%)
Neuroticism	3.8 (4.2%)
Urbanicity	
Lowest	1164 (17%)
High	3071 (45%)
Highest	2622 (38%)
Trauma	845 (12%)
Discrimination	1056 (15%)
Family history of delusions/hallucinations	279 (5%)
Family history depression	1438 (27%)

Individuals with subclinical mania had a 17% risk of subclinical psychosis, compared with only 2% in those without ($P < 0.000$; Table 2). The subclinical psychosis risk increased from 12%, 23% to 83% in individuals with 1, 2 and 3 or more manic symptoms respectively (test for trend: $\chi^2 = 25.7$, $df = 1$, $P < 0.0001$).

3.2. Predictors of comorbidity

In the risk regression model of subclinical psychosis, there was a significant interaction between urbanicity and subclinical mania, indicating a higher risk of comorbidity between subclinical mania and subclinical psychosis for subjects living in more urbanised areas (Table 3). Similar positive interactions were apparent for cannabis use and a family history of depression, indicating more comorbidity in individuals using cannabis and in individuals with familial loading for depression. Although there was no significant interaction between childhood trauma and subclinical psychosis, there was a positive interaction using the outcome of hallucinations only, indicating a higher risk for comorbidity between subclinical mania and hallucinations in subjects with a history of recalled trauma (Table 3). Although the risk for mania and psychosis comorbidity was substantially higher in the expected direction for individuals who were younger (19% versus 14%), those using other drugs than cannabis (38% versus 15%), those with higher levels of neuroticism (20% versus 11%), those with a family history of psychosis (24% versus 17%), those living alone (24% versus 13%) and those in the highest level of social impairment due to physical or psychological problems (29% versus 12% and 17%), none of these differences was statistically significant by conventional alpha (Table 3). No large or significant differences were seen for sex, unemployment, and discrimination, whereas lower education was associated with lower rather than higher comorbidity, although this difference was not statistically significant (Table 3).

3.3. Additivity of predictors

A variable with score 0 to 3 representing the number of predictors (cannabis, urbanicity highest level and

Table 2
Comorbidity of subclinical manic and subclinical psychotic symptoms

Subclinical mania symptoms	Subclinical psychotic symptoms	
	Absent	Present
Absent	6536	165 (2.5%)
Present	129	27 (17.3%)
Test risk difference	$\chi^2 = 23.9$, $df = 1$, $P < 0.0001$	

Table 3
Comorbidity, stratified by moderator values

	Moderator	Comorbidity between psychosis and mania (%) [*]	Interaction between the moderator and psychosis@ χ^2 (p)
Age	Lower median group (18–40)	19	0.5 (0.47)
	Higher median group (41–64)	14	
Sex	Women	16	0.2 (0.63)
	Men	18	
Cannabis	Absent	12	5.4 (0.002)
	Present	36	
Use other drugs	Absent	15	1.2 (0.28)
	Present	38	
Urbanicity [#]	Level 1	5	5.8 (0.018)
	Level 2	14	
	Level 3	23	
Neuroticism	Lower median group (0–3)	11	0.6 (0.44)
	Higher median group (4–28)	20	
Family history psychosis [^]	Absent	17	0.3 (0.60)
	Present	24	
Family history depression [^]	Absent	17	7.1 (0.0076)
	Present	24	
Unemployment	Absent	18	0.5 (0.49)
	Present	14	
Living alone	Absent	13	1.9 (0.17)
	Present	24	
Childhood trauma	Absent	12	2.6 (0.11)
	Present	28	
Childhood trauma: hallucinations only	Absent	3	4.1 (0.044)
	Present	15	
Education	Highest	26	2.9 (0.09)
	High	27	
	Low	11	
	Lowest	14	
Discrimination	Absent	18	0.9 (0.34)
	Present	15	
Psychological problems interfere with social functioning	None	17	0.34 (0.56)
	Little	12	
	More than a little	29	

^{*}proportion of people with subclinical mania, dichotomously defined, who also had evidence of subclinical psychosis, dichotomously defined.

@ tests whether differences in risk are significantly different between different levels of moderator variable.

[#] three levels representing number of persons per square kilometre: 1:0–499; 2:500–1499; 3:1500 and more.

[^] family history of delusions and/or hallucinations (psychosis) or depression, as reported by respondent.

family history of depression) of each individual in the risk set was constructed in order to assess the level of comorbidity at each stratum. This revealed an increase

Table 4

Prediction of incident bipolar disorder: the Post-test probabilities (PP) of developing post-baseline DSM-III-R bipolar disorder in those with subclinical mania at baseline with and without subclinical psychotic symptoms

	PP Post-baseline bipolar disorder	95% confidence interval
No subclinical psychotic symptoms	3.0%	2.5, 3.4
With subclinical psychotic symptoms	9.5%	4.7, 14.4

in subclinical psychosis comorbidity given the presence of subclinical mania, increasing from 6% in those with zero predictors to 12%, 30% and finally 63% in those with 1, 2 and 3 predictors respectively.

3.4. Prediction of incident bipolar disorder

The PP of developing post-baseline DSM-III-R bipolar disorder in those with subclinical mania at baseline given the co-occurrence of subclinical psychosis was 9.5% (2 out of 21 persons; 95%CI: 4.7, 14.4), considerably and significantly (as evidenced by non-overlapping 95% CIs) higher than the probability of developing bipolar disorder in the group without subclinical psychosis at baseline (3 out of 101 persons; PP=3.0%, 95% CI: 2.5, 3.4) (Table 4).

4. Discussion

This study examined the degree of comorbidity between subclinical mania and subclinical psychosis, the predictors of subclinical comorbidity and prospective post-baseline prediction of incident DSM-III-R diagnosis of bipolar disorder. Excluding the lifetime diagnosis for clinical mania and psychosis at baseline, strong associations between subclinical mania and subclinical psychosis were demonstrated. Subclinical comorbidity was predicted by variables that previously have been shown to increase the risk for psychosis such as urban residence, cannabis use, familial loading for depression, and victimisation (trauma with hallucinations as outcome). Subclinical comorbidity was not predicted by other predictors, that previously have been shown to increase the risk for psychosis such as age, gender, use of other drugs, trait anxiety (neuroticism), family history of psychosis, unemployment, single marital status, childhood trauma (without hallucinations), education, discrimination and social impairment due to physical and psychological problems. Coexistence of subclinical psychotic features with subclinical mania was much more predictive of a future diagnosis of bipolar disorder.

4.1. Predictors of subclinical comorbidity

Some of our findings suggest that similar factors that have previously been shown to increase the risk for psychosis and mania at the clinical level, also increase the risk for the co-occurrence for both symptoms at the subclinical level. In our study there was a strong association between urban residence and subclinical comorbidity. Previous studies (Lewis et al., 1992; Marcelis et al., 1998) have shown that urban residence is as a risk factor for psychosis, whereas contradictory findings for affective disorders exist. In some studies, urban residence has been found to be a risk factor for affective disorders (Kessler et al., 1997; Sundquist et al., 2004), but not in others (Mortensen et al., 2003). It was recently shown that urban environment specifically impacts on the psychotic, but not on the affective dimensions of clinical bipolar disorder (Kaymaz et al., 2006), which is compatible with the current findings in the subclinical phenotype.

Use of cannabis has been shown to be a specific risk factor for later psychosis (Andreasson et al., 1987; Henquet et al., 2005; van Os et al., 2002; Zammit and Lewis, 2004; Stefanis et al., 2004b; Fergusson et al., 2003), as well as for the development of mania (Henquet et al., 2006). In this study, only an association between the use of cannabis and subclinical comorbidity was found and not for the use of other drugs.

Although there are several studies showing common genetic contributions to the variance in liability to psychosis and mania at a clinical level (Craddock et al., 2006), in this study no association between familial loading for psychosis and comorbidity between psychosis and mania at a subclinical level was found. However, a strong association between family history of depression and subclinical comorbidity was found. A significant association between trauma with hallucinations as outcome and subclinical comorbidity was found, entirely in line with the findings of a previous study (Hammersley et al., 2003). No association was found between childhood trauma and comorbidity between mania and psychosis at a subclinical level, whereas trauma has been found to be a risk factor for psychosis (Read et al., 2005) as well as bipolar disorder (Hammersley et al., 2003) (Bebbington, 2004; Garo et al., 2005; Levitan et al., 1998).

Although it is a robust epidemiological finding that younger age and male sex increase the risk for psychosis (Johns et al., 2004; Verdoux et al., 1998), inconsistent findings exist for the impact of age and gender on the prevalence in bipolar disorder. Some studies showed an impact of age and gender on bipolar disorder (Gonzalez-

Pinto et al., 2003; Yildiz and Sachs, 2003) whereas others did not find any sex differences (Hendrick et al., 2000). In this study, no association between age and gender and subclinical comorbidity was found, nor was there an association between neuroticism and subclinical comorbidity in spite of findings in literature of a risk-increasing effect of neuroticism on psychosis (Krabbendam et al., 2002; van Os et al., 2001) and mania (Lozano and Johnson, 2001). No associations were found between lower educational achievement, single marital status, discrimination and unemployment in this study, although previous studies have shown impact of these findings on psychosis and increased mental disorders (Chakraborty and McKenzie, 2002; Janssen et al., 2003; Karlsen and Nazroo, 2002; van Os et al., 2000a; van Os et al., 1995). Although for the above mentioned variables no significant association with subclinical comorbidity was found, the risk for mania and psychosis comorbidity was nevertheless substantially higher in the expected direction for individuals who were younger, those using other drugs than cannabis versus those who did not use, those with higher levels of neuroticism versus those with a lower level, those with a family history of psychosis versus those without a family history of psychosis, those living alone versus those living together and those in the highest level of social impairment due to physical or psychological problems versus none, little or more than little. Therefore, the inconclusive findings regarding risk of comorbidity may be likely due to insufficient statistical power. For example, the interaction with family history of depression was significant, whereas the interaction with family history of psychosis was not, despite similar differences in comorbidity. The reason for this was that a family history of psychosis was much rarer than a family history of depression, yielding lower power.

There was a positive interaction between the variable social impairment due to physical and psychological problems and subclinical psychosis, indicating that for a given level of subclinical mania, the coexistence of subclinical psychotic symptoms was more predictive of social impairment, but this interaction was not significant.

To summarise, some of the findings suggest that genetic and non-genetic risk factors for psychosis and mania overlap on lower levels of the continuum, mirroring the risk factors for the clinical disorders. These shared aetiological factors may explain the substantial comorbidity between both disorders.

4.2. Impact of subclinical comorbidity

In addition, comorbidity at a subclinical level was predictive of a future diagnosis of bipolar disorder. The

probability of developing incident bipolar disorder was 3% in the absence of subclinical psychotic symptoms and 10% in the presence of psychotic symptoms, indicating approximately a 7% higher risk of developing future bipolar disorder.

The risk factors for comorbidity that were studied, such as family history, use of cannabis, victimisation, neuroticism and indicators of the wider social environment have all been described before as risk factors for psychosis (Van Os et al., 2005), and thus may act in part by facilitating the formation of more “toxic” combinations of subclinical symptoms of mania and psychosis in the general population with higher probability of transition to clinical disorders. Thus, subclinical symptoms can be seen as intermediary phenotypes of a mood continuum that after exposure to additional risk factors may progress to a full-blown disorder (Hanssen et al., 2005), specifically in the presence of psychotic symptoms at subclinical level.

4.2.1. Methodological issues

This study mainly reports on cross-sectional associations between symptoms of mania and psychosis and demographic and other risk variables and lacks information on temporal relationships between these variables. However, an important finding was that subclinical psychosis was associated with a greater risk of transition to bipolar disorder over time.

Psychosis includes also dimensions of negative symptoms and disorganisation in addition to positive symptoms. However, the CIDI does not include adequate assessments of these dimensions so that their role could not be investigated.

Another limitation of the used instrument is that during this study, only respondents were interviewed and not their relatives. Therefore, under-reporting of (hypo) manic symptoms could have occurred, since these symptoms often are experienced as ego-syntonic by the patient, whereas family members may provide important contextual information. Another limitation of our study is that a lifetime prevalence of a single manic symptom for 2 days, as only assessed by lay interviews, may be underestimated; however there is no reason to assume that this would have affected comorbidity rates and predictors thereof.

Psychotic symptom ratings were assessed by lay interviewers (CIDI ratings of 1–4), whereas the other CIDI ratings (5–6) were assessed by clinicians through telephone interviews in approximately 50% of eligible cases. No clinical reinterview ratings were carried out for the mania symptoms. It is possible that with lay interviewer ratings a degree of misclassification did

occur. However, the CIDI was designed for trained interviewers who are not clinicians and has been found to have high inter-rater reliability (Cottler, 1991; Wittchen et al., 1991), and high test–retest reliability (Semler et al., 1987; Wacker et al., 1990; Wittchen, 1994).

Bias could also have been introduced by differential rating of psychosis due to incomplete clinical reinterview rates at baseline. However, excluding the individuals who were eligible for clinical reinterview but who had not been contacted, thus leaving only those who had been rated by clinicians, did not affect the results.

Our findings depend in part on the assumption that the lay interviewers, using the CIDI, were enough experienced in the discrimination of manic and psychotic symptoms. This assumption has face value since i) the lay interviewers were trained during a three-day course, ii) there was an extensive monitoring and quality checks throughout the entire data collection period (Bijl et al., 1998a), iii) individuals who screened positive for psychosis were reinterviewed by clinicians. The CIDI has been designed for trained interviewers who are not clinicians and has been found to have a high inter-rater reliability (Cottler, 1991; Wittchen et al., 1991) and high test–retest reliability (Semler et al., 1987; Wacker et al., 1990; Wittchen, 1994). Nevertheless, a degree of misclassification may have occurred, although again it is difficult to see how this would have affected the findings relating to predictors of comorbidity.

Acknowledgements

Funded by the Dutch Department of Health.

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Evidence That Patients With Single Versus Recurrent Depressive Episodes Are Differentially Sensitive to Treatment Discontinuation: A Meta-Analysis of Placebo-Controlled Randomized Trials

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Background: Antidepressants are effective in the prevention of relapse after remission from an acute depressive episode. It is unclear, however, to what degree duration of the continuation phase, level of abruptness of antidepressant discontinuation, or the number of previous episodes moderate the prophylactic effect of antidepressants.

Data Sources: Searches were conducted to identify all published randomized, placebo-controlled, double-blind clinical trials available for review by May 2007 on the efficacy of continuation or maintenance treatment of major depressive disorder with either selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) that included patients entering a maintenance phase after achieving remission from the acute phase. The MEDLINE and EMBASE databases were searched using the terms *depression*, *antidepressants*, *discontinuation*, and *maintenance treatment*; this was followed by reference checks of articles thus identified. In addition, the Cochrane Library was also searched using the same terms. Some authors of the identified papers were contacted for specific data.

Data Synthesis: Data were collected from 30 trials with 4890 participating patients. The overall reduction of relapse risk in the maintenance phase was highly significant for both SSRIs (OR = 0.24, 95% CI = 0.20 to 0.29) and TCAs (OR = 0.29, 95% CI = 0.23 to 0.38) over 1 year of follow-up of maintenance treatment. The prophylactic effect appeared to be constant over the length of the continuation phase. Recurrent episode patients experienced less protection from antidepressants over the maintenance phase (OR = 0.37, 95% CI = 0.31 to 0.44) than single episode patients (OR = 0.12, 95% CI = 0.06 to 0.26).

Conclusions: Antidepressants robustly reduce relapse risk in the maintenance phase, regardless of a number of clinical and pharmacologic factors. There is evidence, however, that with increasing number of episodes, patients develop a relative resistance against the prophylactic properties of antidepressant medication.

(*J Clin Psychiatry* 2008;69:1423–1436)

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The authors thank the anonymous referees for their detailed and extremely helpful comments on earlier versions of the manuscript.

Dr. van Os has received grants from or is a speaker for Eli Lilly, Bristol-Myers Squibb, Lundbeck, Organon, Janssen-Cilag, GlaxoSmithKline, Otsuka, and AstraZeneca. Dr. Loonen is a speaker or advisory board member for Eli Lilly, Bristol-Myers Squibb, Lundbeck, Janssen-Cilag, Wyeth, Bional, and AstraZeneca. Dr. Nolen has received grants from the Netherlands Organization for Health Research and Development, Netherlands Organization for Scientific Research, Stanley Medical Research Institute, AstraZeneca, Eli Lilly, GlaxoSmithKline, and Wyeth and is a speaker or advisory board member for AstraZeneca, Cyberonics, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Pfizer, and Servier. Dr. Kaymaz reports no financial or other relationship relevant to the subject of this article.

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Depression often manifests itself as a chronic or a recurrent illness; 15% to 20% of depressed patients experience a chronic course, and 75% to 80% of patients experience recurrent episodes.^{1,2} Therefore, treatment should focus not only on improving symptoms of the acute episode but also on the prevention of relapse (return of symptoms of the index episode) and recurrence (the development of a subsequent episode).³ The efficacy of antidepressants in treating acute episodes (4–6 and up to 12 weeks) has been well established in placebo-controlled studies, although the effect sizes for antidepressant treatment are only moderately larger than for placebo.^{4,5} Moreover, antidepressants are effective in long-term treatment. In a 2003 meta-analysis of 31 randomized trials (4410 participants), Geddes et al.⁶ showed that continuing antidepressant therapy consistently reduced the risk of relapse and recurrence by 70% compared with continuation with placebo, and this seemed to be similar for all classes of antidepressants. They also found no differences in relapse and recurrence rates between patients

with shorter (1–2 months) and longer (4–6 months) treatment after having achieved remission and prior to randomization or between patients with relatively short (6 months) versus longer (up to 36 months) follow-up, suggesting that the reduced risk is largely independent of the duration of treatment before randomization and the duration of the randomly allocated therapy.

Besides the question of how long treatment should be continued once remission has been attained, another important question facing clinicians in their daily practice is, first, to what degree do patients with multiple episodes acquire additional vulnerabilities that could make them more vulnerable not only to discontinuation of the antidepressant per se, but also to the mode of discontinuation (gradual or acute)? The rationale for such a distinction between single and multiple episode patients was proposed by Post and colleagues⁷ in an attempt to account for several phenomena observed in the course of affective illness; they emphasized the importance of preventing episodes with prophylactic treatment to inhibit sensitization. According to the sensitization model, a subgroup of patients exists who with each recurrent episode becomes more vulnerable, or “sensitized,” to affective episode precipitants. The authors suggested that these patients show characteristics of a sensitization or kindling-like process, in which the biochemical and physiologic processes involved in the illness become progressively more easily triggered by the same circumstances or precipitants compared to the first episode.

Therefore, in the literature on relapse prevention by antidepressants, several questions remain unanswered. It is unclear (1) how long treatment should be continued after remission is achieved (e.g., 6 months, 1 year, longer?), (2) whether treatment should be continued longer in patients with multiple episodes compared to single episodes, and (3) how the antidepressant should be discontinued: can it be done abruptly or within 1 week, or should it be tapered off gradually for 1 or more weeks? In the present study, these questions were addressed, with the hypothesis that multiple episode patients would be more sensitive to antidepressant discontinuation, in particular abrupt discontinuation.

METHOD

In 1988, the MacArthur Foundation Research Network on the Psychobiology of Depression convened a task force to examine the ways in which change points in the course of depressive illness until that time had been described and the extent to which inconsistencies in these descriptions might hinder research on this disorder.⁸ Consistent conceptualization and empirical validation of these terms were considered desirable for the following reasons: (1) to be able to improve design, interpretation, and comparison of studies on natural course and treatment;

(2) to be able to clarify the relationship between biological and psychological correlates of illness; (3) to create improved guidelines for evaluation of clinical efficacy of drugs and other treatments by regulatory agencies; (4) to be able to conduct empirically based revisions of diagnostic criteria; and (5) to be able to develop improved treatment guidelines for clinical practice. Guided by these statements, the following definitions were constructed.

Definitions

In the literature, the terms *response*, *remission*, *relapse*, and *recurrence* and the terms describing the different treatment phases (*acute treatment*, *continuation treatment*, and *maintenance treatment*) are not uniformly defined. In this article, the definitions by Frank and colleagues⁸ were followed. The first phase in treatment is acute treatment, aimed at the suppression of the depressive symptoms. Response is defined as a clinically significant reduction of symptoms of depression (e.g., at least 50% reduction of the score on the Hamilton Rating Scale for Depression [HAM-D]), and remission is defined as the remaining of no or only minimal symptoms of depression (e.g., a score of less than 9 points on the HAM-D). During the first 6 months after remission is achieved, the underlying illness may still be present and discontinuation of the treatment can cause reappearance of symptoms of the original episode; this is called a relapse. In this context, *continuation treatment* is the term applied to the prevention of a relapse, i.e., the treatment phase during the first 6 months after having achieved remission. After these 6 months of remission, the underlying disorder is considered resolved, and when a new depressive episode appears after this period, it is called recurrence. The term *maintenance treatment* is applied for a treatment with antidepressants that aims at the prevention of a recurrence.

Types of Studies

We wished to identify all published randomized, placebo-controlled, double-blind clinical trials available for review by May 2007 on the efficacy of continuation or maintenance treatment of major depressive disorder with either selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs) (the 2 groups of comparable and widely used antidepressants with the largest number of trials) in patients who had achieved remission during acute treatment with these antidepressants.

Search Strategy for Identification of Studies

A MEDLINE and EMBASE computerized search using the terms *depression*, *antidepressants*, *discontinuation*, and *maintenance treatment* was conducted and was supplemented with references cited in reports so identified (reference checking). In addition, the Cochrane Library was also searched using the same terms. Some authors of the identified papers were contacted for specific data.

Types of Participants

Trials were eligible for the review if they included patients with major depressive disorder, single or recurrent episode, who were treated with an antidepressant (SSRI or TCA) until remission was attained. These patients had then to be followed up during the continuation and subsequent maintenance phases.

Types of Interventions

Patients obtaining remission and entering the continuation or the maintenance phase had to be randomly divided into at least 2 groups, with at least 1 group receiving active treatment with an antidepressant (SSRI or TCA) and another group receiving placebo, under double-blind conditions.

Data Selection

The search results and the data extracted from the trial reports on participant characteristics, intervention details, and outcome measures were checked by 2 reviewers (N.K. and A.J.M.L.) before analyses. When specific data were not given in the report, the authors were contacted; some authors responded to the 2 efforts we made to contact them, and some did not.

Data were entered into the STATA, version 9, software program (StataCorp, 2005)⁹ for further analyses.

Methodological Quality of Included Studies

The assessment of the methodological quality of the trials was carried out by 2 reviewers (N.K. and A.J.M.L.) who used the same checklist. The most crucial aspects of the included trials for the internal validity were (1) the method of randomization and achievement of a double-blind condition and (2) the reporting of withdrawals and dropout rates and use of a suitable survival analysis.

Data Aggregation

The following data were extracted and tabulated from each paper (see Table 1): number of previous episodes, duration of active treatment, duration of stabilization/continuation treatment, number of subjects, duration of follow-up, and duration of withdrawal of medication. Besides these tabulated data, the numbers of individuals at risk over each follow-up interval (at 3, 6, 9, and 12 months) were extracted from the publications whenever they were mentioned or, if they were not, from the survival curves in these publications.

Data Analysis

Data from the selected randomized controlled trials were combined to estimate the pooled odds ratio (OR) with 95% confidence intervals (CIs) using a random-effects model. The presence of heterogeneity across trials was evaluated using a χ^2 test for homogeneity, testing whether individual trials results varied more than could be

explained by chance alone. When significant heterogeneity was found, possible causes were explored. In addition, meta-regression was used to assess the degree to which important clinical and study quality factors impacted on the meta-analytic results. Meta-regression extends a random-effects meta-analysis to estimate the extent to which 1 or more covariates, with values defined for each study in the analysis, explain heterogeneity in the treatment effects. In meta-regression, the log odds ratio, representing the antidepressant effect size, is regressed on the variables that are hypothesized to explain heterogeneity in the treatment effects.

Potential publication bias was tested for using Begg's test for asymmetry.

As to the question of effectiveness of continuation and maintenance treatment with antidepressants, relapse/recurrence rates after randomization to either continuation of the antidepressant or switch to placebo were compared, whenever possible, over a 1-year follow-up period separately at 3, 6, 9, and 12 months. If relapse/recurrence rates at these assessment points were not presented in the results of the publication, they were calculated when possible, e.g., by estimating these rates from the survival curves that were presented as figures in most of the publications. The effect of time at follow-up on relapse/recurrence rates was examined using meta-regression analysis with time at follow-up (3, 6, 9, or 12 months) as independent variable and the log odds ratio representing antidepressant effect size as the dependent variable. In order to compile the dataset for this analysis, each study with data (i.e., number of relapses/recurrences) at 3, 6, 9, and 12 months was separated into 4 different studies of 3 months' duration each with the variable "time" denoting whether follow-up was at 3, 6, 9, or 12 months. This way, the effect of time on relapse rate could be assessed in the meta-regression of the effect sizes, using the STATA meta-regression routine in STATA (StataCorp, 2005, version 9).⁹ Using this dataset, controlling for time, meta-regression was also applied to investigate whether duration of continuation treatment, after achievement of remission, was associated with the risk of relapse/recurrence after discontinuation of antidepressants. To this end, studies were subdivided according to the duration of continuation treatment prior to randomization as follows: less than 1 month, 1 to 3 months, > 3 to 6 months, and > 6 months (i.e., beyond the continuation phase of 6 months recommended by the guidelines).

Similarly, meta-regression, controlling for time, was used to examine whether mode of discontinuation in controlled studies affected relapse rates by comparing abrupt discontinuation (< 1 week) with gradual discontinuation (tapering for $\geq$ 1 week).

Finally, meta-regression, controlling for time, was used to assess whether clinical features such as the number of previous episodes moderated relapse rates. To this end, the studies were subdivided further into those involving

patients with no previous episode of depression versus those involving patients with multiple episodes, i.e., at least 1 previous episode prior to the index episode. As we had hypothesized that the patients most sensitive to the antidepressant discontinuation would be those with the combination of multiple episodes and an abrupt mode of discontinuation, a number of previous episodes-by-mode of discontinuation interaction term was fitted in the meta-regression model.

In the event that a variable in the meta-regression was found to impact significantly on the meta-analytic result, separate meta-analyses were carried out for the different strata of this variable, so as to clarify the direction and magnitude of group differences in effect size.

A test for selection bias was carried out, visualizing the included studies in a Begg's funnel plot with pseudo 95% confidence limits.

RESULTS

Identified Studies

The search process yielded 44 studies possibly satisfying the inclusion criteria, i.e., the continuation/maintenance treatment was with either an SSRI or a TCA. Fourteen studies were excluded due to methodological limitations: 1 because the study was single blind,¹⁰ 4 because there was no placebo control group,¹¹⁻¹⁴ 1 because the antidepressant in the acute or continuation phase was not the same antidepressant as in the maintenance phase,¹⁵ 4 because lithium was added during the acute phase to achieve remission,¹⁶⁻¹⁹ 1 because the study was not formally published,²⁰ and 1 because patients with bipolar disorder were also included.²¹ We also excluded 1 study²² of maintenance treatment with a 5-year follow-up as it included patients who were also part of the 3-year maintenance study by Frank et al.⁴⁵ One study (McGrath et al.²³) was excluded as it did not mention the number of relapses separately for the medication and placebo arms in this study. Only the active treatment arms, without crossover, and the placebo arm of the studies with different assignment groups in which relapse rates are mentioned separately for the different arms of the study were included.

The characteristics of the 30 studies included in this meta-analysis are listed in Table 1.²⁴⁻⁵³ Some of the studies were 4-armed or 5-armed studies, in which medication was compared to psychotherapy or their combination; from these studies, we only included data from the medication arm and the placebo arm. The 30 trials involved a total of 4890 patients, performed in both primary and secondary care settings, and described 2749 patients who continued with the antidepressant and 2141 patients who were switched to placebo. Fifteen studies were found in which the allocated drug was an SSRI, with a total of 2984 patients, and 15 studies were found in which the allocated drug was a TCA, with a total of 1906 patients.

There were no 3-arm studies with 2 medication arms (e.g., both an SSRI and a TCA) versus placebo.

Duration of Continuation Phase

In order to examine the impact of the prerandomization period (e.g., the duration of the continuation phase), studies were divided in 4 subgroups with a duration of less than 1 month, 1 to 3 months, > 3 to 6 months of continuation phase, and > 6 months of continuation plus maintenance phase.

In the subgroup of trials with a continuation treatment of less than 1 month (i.e., remission achieved for less than 1 month) prior to randomization, 9 trials (1261 patients in total) were found, and of these, 7 trials (954 patients) provided information at 3 months of follow-up, 6 trials (727 patients) provided information at 6 months of follow-up, 3 trials (339 patients) provided information at 9 months of follow-up, and 2 trials (101 patients) provided information at 12 months of follow-up. In the subgroup of trials with 1 to 3 months of continuation treatment prior to randomization, 2 trials (95 patients) provided information at 3 (85 patients), 6 (70 patients), 9 (63 patients), and 12 (59 patients) months of follow-up. In the subgroup of trials with > 3 to 6 months of continuation treatment prior to randomization, 17 trials (3194 patients in total) were found, and of these 17 trials, 14 (2384 patients) provided information at 3 months of follow-up, 13 trials (2104 patients) at 6 months of follow-up, 11 trials (1846 patients) at 9 months of follow-up, and 9 trials (1547 patients) at 12 months of follow-up. Only 1 study was found (Bialos et al.³⁸) with a clearly mentioned treatment period prior to randomization of more than 6 months. Another study, by Cook et al.,⁴² had a duration of 52 weeks, but did not clarify how long the duration of the acute and continuation treatment lasted. These publications were included in the subgroup of studies with a prerandomization period of 3 to 6 months. To examine the impact of time at follow-up (3, 6, 9, and 12 months) on relapse/recurrence rates, we have used meta-regression analysis on pooled results of 30 trials in total (4890 patients) (see Figure 2), 23 trials (3441 patients) providing information at 3 months of follow-up (see Figure 3), 21 trials (2914 patients) at 6 months of follow-up (see Figure 4), 16 trials (2259 patients) at 9 months of follow-up (see Figure 5), and 8 trials (1710 patients) at 12 months of follow-up (see Figure 6).

Number of Previous Depressive Episodes

With regard to the number of episodes prior to the index period, 4 trials (301 participants) included patients with no prior episodes, and 17 trials (2939 participants) included patients with at least 1 episode prior to the index episode. The remaining 9 studies of the total of 30 were left out of the analysis, because some studies included both single- and recurrent episode patients. Some studies

Table 1. Characteristics of the Included Studies

Study	Diagnosis	Diagnostic Criteria	No. of Previous Episodes	Duration of Active Treatment Phase (wk)
Montgomery et al, 1988 ²⁴	MDD	DSM-III	≥ 2	6
Doogan and Caillard, 1992 ²⁵	MDD	DSM-III-R	Not reported	8
Montgomery and Rasmussen, 1992 ²⁶	MDD	DSM-III-R	Not reported	6
Montgomery and Dunbar, 1993 ²⁷	MDD	DSM-III-R	≥ 2	8
Robert and Montgomery, 1995 ²⁸	MDD	DSM-III-R	≥ 2	8
Keller et al, 1998 ²⁹	Chronic depression, MDD, double depression ^a	DSM-III-R, HAM-D	Mixed	12
Reimherr et al, 1998 ³⁰	MDD	DSM-III-R	Not reported	12–14
Terra and Montgomery, 1998 ³¹	MDD	DSM-III-R	≥ 2	6
Hochstrasser et al, 2001 ³²	MDD	DSM-IV	≥ 2	6–9
Klysner et al, 2002 ³³	MDD	DSM-IV	0	8
Mindham et al, 1972 ³⁴	Depression	MRC	Not reported	3–10
Klerman et al, 1974 ³⁵	Depression	DSM-II	0	4–6
Coppen et al, 1978 ³⁶	Depression	MRC	11 patients = 0; 21 patients ≥ 1	Not reported
Stein et al, 1980 ³⁷	MDD	Feighner ^b	≥ 1	6
Bialos et al, 1982 ³⁸	Depression	RDC	Chronic depression	Not reported
Kane et al, 1982 ³⁹	Depression	RDC	≥ 2	Not reported
Glen et al, 1984 ⁴⁰	Depression	MRC	0	Average 8½
Prien et al, 1984 ⁴¹	Depression	RDC	≥ 1	Not reported
Cook et al, 1986 ⁴²	MDD	RDC	≥ 1	Not reported
Georgotas et al, 1989 ⁴³	MDD	RDC	≥ 3	7–9
Rouillon et al, 1989 ⁴⁴	MDD	DSM-III	≥ 1	8
Frank et al, 1990 ⁴⁵	Depression	RDC	≥ 2	Not reported
OADIG, 1993 ⁴⁶	MDD	RDC	50% = 1; 50% ≥ 1	16
Reynolds et al, 1999 ⁴⁷	MDD	RDC	Average 5	Not reported
Alexopoulos et al, 2000 ⁴⁸	MDD	RDC, DSM-IV	Most = 1 or > 2	Not reported
Wilson et al, 2003 ⁴⁹	MDD	DSM-III-R, HAM-D	0	8
Gilaberte et al, 2001 ⁵⁰	MDD	DSM-III-R	≥ 1	8
Schmidt et al, 2000 ⁵¹	MDD	DSM-IV	Mixed	13
McGrath et al, 2006 ⁵²	MDD	DSM-IV	Chronic depression	12
Perahia et al, 2006 ⁵³	MDD	DSM-IV	≥ 1	12

^aMajor depression with antecedent dysthymic disorder.

^bFeighner et al. 1972 criteria.

Abbreviations: CGI = Clinical Global Impressions scale, CGI-S = Clinical Global Impressions-Severity of Illness scale,

GAS = Global Assessment Scale, HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

included only patients with a chronic depressive disorder or did not specify the number of previous episodes.

Mode of Discontinuation of the Antidepressant

Antidepressant medication was discontinued abruptly (< 1 week) in 22 trials (4320 participants) and gradually (≥ 1 week) in 8 trials (630 participants). No studies were found that included both abrupt and gradual discontinuation.

Publication Bias

The distribution of effect size–related measures relative to sample size–related measures did not suggest publication bias in the studies used for this meta-analysis (Figure 1).

Treatment Effects

Overall, the results showed that continuing antidepressant therapy consistently reduced the risk of relapse (OR = 0.30, 95% CI = 0.25 to 0.35, $p < .001$) compared to placebo (Figure 2), with no significant heterogeneity detected ($\chi^2 = 40.21$, $df = 29$, $p = .081$). This effect was highly significant for SSRIs (OR = 0.24, 95% CI = 0.20 to 0.29, $p < .001$) as well as for TCAs (OR = 0.29, 95% CI = 0.23 to 0.38, $p < .001$).

Using meta-regression, the overall relapse-reducing effects of the SSRIs were not significantly different from those of the TCAs (meta-regression coefficient = -0.30 , 95% CI = -0.78 to 0.17 , $p = .209$). However, it should be noted that none of the studies involved (next to placebo) a head-to-head comparison of TCAs versus SSRIs.

Duration of Stabilization/ Continuation Phase (prerandomization phase) (wk)	No. of Patients in Trial	Criteria for Relapse/Recurrence	Duration of Follow-Up (mo)	Withdrawal of Medication (wk)
24	Fluoxetine = 88, placebo = 94	HAM-D > 18	12	< 1
0	Sertraline = 185, placebo = 110	Clinical criteria, CGI $\geq$ 4	11	3
0	Citalopram = 105, placebo = 42	MADRS $\geq$ 22	6	< 1
0	Paroxetine = 68, placebo = 67	CGI $\geq$ 4, clinical criteria	12	< 1
0	Citalopram = 152, placebo = 74	MADRS $\geq$ 25, clinical criteria	6	< 1
16	Sertraline = 77, placebo = 84	DSM-III criteria for at least 3 wk, CGI $\geq$ 4, HAM-D $\geq$ 4 points higher than maintenance phase baseline	19	Maximum 3
0	Fluoxetine = 102, placebo = 96	HAM-D $\geq$ 14 for 3 successive wk, DSM criteria for minimum 2 wk	12 ^{1/2}	< 1
18	Fluvoxamine = 109, placebo = 94	Clinical criteria	12	< 1
16	Citalopram = 132, placebo = 132	MADRS $\geq$ 22 confirmed at 3–7 d, CGI $\geq$ 5	12–19	< 1
16	Citalopram = 60, placebo = 61	MADRS $\geq$ 22	12	< 1
0	Amitriptyline = 50, placebo = 42	Clinical criteria on monthly screenings	6	< 1
0	Amitriptyline = 25, placebo = 25	Clinical criteria	8	< 1
6	Amitriptyline = 16, placebo = 16	Increase in symptoms sufficient to warrant hospital admission	12	< 1
2	Amitriptyline = 28, placebo = 27	Clinical criteria	6	< 1
192	Amitriptyline = 7, placebo = 10	Clinical criteria	6	3
24	Imipramine = 6, placebo = 6	RDC, clinical criteria	24	< 1
0	Amitriptyline = 8, placebo = 9	Clinical criteria	36	2
Not reported	Imipramine = 39, placebo = 34	RDC, GAS $\leq$ 60, clinical criteria	24	< 1
$\geq$ 52	TCA = 6, placebo = 9	Clinical criteria	8	4–8
16	Nortriptyline = 13, placebo = 23	RDC, HAM-D $\geq$ 16	12	< 1
24	Maprotiline = 767, placebo = 374	MADRS > 27 or > 25 for 2 wk	12	< 1
17	Imipramine = 28, placebo = 23	RDC, HAM-D $\geq$ 15, Raskin $\geq$ 7	36	< 1
8	Dothiepin = 33, placebo = 36	MADRS > 10, clinical criteria	24	< 1
16	Nortriptyline = 28, placebo = 29	RDC	36	6
16	Nortriptyline = 22, placebo = 21	RDC, DSM-IV criteria, HAM-D $\geq$ 17	24	10
16–20	Sertraline = 56, placebo = 57	HAM-D $\geq$ 13, DSM-III-R clinical criteria	24	< 1
24	Fluoxetine = 70, placebo = 70	HAM-D $\geq$ 18, CGI $\geq$ 4, DSM-III-R	12	< 1
Not reported	Fluoxetine = 189, placebo = 122	Criteria for depressive episode determined by the SCID-P, CGI-S $\geq$ 2	25	< 1
24	Fluoxetine = 131, placebo = 131	2 wk of ratings of less than “much improved” on the CGI, compared with ratings at study entry	8	< 1
24	Duloxetine = 136, placebo = 142	CGI $\geq$ 2 compared to baseline, MINI criteria for MDD	^{1/2}	1

Abbreviations continued: MDD = major depressive disorder, MINI = Mini-International Neuropsychiatric Interview, MRC = U.K. Medical Research Council, OADIG = Old Age Depression Interest Group, Raskin = Raskin Depression Scale, RDC = Research Diagnostic Criteria, SCID-P = Structured Clinical Interview for DSM-IV patient version, TCA = tricyclic antidepressant.

Comparing the relapse rates as a function of time at follow-up revealed that antidepressants at 3 months of follow-up significantly reduced relapse rates compared to placebo (OR = 0.25, 95% CI = 0.17 to 0.36, $p < .001$) (Figure 3). At further follow-up, this remained unchanged at 6 months (OR = 0.19, 95% CI = 0.13 to 0.29, $p < .001$), at 9 months (OR = 0.29, 95% CI = 0.21 to 0.40, $p < .001$), and at 12 months (OR = 0.27, 95% CI = 0.12 to 0.60, $p = .001$) (Figures 4–6). Meta-regression confirmed this result: with longer follow-up, there was no significant additive relapse-reducing effect, neither at 6 months compared to the first 3 months (meta-regression coefficient = -0.24 , 95% CI = -0.77 to 0.28 , $p = .367$), nor at 9 months compared to the first 3 months (meta-regression coefficient = 0.14 , 95% CI = -0.44 to 0.72 , $p = .635$),

Figure 1. Begg's Funnel Plot With Pseudo 95% Confidence Limits

Abbreviation: OR = odds ratio.

Figure 2. Recurrence in the Antidepressant and Placebo Groups in the Pooled Analysis of All Included Studies

^aPooled odds ratio and CI in random-effects model.
Abbreviations: CI = confidence interval, OADIG = Old Age Depression Interest Group.

nor at 12 months compared to the first 3 months (meta-regression coefficient = 0.10, 95% CI = -0.65 to 0.85, $p = .790$).

Duration of Continuation Phase

In meta-regression, the prerandomization periods of 1 to 3 months and of > 3 to 6 months after achievement of remission showed no significantly different relapse-reducing effect of the antidepressant compared to a pre-randomization treatment period of less than 1 month (meta-regression coefficient = 0.41, 95% CI = -0.73 to 1.57, $p = .478$ and meta-regression coefficient = 0.20, 95% CI = -0.26 to 0.68, $p = .389$, respectively).

Number of Previous Depressive Episodes

The meta-regression comparing patients with recurrent episode(s) versus those with a single episode revealed a significant positive regression coefficient, indicating less antidepressant benefit for patients with recurrent episodes (meta-regression coefficient = 1.6, 95% CI = 0.60 to 2.59, $p = .002$). Meta-analyses stratified for this variable revealed that the pooled OR for relapse in single episode patients was considerably lower (OR = 0.12, 95%

CI = 0.06 to 0.26, $p < .001$), without significant heterogeneity ($\chi^2 = 10.79$, $df = 7$, $p = .148$), compared to the OR for relapse in recurrent episode patients (OR = 0.37, 95% CI = 0.31 to 0.44, $p < .001$), also without significant heterogeneity ($\chi^2 = 23.15$, $df = 22$, $p = .393$).

Mode of Discontinuation of the Antidepressant

With regard to the question of possible moderation of the effect size of antidepressant as a function of mode of discontinuation of the antidepressant, it was found that the relapse rates in studies with gradual discontinuation of the antidepressant (i.e., ≥ 1 week) were not different from those in studies with abrupt discontinuation (i.e., < 1 week) (meta-regression coefficient = -0.56, 95% CI = -1.37 to 0.24, $p = .174$).

Interaction Between the Number of Previous Episodes and Mode of Discontinuation of the Antidepressant

In the meta-regression, there was a significant positive interaction between the variables number of previous episodes and mode of discontinuation (meta-regression coefficient = 2.15, 95% CI = 1.01 to 3.29, $p < .001$). Thus, in the recurrent episode patients, abrupt discontinuation was

Figure 3. Recurrence in the Antidepressant and the Placebo Groups in the Pooled Analysis at 3 Months of Follow-Up in the Maintenance Treatment

^aPooled odds ratio and CI in random-effects model.

Abbreviations: CI = confidence interval, OADIG = Old Age Depression Interest Group.

Figure 4. Recurrence in the Antidepressant and the Placebo Groups in the Pooled Analysis at 6 Months of Follow-Up in the Maintenance Treatment

^aPooled odds ratio and CI in random-effects model.

Abbreviations: CI = confidence interval, OADIG = Old Age Depression Interest Group.

^aPooled odds ratio and CI in random-effects model.
Abbreviations: CI = confidence interval, OADIG = Old Age Depression Interest Group.

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Abbreviations: CI = confidence interval, OADIG = Old Age Depression Interest Group.

associated with a lower relapsing preventive effect of antidepressants (OR = 0.32, 95% CI = 0.27 to 0.38, $p < .001$; heterogeneity: $\chi^2 = 57.20$, $df = 41$, $p = .048$), compared to multiple episode patients with gradual discontinuation (OR = 0.11, 95% CI = 0.06 to 0.21, $p < .001$; heterogeneity: $\chi^2 = 8.30$, $df = 9$, $p = .504$), with nonoverlapping confidence intervals of the ORs in the 2 groups.

In single episode patients, no such large difference was apparent, and confidence intervals were largely overlapping (abrupt: OR = 0.10, 95% CI = 0.03 to 0.28, $p < .001$; gradual: OR = 0.19, 95% CI = 0.04 to 0.87, $p = .032$). The significant heterogeneity in the meta-analysis of recurrent episode patients with abrupt discontinuation was largely due to 1 small study with an unusually large effect size in

the opposite direction (Robert and Montgomery²⁸). This study has a meta-analytic weight of less than 1%; therefore, excluding it has little impact on the effect size (but does reduce heterogeneity). Exclusion of this study from the analysis reduced heterogeneity ($\chi^2 = 46.00$, $df = 39$, $p = .205$; $OR = 0.32$, 95% $CI = 0.27$ to 0.37 , $p < .001$).

DISCUSSION

On the basis of the pooled results of 30 randomized clinical trials, it can be concluded that treatment with an antidepressant results in an approximately 70% reduction of risk of relapse. Thus, the current study confirms the effectiveness of continuation treatment with antidepressants once remission has been achieved, as was reported in previous meta-analyses by Loonen et al.,³ Geddes et al.,⁶ and Viguera et al.⁵⁴ In agreement with the latter 2 meta-analyses, it was found that the difference between active medication and placebo was not greater in the studies with SSRIs compared to the studies with TCAs. However, it should be emphasized that no studies were found in which SSRIs and TCAs were compared head-to-head with each other.

In this meta-analysis, several additional questions concerning the continuation and maintenance treatment of depressive disorder were addressed.

Duration of Continuation Phase

Regarding the first question (of how long treatment with antidepressants should be continued once remission has been attained), no significant difference was found between studies with patients who were randomized within 1 month after having achieved remission compared to those in which patients were randomized after a continuation treatment of 1 to 3 months or after 3 to 6 months. This is in line with the results of previous meta-analyses^{6,54} that also did not find a difference in relapse rates in relation to the duration of the stabilization prior to discontinuation of the antidepressant.

In answering the question of how long antidepressants should be continued, another perspective can be gained from the comparison of relapse/recurrence rates over the follow-up at 3, 6, 9, and 12 months after randomization. We found significant relapse-reducing effects of antidepressants compared to placebo at 3, 6, and 9 months as well as 12 months of follow-up. However, the difference between antidepressant and placebo was already achieved within 3 months after randomization, with no additional reduction in risk at 6, 9, and 12 months compared to the effect already obtained during the previous periods (up to 3, 6, and 9 months, respectively).

Unfortunately, it was not possible to include studies in which patients were randomized during maintenance treatment, i.e., more than 6 months after remission was achieved. The only available data are from 2 small stud-

ies. The first was by Bialos et al.,³⁸ who studied 17 patients who had been receiving long-term amitriptyline treatment. Eight of 10 patients who had their medication tapered and discontinued had a relapse within 4 months compared to none of the 7 control subjects during the 6 months of the study. The second small study was by Cook et al.,⁴² who studied 15 patients who had been receiving a long-term treatment with a tricyclic antidepressant agent. None of the 9 patients who continued on active medication experienced a relapse, whereas 3 of the 9 patients switched to placebo experienced a relapse. With the exception of these small studies, no other studies have specifically addressed the question of whether treatment with antidepressants should be continued longer than 6 months after remission is achieved.

On the basis of the above data taken together, it is not possible to give recommendations for an optimal duration of continuation and maintenance treatment with antidepressants. In fact, there is also no evidence from the reviewed studies of the effect of discontinuation of antidepressants to justify the defined distinction between continuation treatment (up to 6 months) and maintenance treatment (beyond 6 months).

Number of Previous Depressive Episodes

A history of severe and frequently recurring depressive episodes is considered to be a plausible clinical predictor of increased risk of relapse or recurrences after discontinuation of the antidepressant.^{22,26,55}

Regarding the second question (of whether treatment should be continued longer in patients with recurrent episodes than in patients who have suffered from a first or second episode), it was found that the reduction in relapse rates was greater for recurrent episode patients compared to single episode patients. In fact, the results support previous findings that patients with 1 or more previous depressive episodes have significantly less benefit from the relapse-reducing effect of the antidepressant than patients with a first episode.^{29,54,56} Thus, the results suggest that with longer duration of illness, the risk of relapse is more difficult to control, conforming to the sensitization hypothesis proposed by Post et al.⁷ In addition, the data showed that the reduction in the protective effect of antidepressants was specifically evident in the subgroup of patients in which the antidepressant was discontinued abruptly. Post et al. hypothesized that stress of a particular type, intensity, and intermittency may produce sensitization in a fashion similar to the behavioral sensitization. Even in cases of anticipated stresses or imagined losses, if sufficiently conditioned, the behavioral, physiologic, and biochemical alterations usually associated with an affective episode might be produced. It may also explain how stress-induced mood alterations might become so sensitized that they also occur spontaneously. However, it should also be emphasized that it was not possible to

specifically address the question of whether maintenance treatment is especially indicated for patients with recurrent depression, again because there are no studies in which patients were randomized more than 6 months after having achieved remission.

Mode of Discontinuation of the Antidepressant

Regarding the third question (of how quickly the antidepressant should be discontinued), it was found that relapse rates in studies in which patients did discontinue medication abruptly (i.e., < 1 week) were not different from rates in studies in which patients gradually discontinued their antidepressant (i.e., ≥ 1 week), but that instead mode of discontinuation was relevant only for the particular subgroup of recurrent episode patients. This subgroup effect quite likely explains why Viguera et al.⁵⁴ found that relapse rates off medication did not differ significantly between studies involving rapid discontinuation and those in which tapering was more gradual for the total group of different types of antidepressants that they included, as the interaction with number of previous episodes was not investigated in that study. Differential distribution of recurrent episode patients may explain why Geddes and colleagues⁶ reported an excess of relapse immediately following discontinuation of the antidepressant in the first month of drug discontinuation. Thus, when the interaction with recurrent episode patients is modeled, there is clear evidence that acute withdrawal of medication might induce a relapse, a problem that has also been identified for lithium, for which acute withdrawal can lead to manic relapses,^{57–60} and antipsychotics, for which a higher risk of psychotic relapse was found within 6 months of discontinuation, particularly in hospitalized patients and patients in whom the antipsychotics were withdrawn abruptly.⁶¹

Other Factors

One of the possible mechanisms for the high relapse rates in the first 3 months of randomization may be associated with differences in the half-lives of the various antidepressant agents,^{62,63} assuming that the shorter the half-life of the antidepressant, the greater the risk of relapse. However, addressing this question with adequate precision was not possible, since the range of half-lives of the antidepressants used in the different studies is extremely heterogeneous and in addition imprecise, given a great level of interindividual variation, depending on whether the patient is a fast or a slow metabolizer and depending on gender- and age-specific aspects of the elimination of the antidepressant.

Consequences

Several guidelines on the treatment of patients with depressive disorder have addressed the issue of long-term treatment with antidepressants: continuation treatment during the first 6 months after achievement of remission

and maintenance treatment thereafter. We looked at the different guidelines and compared the recommendations with the findings of this study.

The recommendations in most guidelines^{64–67} stating that patients should be treated for at least 6 months after having achieved remission, and especially that patients with frequent/more previous episodes should receive maintenance treatment, cannot be supported on the basis of the current findings. More specifically, any recommendation about maintenance treatment is not evidence based, due to the fact that studies in which patients were randomized more than 6 months after having achieved remission are lacking. The ORs reported in this article indicate that gradual discontinuation leads to more relapse than abrupt discontinuation. However, it is not possible to differentiate to what extent the smaller OR for single episode studies (OR = 0.12) than for recurrent episode studies (OR = 0.36) can be explained by more relapse with placebo in single episode studies or by less relapse with antidepressant medication in single episode studies. Further investigation of the above mentioned possible pathways for smaller ORs is warranted before firm conclusions can be drawn. Furthermore, in the group of patients with recurrent depressive episodes, those with abrupt discontinuation of the antidepressant appeared to benefit less from the relapse-reducing effect of the antidepressant (OR = 0.32) than those with gradual discontinuation (OR = 0.11). The interpretation of this finding is that since the relapse rate during continuing treatment with an antidepressant should not be different in these studies, the ORs can arguably only be taken to indicate that gradual discontinuation leads to more relapse in placebo groups than abrupt discontinuation. This is a somewhat counterintuitive finding and suggests that findings resulting from models including interaction terms may be due to chance. Furthermore, gradual withdrawal can be recommended in order to prevent other withdrawal symptoms.^{68–70}

Another issue is how to perform continuation or maintenance treatment. Some studies detailing the management of a relapse or a recurrence point out that patients who did relapse in the continuation phase after initially having responded to an antidepressant can benefit from an increase in the dose of the same antidepressant or from an increase using an enteric-coated antidepressant initially dosed once a week to twice a week.^{71,53,63} In the case of a recurrence after the discontinuation of medication in the maintenance phase, patients can benefit from a reinstatement of the antidepressant. We did not address these aspects in our meta-analysis.

Limitations

The results of our study should be seen in the light of several methodological limitations.

Several reports did not specify certain relevant details, such as the specific antidepressant studied (some reports

just mentioned TCA), doses of the antidepressant, the illness history and more specifically the precise number of previous depressive episodes, the precise duration of treatment after achievement of remission and prior to randomization, and in some studies the mode of discontinuation of the antidepressant. Diagnostic criteria varied, and some studies included an unspecified number of patients with other disorders such as a depression in the course of bipolar II disorder, dysthymia, atypical depression/depression not otherwise specified, or a major depressive episode with a significant comorbid disorder. When relevant details could not be retrieved, the studies were excluded from the subanalyses.

Definitions of remission as well as of relapse/recurrence usually varied between the studies from formal definitions including clinical assessment with application of diagnostic criteria or the use of rating scales, to more global criteria such as worsening of depressive symptoms severe enough to warrant hospitalization or re-institution of antidepressant treatment. Therefore, it remained unclear in some studies to what degree patients actually had attained full remission prior to randomization and/or to what degree they indeed suffered from a relapse or recurrence of a formal major depressive episode.

The trials were also heterogeneous in terms of diagnostic criteria, dropout rates, the power at the start of the trial, drugs used, and outcome criteria (Table 1). Although the main meta-analytic result did not display significant heterogeneity, the *p* value was close to .05, suggesting underlying sources of variance. Some of these factors were most likely identified in the meta-regression, in particular the number of previous depressive episodes and the interaction of this variable with mode of discontinuation. Further exploration of other potential variables contributing to heterogeneity, such as age, gender, year of publication, or drug regimen, was not possible due to the limitations inherent to all meta-analyses performed without access to individual patient data, and potential differences between trials in the definition and validation of end points as well as the clinical characteristics of the randomized patients.

Most of the patients participating in the trials consisted of patients in secondary care settings with a more severe and often recurrent type of depressive disorder and thus a high risk of relapse. Patients with milder depressive disorders, such as patients treated in primary care, were underrepresented, so that we can make no inference about the generalizability of our results to this group of patients.

Whether the relapse rates can be explained by the degree of resistance in patients participating in the different studies remains unclear, since the degree of resistance to therapy, prior to participation, was not mentioned in the studies included.

Another limitation is that our results may be subject to publication bias as negative trials are more likely to re-

main unpublished.⁷² This is a general limitation of any conclusion based on perusal of the literature. Using a Begg's funnel plot, however, it was found that there was symmetry in the relationship between effect size and sample size (see Figure 1), with only a slight overrepresentation of small studies with a positive result.

Drug names: citalopram (Celexa and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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CHAPTER 4

Prodromal studies of psychosis

DSM-5 and the 'Psychosis Risk Syndrome': Babylonian Confusion

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The notion that the important paradigm shift in clinical psychiatry, associated with early intervention, should now become a diagnostic issue is misguided. The 'risk' in Psychosis Risk Syndrome will not make sense to treatment-seeking patients with distressing symptoms and real need for care, is based on the notion that labeling people with invalid diagnostic terms has more clinical relevance than simply addressing care needs, is contingent on elusive sampling strategies posing as precise diagnostic criteria, and is associated with a false-positive rate of at least 90% in the year after diagnosis. In the 21st century, opinion-based diagnostics continues to pose a threat to the process of diagnostic revision.

Keywords: Psychosis; Diagnosis; Risk; Schizophrenia; DSM-5

Introduction

DSM-5, for the first time in the history of psychiatry, is considering the inclusion of a Psychosis Risk Syndrome as a category (www.dsm5.org). The good thing is that the proposal stems from increased efforts to intervene early in psychotic disorder. Early intervention improves subsequent course and outcome given that psychotic disorders, arising during adolescence and early adulthood, disrupt important maturational tasks and increase the risk of long term exclusion from meaningful societal participation. The international efforts that have been developed towards intervening earlier during the initial manifestations of psychotic illness have had a major impact, and are an example of how outstanding early pioneering work can grow into a true paradigm shift in clinical psychiatry (Cannon et al., 2008; McGlashan et al., 2006; McGorry et al., 2002). This exceptional work serves as an example to us all.

There is also a downside however. The same enthusiasm that created the paradigm of early intervention is now used to turn early intervention into a diagnostic issue, based on flawed reasoning. The word "risk" is now being used in the Psychosis Risk Syndrome proposal conceptually has nothing to do with risk, and more to do with labeling and elusive sampling strategies. Furthermore, no additional diagnostic category is required: DSM already has a category where early psychotic states can be classified. Below, these issues will be discussed in more detail.

If one already is help-seeking and in need of care, how can one still be at risk of something?

The proposed criteria for the Psychosis Risk Syndrome stipulate that "*symptoms are sufficiently distressing and/or disabling to the patient and/or others to lead to help-seeking*". This raises several interesting issues. The first issue is to do with the concept of risk. If individuals already have reached services and are in need of care, how can it be that they are still at risk of something? Clearly these individuals are "cases in

need of care”, therefore they are no longer “at risk” because they already have reached a clinical outcome. In DSM terms, they fulfil criteria for *Psychotic Disorder, Not Otherwise Specified* (NOS). In fact, the NOS category is ideal as it is commonly used to describe psychotic states early on in the diagnostic process, when it is not clear how best to classify symptoms. As a patient’s condition becomes better understood with the passage of time, the “NOS” can often be replaced by a more precise category. It is highly confusing for a patient with specific psychotic symptoms, which do not appear “attenuated” to him, and for which he is seeking treatment, to hear that his diagnosis is that he is *at risk* of something: the patient does not feel *at risk*, he feels in need of treatment for real problems.

The argument of the Psychosis Risk Syndrome advocates is that the “thing” these individuals are at risk for is a diagnostic label such as *schizophrenia*: they may be in need of treatment, but they do not meet criteria for schizophrenia. For example, in the North American Multicentre study, 56% of treatment-seeking high risk individuals “converted” to schizophrenia (Cannon et al., 2008; Woods et al., 2009). It could be argued, however, that a (ICD, RDC, DSM) diagnosis of schizophrenia represents an odd outcome for risk defined as a state of symptomatic treatment-seeking. Psychotic disorders, spread over a myriad of diagnostic categories in the different classification systems, in reality represent highly variable syndromal clusters of continuous psychotic and affective symptom dimensions, in combination with variable degrees of motivational and neurocognitive impairments (van Os & Kapur, 2009). The notion that a person may be *at risk* for a specific diagnostic category such as schizophrenia only makes sense if (ICD, DSM, RDC) diagnoses like “schizophrenia” represent valid nosological entities, i.e. “exist”. As the scientific evidence for the hypothesis of valid nosological entities is very weak (van Os & Kapur, 2009), it is difficult to see how any person may be helped by being called “at risk” of meeting criteria for labels that do not represent disease entities. The obsession with arbitrary diagnostic labels in psychiatry apparently has taken on such proportions that a patient with real symptoms and real need for care now must remain in the category “at risk” as long as he does not meet criteria for a non-existent and non-relevant diagnostic label.

How “risky” is the risk, and how replicable is it?

The reason the criterion of distress and treatment seeking was included in the Psychosis Risk Syndrome is because of a very interesting, and hitherto unresolved issue. Attenuated psychotic symptoms are weak predictors of transition to psychotic disorder in unselected general population samples, but become strong predictors of psychotic disorder in selected samples of help-seeking individuals in the ultra-high risk literature. For example, Hanssen and colleagues studied the outcome of psychotic experiences with onset in the past year, which conform to the criterion of the Psychosis Risk Syndrome (symptoms must have begun in or significantly worsened in the past year) (Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005). A two-year follow-up of 79 of these individuals revealed that 6 converted to clinical psychotic disorder. The one-year incidence rate therefore is 3.8% (6/158 person-years). A yearly risk of 3.8% is not negligible, but cannot be considered very useful for the purpose of prediction, particularly as longer term follow-up studies of up to 25 years have shown that risk of conversion is spread evenly over the follow-up period (Werbeloff et al., 2009). The ultra-high risk literature, however, displays a different trend. For example, in the

Multisite North-American study (Cannon et al., 2008), 82 out of 291 patients converted over a period of 2.5 years, resulting in an incidence rate of 11.3%, around three times higher than the Hanssen study. How to explain these differences? Clearly, the difference must reside in the way the samples were collected and "enriched" with risk. Hanssen and colleagues conducted a follow-up of a representative general population sample, whereas ultra-high risk samples invariably are opportunistic, each study using a different, unique strategy that cannot be replicated. For example, the sampling strategy of the ultra-high risk North-American study was described as: "*Each site recruited potential subjects through clinical referrals as stimulated by talks to school counselors and mental health professionals in community settings*".

Therefore, two questions arise. First, is a yearly risk of around 10% something that needs to be diagnosed as a "risk syndrome"? For example, the yearly risk for any person in the general population to develop any kind of psychiatric disorder is around 5–10%, depending on how inclusive the list of disorders is. Clearly, we are all at risk at any moment during our lives. Is it necessary to specifically label individuals with a 10% risk, even if it concerns a severe disorder? Have we become so health conscious that we take it for granted that 90% of those diagnosed with the Psychosis Risk Syndrome in fact are not at risk in the year after the diagnosis?

The second question is also important: How is it possible to introduce a new diagnostic category that essentially is the product of a non-replicable elusive sampling strategy occasioning a 300% enrichment in risk, compared to representative general population samples? Surely the diagnostic criteria should also stipulate how clinicians should go about collecting a sample with attenuated psychotic symptoms in such a way that the result is an enriched group yielding 10% conversion per year, instead of the much lower rate that they can expect from individuals with attenuated symptoms in the general population? In other words, the "risk" in the Psychosis Risk Syndrome is contingent on a sampling enrichment strategy that remains indefinable. However, the criteria of the Psychosis Risk Syndrome misleadingly make no mention of this.

Conclusion

In conclusion, the appearance of Psychosis Risk Syndrome in the draft of DSM-5 exemplifies how diagnostic revisions in psychiatry remain at risk of opinion-based rather than evidence-based changes.

Acknowledgements

Nil Kaymaz was supported by the Netherlands Organisation for Scientific Research (NWO), project number: 017.002.048. Jim van Os is member of the APA DSM-V Psychotic Disorders Work Group. The views expressed are his own.

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The case of the missing evidence: Do psychotic experiences predict clinical outcomes in unselected population-based samples? A systematic review and meta-analysis, enriched with new results.

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Abstract

Objectives: The reported 10%-20% yearly conversion rate from psychotic experience to clinical psychotic outcome forms the major rationale for the practice of intervention in individuals at ultra high-risk, and the proposed DSM-5 Psychosis Risk Syndrome. However, the base rate of transition from subthreshold psychotic experience (the exposure) to clinical psychotic disorder (the outcome) in unselected representative population-based samples is unknown.

Methods: A systematic review and meta-analysis was conducted of representative, longitudinal population-based cohorts with baseline assessment of subclinical psychotic experiences and follow-up assessment of psychotic and non-psychotic clinical outcomes.

Results: Six cohorts were identified with 3-24 year follow-up of baseline psychotic experiences. The yearly risk of conversion to a clinical psychotic outcome in exposed individuals (0.56%) was 3.5 times higher than for individuals without psychotic experiences (0.16%). Conversion risk increased with the number, certainty, frequency, persistence and degree of affective dysregulation of psychotic experiences. There was also evidence of specificity, as psychotic experiences only weakly predicted non-psychotic clinical outcomes.

Conclusions: Subclinical psychotic experiences index psychometric risk for psychotic disorder. However, the discrepancy between the 10% conversion rate in the high-risk literature and the 0.56% conversion base rate in unselected population-based samples points to the crucial influence of sample enrichment strategies through community awareness campaigns and other selective alterations of the permeability of filters on the pathway to mental health care that lie at the heart of all ultra high-risk studies. Sample enrichment strategies, rather than clinical high-risk criteria *per se*, may be the critical factor determining the success of high-risk early intervention initiatives.

Key words: Psychotic Disorders, Risk, Meta-analysis, Prevention, Delusions, Hallucinations

Introduction

Psychotic disorders typically affect young people, disrupting critical maturational tasks. This fact, together with the observation that longer duration of untreated psychosis predicts poorer outcome, provides a powerful rationale for intervening as early as possible¹⁻³. Given the fact that psychotic disorders are usually preceded by sometimes lengthy prodromes, attempts have been made to intervene when individuals are in the early throws of a psychosis prodrome or 'at risk mental state'^{4, 5}. However, early intervention based on risk can only be considered productive if samples are sufficiently enriched with cases that will actually make the conversion to a clinical psychotic disorder in a reasonably short period of time^{6, 7}. For example, if the risk of conversion in an 'at-risk mental state' sample is 5% over the course of a year (i.e. at least 100 times higher than the incidence of psychotic disorder in the general population), 95% of the sample would be treated unnecessarily if the sample underwent preventive pharmacological or psychotherapeutic treatment. Even if the treatment would be 50% effective in preventing conversion to a psychotic disorder (i.e. half of the 5% would be prevented from making a conversion), the number needed to inconvenience to prevent one case of conversion would be 40 (calculated as: $100/2.5$), arguably too high for cost-effective use of sparse resources.

In order to shift the above mathematical considerations to more favourable values, a considerable amount of literature now exists on attempts to enrich samples in such a way that the risk of conversion is high enough for effective intervention⁸. Sample enrichment strategies may include advertising, increasing awareness in the community and targeting teachers and primary care physicians. Sample enrichment strategies are not usually described in detail so that standardized approaches have not been developed. For example, the sample enrichment strategy of the multisite North-American study on prediction of psychosis was described as: *"Each site recruited potential subjects through clinical referrals as stimulated by talks to school counselors and mental health professionals in community settings"*⁹, whereas in the European Prediction of Psychosis Study¹⁰ it was described as: *"Knowledge about early warning signs (eg, concentration and attention disturbances, unexplained functional decline) and inclusion criteria was disseminated (through local workshops, articles in professional journals and newsletters, informational flyers, and Web sites) to mental health professionals as well as institutions and persons who might be contacted by at-risk persons seeking help"*. Using these unspecified enrichment strategies, and combining them with criteria on presence of "attenuated" or "transitory" psychotic experiences, family history and decline in functioning¹¹ initially appeared to yield samples with high conversion rates of up to 54% over 12 months⁸. However, more recent and more systematically conducted studies in North America and Europe concur in finding 12-month cumulative conversion rates of 11.3% (82 out of 291 patients over a period of 2.5 years);⁹ and 10.1% (37 out of 245 subjects over 18 months);¹⁰ respectively.

A major and hitherto unresolved issue regarding the interpretation of these studies is that the base risk of conversion given expression of subclinical psychotic experiences in the general population is not known. Therefore, to date it remains unknown to what degree the 10% conversion rate in enriched samples is due to (i) non-standardized and therefore non-replicable sample enrichment strategies including awareness and education campaigns, (ii) specific criteria involving family history or decline in functioning and (iii) presence of subclini-

cal psychotic experiences^{6, 12}. In addition, research suggests that the risk for non-psychotic outcomes may also be increased, but non-psychotic disorders as an outcome of subclinical psychotic experiences are rarely reported⁶.

In order to address this issue, we reviewed the literature on the risk of developing psychotic disorder given earlier expression of subclinical psychotic experiences in representative, general population samples. To this end, the method of systematic review and meta-analysis was used, as these generally provide a transparent and quantitative approach to identify, summarise and critically appraise relevant studies, enabling an integrated presentation of results. Furthermore, systematic review and meta-analysis can address meta-hypotheses over and above primary studies by quantitative exploration of the patterns of results from single investigations. Specific aims of this meta-analysis were: (i) to examine the risk of conversion to psychotic disorder given presence of subclinical psychotic experiences in representative general population samples, (ii) to examine the risk of conversion to non-psychotic disorder given presence of subclinical psychotic experiences in representative general population samples, (iii) to examine which symptom factors moderate risk of conversion. In order to achieve these goals, methodology for systematic review as laid down in Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines¹³ was applied. For some studies, additional analyses were conducted in the original data in order to be able to also report non-psychotic outcomes that had not been included in the original publications.

Methods

A computerized search strategy was developed to sensitively query the MEDLINE, PsycINFO and EMBASE databases to identify potentially relevant articles in English, Spanish, German, French or Dutch, published from 1951 to April 2010. A sensitive search string was composed with medical subject headings, specific for each database, for concepts relating to “subclinical psychotic experience”, “psychotic disorder” and “conversion/transition”. Reference lists of articles thus identified were screened in order to encounter additional articles. In addition, a process of forward and backward citation tracking was executed using the Web of Science database. Finally, researchers with expertise in the field were contacted in order to identify additional data potentially relevant for the meta-analysis. Thus, original individual participant data from two cohort studies, the NEMESIS study^{14, 15} and the EDSP study^{16, 17}, were subjected to additional analyses in order to add information on non-psychotic outcomes, not published before, to the meta-analysis database.

In order to reduce methodological variations of studies to be entered in the meta-analysis, a priori criteria for inclusion were formulated. Thus, data of published studies were added to the meta-analysis database if they (i) were published in a peer-reviewed journal after 1950; (ii) were written using the English, Spanish, French, German or Dutch language; (iii) represented a population-based follow-up study of individuals with and without a defined measure of subclinical psychotic experiences at baseline (the *exposure*) and (iv) provided cumulative incidence rates (or data allowing computation of these) of defined psychotic disorder outcomes (the *outcome*).

Two investigators independently screened citations and selected publications for further consideration on the basis of consensus, using three consecutive filters. The first selection

filter was at the level of citations, applying the broad criterion of relevance for the topic of the meta-analysis. The second selection filter was applied at the level of abstracts, excluding studies that did not meet a single inclusion criterion as defined above. The final filter was based on inspection of full-text articles. In the case of multiple reports involving a single study population, the publication with the largest sample size and/or the longest follow-up was selected.

In the next step, two investigators independently extracted quantitative and qualitative data from each selected publication. Qualitative data included factors impacting on internal validity such as methodological and design features as well as the potential for confounding as well as bias due to differential attrition or possible differential assessment of exposure and/or outcome. Quantitative data included cumulative conversion rates as a function of baseline exposure status (i.e. with and without subclinical psychotic experiences). Data pertaining to studies using continuous exposure measures were extracted and analysed according to the original continuous exposure format, and additionally analysed as a dichotomous exposure in order to facilitate comparison of results across studies. Dichotomisation was carried out by contrasting, in the case of three-level exposure variables (e.g. no symptoms, weak symptom, strong symptom), the highest category versus the lowest two. In the case of four-level exposures, the highest category was similarly compared to lowest three. In case data could not be extracted in a format suitable for meta-analysis, authors were contacted for re-analysis of the original data in the required format.

Table 1A was compiled to provide a descriptive summary of selected studies, showing, for both psychotic and non-psychotic outcomes, the principal study characteristics including populations, observation periods, exposure and outcome definitions, main results and sample and study design features. Tables 1B and 1C show the quantitative data extracted from each study for psychotic and non-psychotic outcomes, respectively.

Approach to meta-analysis

Data from the selected studies were combined to estimate pooled rates with their corresponding 95% Confidence Intervals (CIs) under a random effects model, assuming that true effects were randomly distributed around the mean effect size. The random effect model presumes that variation in samples and design factors will occasion different true effect sizes across studies and represented a valid *a priori* choice given the fact that methods and populations across studies did not correspond to a degree that they could be regarded as estimating the same underlying effect. The between-study variance in the random effects model reflects heterogeneity across studies, the magnitude of which was evaluated using a chi-square test for heterogeneity, testing whether individual studies varied more than could be explained by chance alone. In the phase of reading and comparing the articles, various hypotheses for heterogeneity were identified. In case significant heterogeneity was encountered, possible causes were explored by analysing subgroups as well as by including variables occasioning heterogeneity (modifiers) in meta-regression analyses.

Additional analyses undertaken in original datasets

For the specific purpose of the meta-analysis, exposure and outcome data as reported in the NEMESIS study by Hanssen and colleagues¹⁸ and the EDSP study by Dominguez and colleagues¹⁹ were subjected to additional analyses. Both the NEMESIS and EDSP studies followed general population cohorts, interviewing the entire cohort with the CIDI on three occasions (EDSP: T0, T2 and T3; NEMESIS: T0, T1 and T2) over time^{14, 15, 16, 17}. In the NEMESIS study, fresh analyses were conducted to provide additional risk estimates for prevalent exposure (defined as lifetime report of subclinical psychotic experiences at T0, as described in²⁰) in addition to the incident exposure reported in the original paper¹⁸. In both the NEMESIS and the EDSP data sets, additional analyses were conducted with the following non-psychotic outcomes: T2 (NEMESIS) or T3 (EDSP) CIDI diagnosis of bipolar disorder, excluding individuals with a similar diagnosis at T0/T1 (Nemesis) or T0/T2 (EDSP)²¹⁻²⁴; T2 (NEMESIS) or T3 (EDSP) CIDI diagnosis of depressive disorder, excluding individuals with a similar diagnosis at T0/T1 (NEMESIS) or T0/T2 (EDSP) and individuals with a T2 (NEMESIS) or T3 (EDSP) CIDI diagnosis of bipolar disorder²¹⁻²⁴; T2 (NEMESIS) or T3 (EDSP) CIDI diagnosis of anxiety disorder, excluding individuals with a similar diagnosis at T0/T1 (NEMESIS) or T0/T2 (EDSP) as well as individuals with a T2 (NEMESIS) or T3 (EDSP) CIDI diagnosis of depressive disorder or bipolar disorder^{14, 15, 25}. All extra analyses were conducted in strict accordance with the methodology described in the original studies and therefore are not reported in detail again here (details available upon request).

Statistical analysis

All analyses were performed using Stata 11²⁶. A data file including data pertaining to both psychotic and non-psychotic outcomes was constructed. One study reported 5 different psychotic outcomes²⁷ – these were combined into a single psychotic outcome.

First, dichotomised exposures were analysed. For these analyses, each record in the data included sample size, number of subjects with a negative outcome, years of study follow up and information on modifiers. Using the first three variables, rates per 100,000 person years were calculated. For each study, at least two records were filled (exposed, non-exposed). More records were used when rates were stratified by possible outcome modifiers (psychotic/non-psychotic disorder, hospital admission yes/no, incident/prevalent exposure, see below). Bar charts were generated to present the rates per study for psychotic as well as non-psychotic outcomes^{28, 29}.

A meta-analysis stratified by exposure and by type of outcome (psychotic/non-psychotic) generated forest-plots (Stata METAN command). Subsequently, the rates were analysed using meta-regression analysis (Stata METAREG command). As rates are not normally distributed, and because the number of studies was small and heterogeneity was expected, meta-regression was repeated using 1000 permutations (Stata METAREG command with option PERMUTE). In addition, meta-regression analyses were repeated for more homogeneous subsets of studies (as described below).

Second, in order to study dose-response effects, exposures were analysed as three-level variables including 3 categories of graded severity/frequency where available; if there were 4 categories, the two lowest categories were combined to create a similar three-level exposure

variable. For this analysis, rates were also presented in a figure and meta-regression analysis was performed.

Results

Search results

The search yielded 7 articles with data that were pertinent to the meta-analysis as specified in the criteria above. One study³⁰ was excluded as it concerned a subgroup of persons included in the study by Chapman and colleagues²⁷, already included in the meta-analysis.

The characteristics of the 6 studies, included in the meta-analysis, are listed in table 1A. All studies had general population sampling frames (two birth cohorts^{31, 32}, three representative general population cohorts^{18, 19, 33}) although in one study the selection was limited to undergraduate students²⁷; follow up varied from 3 years to 24 years. All studies reported on variably defined psychotic experiences in the general population and the rate of transition to variably defined psychotic and non-psychotic clinical outcomes. One study used high level of schizotypy as predictor²⁷, all other studies used CIDI or related measures of psychotic experiences. Non-psychotic outcomes were depression, mania, anxiety disorder and admission to hospital for non-psychotic disorder. Some studies described various exposure subgroups, varying from classification on the basis of number of symptoms (no symptom, single symptom, multiple symptoms); frequency/certainty of psychotic symptom (no symptom, “weak” symptom and “strong” symptom); psychopathological context (no symptom, symptom without depression, symptom with depression); degree of persistence over 5 years (present at none, one, two or three assessments over 5 years). Some studies also described rates as a function of combinations of subgroups (e.g. multiple symptoms with and without comorbid depression¹⁸). All 6 studies reported on psychotic clinical outcomes, and 5 studies additionally reported on other, non-psychotic, clinical outcomes. For one study¹⁸, measures of both incident (psychotic experiences with first onset in the previous year) and prevalent (lifetime presence of psychotic experiences) exposure were available. One study³³ reported service-based clinical outcomes, defined as admission to hospital.

Tabel 1A Qualitative description of longitudinal studies in representative samples studying predictive value of subclinical psychotic experiences (exposure) for transition to clinical psychotic and non psychotic disorders (outcome)

Study ID	Study type and goals	Sample size (N)	Mean age baseline and follow up (Years)	Baseline PSYCHOTIC predictor (exposure)	Follow-up clinical psychotic outcome	Follow-up clinical non-psychotic outcome	Assessment type/ Instruments: Baseline Exposure follow-up Outcome
Chapman et al., 1994	10-year follow-up of undergraduate students with low and high scores on four schizotypy scales	Of 7800 students, 534 subjects were selected for 10-year follow-up; n=508 (95%; 355 exposed, 153 non-exposed) had outcome assessment	20-30 years	Scoring ≥ 1.96 SD on any of the four scales (exposed, n=375) and < 0.5 SD above the mean on each scale (159; non-exposed).	DSM-III-R diagnosis: 1) Schizophrenia 2) Psychosis Not Otherwise Specified 3) Delusional disorder 4) Psychotic bipolar disorder 5) Psychotic depression	DSM-III-R: diagnosis: 1) Mania/ Bipolar disorder 2) Depression 3) Hypomania	BASELINE: Self-reported psychosis proneness scales: a) Physical Anhedonia b) Perceptual Alteration c) Magical Ideation d) Impulsive Nonconformity FOLLOW-UP: Clinical interview face to face using the SADS-L and Personality Disorder Exam (PDE)
Poulton et al., 2000	Birth cohort assessed at age 11 years for presence of delusions and hallucinations and at age 26 years for presence of psychiatric disorder	Baseline n=1019 FU n=972 (95%) Risk set: n= 761	11-26 years	Self-reported psychotic DISC-C symptom: 1) No-symptom 2) Weak symptom (score 1= likely) 3) Strong symptom (score 2= definitely)	DSM-IV Schizophreni-form disorder	DSM-III diagnosis: 1) Mania 2) Depression 3) Anxiety disorder	BASELINE: Self-reported using DISC-C (administered by child psychiatrist) FOLLOW-UP: Clinical interview by health worker using DIS,
Hanssen et al., 2005	3-year longitudinal general population cohort study (NEMESIS) assessing psychotic symptoms and psychiatric disorders at three time points (baseline, year 1 and year3)	T0 ¹ : 7076 T1: 5618 (79 %) T2: 4848 (68 %) Risk set for analysis: 4042	41-43 years	1. T1 Incident CIDI self-reported CIDI psychotic symptom, plus: a) single vs. multiple b) with vs. without depression 2) TO Lifetime CIDI self-reported psychotic symptom, plus: a) single vs. multiple c) with vs. without depression	T2 diagnosis of Clinical Psychotic Disorder based on BPRS severity of psychosis and CAN need for care.	(see below)	BASELINE CIDI interview at all three measurement points by trained interviewers plus clinical re-interview of individuals scoring positive FOLLOW-UP CIDI interviews by trained interviewers and telephone clinical re-interview by clinician for persons scoring positive on CIDI psychosis items; BPRS and need for care scored by clinician

Welham et al., 2008	Birth cohort: (1981-1983) assessed after 5 and 14 years for psychotic symptoms and after 21 years for screen-positive non-affective psychotic disorder (SP-NAP)	Birth: n=7223; age 14 years: n=5172(72%); age 21 years: n=3801(53 %), Risk set: 3573	14-21 years	Self-reported Youth Self Report item age 14: "I hear sounds or voices that other people think aren't there" – rarely/never vs. sometimes/often	Caseness: CIDI DSM-IV non-affective psychotic disorder or past medical diagnosis of schizophrenia	---	<u>BASELINE</u> Youth Self Report hallucination item <u>FOLLOW-UP</u> CIDI + self-reported past diagnosis of schizophrenia
Dominguez et al., 2009	10-year longitudinal general population cohort study, assessing mental health four times over a period of 10 years. Clinical outcomes were assessed over a 5-year period (from T2 to T3)	Analyses restricted to youngest group aged 14-17 at baseline (T0: n= 1395, T1: n= 1228, T2: n=1169, T3: n= 1022 (73%)). Risk set for analysis: n=845	14-24 years	Degree of persistence over the 5 years from T0-T2 of self-reported SCL90-R psychotic/paranoid symptoms in the highest 10% of scores: once, twice or thrice.	T3 Diagnosis of clinical psychotic disorder based on (i) help-seeking, (ii) service use and (iii) impairment	(see below)	<u>BASELINE</u> : Self report questionnaires (SCL90-R) at T0, T1 and T2 <u>FOLLOW-UP</u> : DIA-X/M-CIDI administered as clinical interview by clinical psychologists
Werbeloff et al., 2009	24-year follow-up through national case register of general population cohort assessed for presence of psychotic symptoms at baseline	4914 community subjects (subjects with psychotic disorder were screened and excluded) Risk set for analysis: 4726	29-52	Self reported psychotic experiences: 0=no symptom 1= weak symptom (rarely / sometimes) 2=strong symptom (often / very often)	ICD 10 register Non-affective psychotic disorder	ICD 10 register diagnosis: Non-psychotic disorder	<u>BASELINE</u> : Clinical interview (mental health worker) using the PERI (Hebrew version); a subsample was interviewed by a psychiatrist using the SADS <u>FOLLOW-UP</u> : National case-register clinical hospital diagnosis NEMESIS: see Hansen et al. (2005)
Current report	Additional data analysis of A) Hansen et al (2005) NEMESIS study B) Dominguez et al (2009) EDSP study:	NEMESIS : see Hansen et al (2005) B) EDSP: risk set differs from Dominguez et al (2009) as not restricted to youngest cohort; risk sets were n=1876, n=1608 and n=1221 for bipolar disorder, depression and anxiety, respectively	NEMESIS: see Hansen et al (2005) B) EDSP: see Dominguez et al (2009)	NEMESIS: see Hansen et al (2005) B) EDSP: differs from Dominguez et al (2009): exposure was presence of any T2 CIDI psychotic symptom	---	DSM-III-R/IV: NEMESIS: T2 1) Bipolar d.o. 2) Depression 3) Anxiety d.o. EDSP: T3 1) Bipolar d.o. 2) Depression 3) Anxiety disorder	NEMESIS: see Hansen et al. (2005) EDSP: see Dominguez et al. (2009)

^a = T0 baseline; T1 first follow-up, T2 second follow-up, T3 third follow-up; SADS: Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L) (Endicott & Spitzer, 1978)DISC: Diagnostic Interview Schedule for Children (Costello, Edelbrock, Kalas, Kessler & Klaric, 1982; NIMH DIS for Children: Child Version); DIS: Diagnostic Interview Schedule for DSM-IV (Robins, Cottler, Bucholz & Compton, 1995); CIDI: Composite International Diagnostic Interview (WHO, 1992); YSR: Youth Self Report questionnaire (Achenbach T, 1991); SCL-90-R: Self Report Symptom Checklist-90-R (Derogatis & Cleary, 1997); DIA-X/M-CIDI: updated version of the World Health Organization's CIDI version (Wittchen & Pfister, 1997; DIA-X Versions of the WHO CIDI); PERI: Psychiatric Epidemiology and Research Interview (Shrout, Dohrenwend & Levav, 1986 Hebrew version: Roberts & Vernon, 1981); BPRS: Brief Psychiatric Rating Scale (Overall & Gorham, 1962); CAN: Camberwell Assessment of Need (Slade, Phelan, Thornicroft & Parkman, 1996)

Description of the possible modifiers as causes of heterogeneity of the studies

Four studies^{18, 19, 31, 32} used similar methodology for exposure and outcome assessment based on the Composite International Diagnostic Interview³⁴ whereas other studies^{27, 33} used different instruments. Similarly, all studies reported exposure assessment based on prevalence estimates whereas one study also reported assessment of incident exposure¹⁸. Another important factor was that one study provided outcomes based on hospital admission³³, whereas all other studies were independent of health care use. Thus, three modifiers were included in meta-regression analyses (psychotic/non-psychotic disorder, hospital admission yes/no and incident/prevalent exposure); in addition sensitivity analyses excluded results that were outliers with respect to outcome assessment (hospital admission in the study by Werbeloff and colleagues³³).

Results for dichotomous exposure meta-analysis

Original study results

Findings from individual studies are summarised in tables 1B (psychotic outcomes) and 1C (non-psychotic outcomes).

Table 1B Longitudinal studies in representative samples studying predictive value of subclinical psychotic experiences (exposure) for transition to psychotic disorders (outcome): qualitative data

Study	Type outcome	Type exposure	N exposed	Riska exposed	N non-exposed	Riska non-exposed (n, %)	Reported relative risk
Chapman et al., 1994	Schizophrenia Psychosis NOS Delusional disorder Psychotic BPD Psychotic MDD	High schizotypy	355	4 (1.1%)	153	1 (0.3%)	
			355	3 (0.9%)	153	0 (0%)	
			355	1 (0.3%)	153	0 (0%)	
			355	3 (0.9%)	153	0 (0%)	
			355	1 (0.3%)	153	1 (0.3%)	
Poulton et al., 2000b	Schizophreniform disorder	No symptoms	---	---	654	13 (2%)	1c
		Weak symptoms	95	9 (9.5%)	---	---	5.1 (1.7, 18.3)
		Strong symptoms	12	3 (25%)	---	---	16.4 (3.9, 67.8)
Hanssen et al., 2005	Clinical psychotic disorder	T1 No incident PE	---	---	3964	5 (0.1%)	1c
		T1 Incident PE	79	6 (7.6%)	---	---	65.1 (19.4, 218.1)
		T1 Incident single PE	60	2 (3.3%)	---	---	27.3 (5.2, 143.6)
		T1 Incident multiple PE	19	4 (21.1%)	---	---	211.2 (51.6, 864.1)
		T1 Incident PE with depression	34	5 (14.7%)	---	---	136.5 (37.4, 497.1)
		T1 Incident PE without depression	45	1 (2.2%)	---	---	18.0 (2.1, 157.2)
		T1 Incident multiple PE with depression	10	4 (40.0%)	---	---	527.9 (113.2, 2460.9)
		T0 No prevalent PE	---	---	4045	7 (0.2%)	1c
		T0 Prevalent PE	746	26 (3.5%)	---	---	20.8 (9.0, 48.1)
		T0 prevalent single PE	447	2 (0.5%)	---	---	2.6 (0.5, 12.5)
		T0 prevalent multiple PE	299	24 (8.0%)	---	---	50.3 (21.5, 117.9)
		T0 prevalent PE with depression	463	22 (4.8%)	---	---	28.8 (12.2, 67.8)
		T0 prevalent PE without depression	283	4 (1.4%)	---	---	8.3 (2.4, 28.4)
Welham et al., 2008	SP-NAP	T0 prevalent multiple with depression PE	213	21 (9.9%)	---	---	63.1 (26.5, 150.2)
		Self-reported auditory hallucinations	451	18 (4.0%)	3112	38 (1.2%)	
		Level 0	---	---	666	23 (3.7%)	1.0c
		Level 1	132	6 (5.3%)	---	---	1.5 (0.6 – 3.7)
		Level 2	33	4 (16.0%)	---	---	5.0 (1.6-15.9)
Werbeloff et al., 2010d	Hospitalization for non affective psychosis	Level 3	14	3 (27.3%)	---	---	9.9 (2.5-39.8)
		No symptoms	---	---	1306	2 (0.1%)	1c
		Weak symptoms	2614	13 (0.5%)	---	---	3.6 (0.8, 16.7)
		Strong symptoms	652	8 (1.3%)	---	---	9.5 (1.9, 47.2)

a=transition rate in the group with psychotic experiences; b= The ORs remained virtually unchanged after controlling for sex, social class origins and age 11 IQ scores.c= Reference category, OR= Odds Ratios; d=weighted results; e= mostly adjusted ORs from published studies, some ORs for NEMESIS and EDSP studies were calculated on the basis of new analyses for the current paper; NEMESIS study: Netherlands Mental Health Survey and Incidence Study, a longitudinal general population study. EDSP study = Early Developmental Stages of Psychopathology Study; SPE = Subclinical Psychotic Episode; Type instruments: SADS: Schedule for Affective Disorders and Schizophrenia-Lifetime version (SADS-L); DISC: Diagnostic Interview Schedule for Children. DIS: Diagnostic Interview Schedule for DSM-IV; CIDI: Composite International Diagnostic Interview; CBCL: Childhood Behavior Checklist; YSR: Youth Self Report questionnaire; SCL-90-R: Self Report Symptom Checklist-90-R; BIA-X/M-CIDI: updated version of the World Health Organization's CIDI version. PERI: Psychiatric Epidemiology and Research Interview; Outcome: SCZ = Schizophrenia, SCF = Schizophreniform disorder, DD = Delusional Disorder, Brief PD = Brief Psychotic Disorder, Psychosis NOS = Psychosis not otherwise specified, Psychotic BPD = Psychotic Bipolar Disorder, Psychotic MDD = Psychotic Major Depressive Disorder.

Table 1C Longitudinal studies in representative samples studying predictive value of subclinical psychotic experiences (exposure) for transition to non-psychotic disorders (outcome): quantitative data

Study	Type outcome	Type exposure	N exposed	Risk exposed ^a (n, %)	N non-exposed	Risk non-exposed (n, %)	Reported relative risk ^c
Chapman et al., 1994	Major depression	High schizotypy	355	103 (29%)	153	31 (20.3%)	---
	Mania		355	7 (2.0%)	153	0 (0%)	---
	Hypomania		355	15 (4.2%)	153	2 (1.3%)	---
Poulton et al., 2000	Major depression		---	---	654	99 (15.2%)	---
			95	19 (20.0%)	---	---	---
			12	1 (8.3%)	---	---	---
	Mania	No symptoms (n=654)	---	---	654	13 (2.0%)	---
		Weak symptoms (n=95)	95	1 (1.1%)	---	---	---
		Strong symptoms (n=12)	12	0 (0.0%)	---	---	---
	Anxiety disorder		---	---	654	144 (22.0%)	---
95			32 (33.7%)	---	---	---	
12			4 (33.3%)	---	---	---	
Werbeloff et al., 2010 ^d	Hospitalization for non psychotic disorder	No symptoms			1308	4 (0.3%)	1 ^b
	Weak symptoms		2616	16 (0.6%)	---	---	1.6 (0.5, 4.7)
	Strong symptoms		650	7 (1.0%)	---	---	2.1 (0.6, 7.5)
NEMESIS current analysis	Major depression	≥ 1 psychotic symptom lifetime	491	33 (6.7%)	3374	110 (3.3%)	2.1 (1.4-3.2)
	Mania		695	6 (0.9%)	3972	6 (0.2%)	5.8 (1.9-17.9)
	Anxiety disorder		417	14 (3.4%)	3169	58 (1.8%)	1.9 (1.03-3.4)
EDSP current analysis	Major depression	≥ 1 psychotic symptom lifetime	304	28 (9.2%)	1304	79 (6.0%)	1.6 (1.01-2.5)
	Mania		383	4 (1.0%)	1493	0 (0%)	∞
	Anxiety disorder		219	22 (10.1%)	1002	76 (7.6%)	1.4 (0.8-2.2)

^a = transition rate in the group with psychotic experiences^b = Reference category; ^c = mostly adjusted ORs from published studies, some ORs for NEMESIS and EDSP studies were calculated on the basis of new analyses for the current paper.

OR= Odds Ratios. NEMESIS study: Netherlands Mental Health Survey and Incidence Study, a longitudinal general population study. EDSP study = Early Developmental Stages of Psychopathology Study.

∞ OR infinite as no transition in non-exposed

weighted results

All studies showed that subclinical psychotic experiences strongly predicted clinical psychotic outcomes. The 3-24 year risk for the exposed was in the range of 5%-25%, substantially higher than the corresponding risk in the non-exposed (ranging from 0.1-3.7%), with 3-24 year odds ratios in excess of 10 for the strongest level of exposure (Table 1B). A degree of outcome specificity was clearly present, as ORs for non-psychotic outcomes were mostly in the order of 2 (Table 1C).

Meta-analysis

In order to facilitate comparison, rates for all studies were uniformly transformed to express incidence of psychotic and non-psychotic outcomes per 100,000 person-years (Fig. 1a and Fig. 1b). This confirmed the pattern of results in Tables 1B and 1C, in that the incidence of psychotic clinical outcome in the exposed was much higher than in the non-exposed, and that the difference in incidence between exposed and non-exposed was much greater for psychotic than for non-psychotic clinical outcome. In addition, the results showed that the absolute risk for clinical outcome in the only study based on hospital admission³³ was only a fraction of the risk in studies that did not depend on service use.

Figure 1 Rate per 100,000 person years of psychotic (a) and non-psychotic (b) outcomes in exposed and unexposed subjects (prevalent exposure only).

Meta-analysis results for psychotic (Fig. 2a) and non-psychotic (Fig. 2b) clinical outcomes (for the Hanssen study, based on NEMESIS data¹⁸, results with prevalence exposure were included), show that the combined yearly incidence rate of psychotic clinical outcome given the presence of a prevalent subclinical psychotic experience was 159 per 100,000 person-years (0.2% per year) in the non-exposed, and 558 per 100,000 person-years (0.6% per year) in the exposed. For the non-psychotic outcomes, yearly transition incidence rates for exposed and non-exposed were 1.8% and 2.6%, respectively. For non-psychotic outcomes, confidence intervals were wide and for both psychotic and non-psychotic outcomes, confidence intervals overlap (Fig. 2a and Fig. 2b), indicating that the difference in yearly incidence rate between exposed and non-exposed was non-significant for both psychotic and non-psychotic clinical outcome. Heterogeneity was large (psychotic outcome non-exposed: $\chi^2=81.6$, $df=5$, $p<0.001$; psychotic outcomes exposed: $\chi^2=54.1$, $df=5$, $p<0.001$; non psychotic outcomes non-exposed: $\chi^2 = 666.9$, $df=4$, $p<0.001$; non psychotic outcomes non-exposed: $\chi^2=235.4$, $df=4$, $p<0.001$).

Figure 2 Forest plot of rates per 100,000 person years in each study for the exposed and the non-exposed of psychotic (a) and non-psychotic (b) outcomes, prevalent exposure only.

(a)

(b)

Meta-regression, including the four studies that used similar CIDI-based methodology for exposure and outcome assessment^{18, 19, 31, 32} suggested that the effect of subclinical psychotic experiences on psychotic clinical outcome was significant (difference in incidence between exposed and non-exposed 648 per 100,000 person-years, $p=0.043$), whereas the effect for non-psychotic clinical outcome, although directionally similar, was not statistically significant (difference in incidence 694 per 100,000 years, $p=0.31$)(Table 2). Meta-regression using permutations showed similar or more conservative p-values (non-psychotic outcomes exposure $p=0.52$; psychotic outcomes exposure $p=0.11$; T-values were all in the same direction).

Table 2 Meta-regression results stratified by psychotic/non-psychotic outcome including the four studies that used similar methodology for exposure and outcome assessment based on the Composite International Diagnostic Interview^{18, 19, 31, 32}.

non-psychotic outcomes (6 records)			psychotic outcomes (8 records)		
regression coefficient	95% CI	p-value	regression coefficient	95% CI	p-value
Exposure* 694	-953; 2342	0.31	648	28; 1269	0.043

*Exposure was the measure of subclinical psychotic experiences used (see Table 1)

Modifier effects

Including all studies, all psychotic and non-psychotic outcomes and all identified modifiers in a meta-regression analysis (Table 3) revealed that (i) rates were significantly lower for psychotic outcomes, (ii) rates were significantly higher in the exposed group, (iii) incident expo-

sure was not a modifier and (iv) the one study analysing hospital admissions reported significantly lower rates.

Table 3 Meta-regression results, including all categories of all modifiers in one meta-regression model.

(24 records)	regression coefficient	95% CI	p-value
Exposure*	-1706	-2411; -1001	0.000
Psychotic	771	73; 1470	0.03
Hospital admission	-1590	-2440; -740	0.001
Incident exposure*	120	-1361; 1602	0.87

*Exposure was the measure of subclinical psychotic experiences used (see Table 1)

Results for dose-response meta-analysis

Original study results

Where examined, studies reported clear dose-response relationships for variably defined levels of exposure severity (certainty of symptom, frequency of symptom, number of symptoms, persistence over time, comorbid depression) in relation to risk of transition to psychotic clinical outcome (Tables 1A and 1B). Only weak evidence for dose-response was present for non-psychotic clinical outcome (Tables 1A and 1C).

Meta-analysis

Transformation of all studies to the same person-year denominator showed comparable dose-response effects for psychotic clinical outcome, also for the study reporting hospital-based outcomes³³ and incident exposure assessment¹⁸. Thus, bars in Fig. 3 show that rates increase when exposure severity increases. Meta-regression including the three studies with linear multiple categories of exposure^{19, 32 18} showed statistically a significant linear increase in yearly incidence per unit increase in exposure severity ($\beta=962$, $p=0.002$).

Discussion

Subjects with a history of subclinical psychotic experiences displayed higher yearly rates of psychotic clinical outcome which was largely specific as the evidence for an increase in non-psychotic clinical outcome was inconclusive. There was evidence for dose-response associated with number, certainty, frequency, persistence and level of affective comorbidity of psychotic experiences.

Subclinical psychotic experiences as psychometric expression of risk for psychotic disorder

In combination, these studies provide strong evidence for the validity of the notion that subclinical psychotic experiences represent psychometric risk for later psychotic clinical outcome. Although it could be argued that CIDI measures of clinical outcome yield high rates of false-positives, the predictive value of subclinical psychotic experiences was also apparent in

predicting the “hard” outcome of hospital admission. Additional validity is suggested by the presence of dose-response and specificity.

Comparison with ‘high risk’ in the ultra high-risk literature

As mentioned earlier, the two more recent systematic European and US studies on yearly rate of transition in help-seeking individuals with ‘high risk’ psychotic experiences is around 10%^{9, 10}. As for the great majority of individuals in these studies high risk criteria were fulfilled because of the presence of the same “attenuated” or “transitory” psychotic experiences as reviewed here, the discrepancy between the yearly risk of 0.6% in the population-based studies reviewed here and the 10% in the high-risk studies presented in the ultra high-risk literature requires an explanation. Even if we assume that the yearly risk of conversion in the representative population-based studies may be as high as 1%, allowing for the possible underestimation associated with non-linear transition patterns over time (see below), and focussing on the most severe level of psychotic experiences, the at least 10 times higher yearly conversion rate in help-seeking individuals presented in the ultra high-risk literature is remarkable. An important factor that at least in part explains the discrepancy is the unspecified sample enrichment strategies that have been employed in the ultra high-risk studies. These studies show that by conducting extensive community awareness campaigns, it is possible to select help-seeking individuals with psychometric risk in such a way that a 10% yearly conversion rate is brought about. The fact that many studies now have shown that this is possible represents an important milestone for early intervention, and may benefit many individuals at high risk for psychotic illness. The problem, however, is that the high yearly risk of conversion observed in the ultra high-risk literature is invariably attributed to variably defined high risk criteria, the main one being presence of “attenuated” or “transitory” psychotic experiences, whereas the current meta-analysis demonstrates that the contribution of psychotic experiences *per se* is quite low. Therefore, what can be deduced is that the critical factor feeding prediction of conversion is the use of hitherto largely unspecified sample enrichment strategies through community awareness campaigns and other means of selective alteration of the permeability of the filters on the pathway to mental health care. The current results suggest that these sample enrichment strategies, rather than clinical high risk criteria *per se*, are the critical factor allowing for the successful completion of the first stage of any high-risk early intervention initiative: to generate a sampling frame at high enough risk to consider the use of intervention in the first place. Therefore, there is an urgent need to clearly describe and operationalise these strategies.

The fact that psychotic experiences were relatively specific in predicting psychotic outcomes is disappointing from the point of view of intervention at the stage of risk, as the ‘yield’ of such interventions is logically much greater if risk is associated with a much broader outcome than clinical psychosis alone.

Relevance for the DSM-5 Risk Syndrome

For the reasons outlined above, the current results are relevant for the debate regarding the possible inclusion of a Psychosis Risk Syndrome (PRS) in DSM-5. If the risk function in PRS is occasioned not by psychometric criteria but instead is largely fed by unspecified sample en-

richment strategies that are not mentioned in the criteria, the inclusion of PRS in DSM-5 would be misleading and likely confuse its users¹². Therefore, if PRS is to be included in DSM-5, operationalised criteria for sample enrichment strategies need to be added. However, given the paucity of data on replicable strategies to occasion sample enrichment, this may be premature.

Methodological issues

In calculating yearly incidence rates, the assumption was that the rate of transition would be spread evenly over the follow-up periods. This may not be valid, as there is some evidence that transition rates may be higher in the first 5-10 years³³. Therefore, yearly incidence rates in two studies with longer follow-ups^{31, 32} may vary and be somewhat higher in the earlier phases of the follow-up. Similarly, rates may vary according to age and sex, factors that could not be taken into account. Nevertheless, most studies were carried out in young people in the similar age range as samples in ultra-high risk studies.

The study by Chapman and colleagues²⁷ was carried out in a sample of students; students are easy to recruit, but deviate from the general population as they are of younger age and higher educational level, associated with higher and lower level of psychotic experiences, respectively³⁵. Inferences drawn from student data may therefore not be generalisable to the general population. Nevertheless, the pattern of results in the study with the student population was very similar to that of the others, and excluding the study in the meta-regression showed similar results.

Because the present analysis included only six studies and the analyses focussed on rates rather than odds ratios, funnel plots are difficult to interpret. Publication bias cannot be ruled out. However, given the rarity of these types of studies and the fact that included studies cannot be considered as small yet with large effect size, publication bias is unlikely.

Permutation methods within meta-regression have been developed and implemented in Stata²⁶. Permutation is necessary because meta-regression gives increased rates of false-positives when the number of studies is small and when heterogeneity is present³⁶. In addition, in the present study the outcomes, which are rates, are not normally distributed, another reason to conduct permutations. As expected, p-values were more conservative after permutations, but because results were similar original coefficients and p-values were presented.

Acknowledgements

This project was supported by the Netherlands Organisation for Scientific Research (NWO) under project number: 017.002.048.

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CHAPTER 5

Summary

General comments

In this thesis, several studies are described concerning the *developmental* and *affective* aspects of schizophrenia and bipolar disorder, in terms of where they differ and overlap, and how that potentially overlaps in the *prodrome*.

Examination of the developmental and non-developmental risks of affective and non-affective psychotic disorders has important diagnostic implications, which led us to include work focusing on examination of diagnostic likelihood ratios of developmental and non-developmental risks in relation to the diagnoses of schizophrenia and bipolar disorder. This is discussed in Chapters 2 and 3.

The study of the developmental domains of affective and non-affective psychosis was carried out by examining areas where they differ and overlap in genetic and environmental factors shared by these two disorders (Chapter 3). In addition, several aspects of the prodrome, in terms of the distinction between bipolar disorder and schizophrenia, were investigated, examining the view that transition from subclinical states of psychometric risk in the general population to psychotic disorder can be viewed from the perspective of a psychosis continuum. In order to investigate this, aspects of the epidemiology of psychotic experiences in the general population, which may predict transition to various clinical psychotic disorders, was investigated (Chapter 4).

In the above-mentioned studies, data pertaining to both the NEMESIS and the EDSP data were examined. Additionally, we examined evidence from the literature using the methodology of qualitative and quantitative review of both observational and experimental studies.

Our findings

In **Chapter 2**, the developmental domains of affective and non-affective psychosis – in particular schizophrenia and bipolar disorder – were investigated. A common and well accepted position regarding the causes of psychiatric disorders, especially with schizophrenia, is the supposition of a multifactorial component (Johns & Van Os, 2001) similar to chronic physiological disease such as diabetes or cardiovascular disease. In the case of schizophrenia and bipolar disorder, this generally is taken to indicate that apart from the genetic component – with reported heritabilities of around 80% for schizophrenia and bipolar disorder – environmental factors may play a role as well. However, it is unclear what impact genetic and environmental factors have in terms of *attributable fraction* within these highly heritable diagnostic constructs. It is also unclear to what extent genetic factors play in their contribution to domains generally taken to reflect aberrant neurodevelopment, such as brain structural alterations associated with these disorders. Since pathophysiological findings demonstrate that there are brain changes in most psychiatric disorders, we wanted to investigate to what extent there is a genetic contribution to the development of brain structures. We also wanted to see if this genetic influence is also the cause of the brain changes in schizophrenia, because the brain changes in schizophrenia have been investigated more extensively than in any other psychiatric disorder.

In the *first* article, '*Heritability of structural brain traits: an endophenotype approach to deconstruct schizophrenia*', a literature search on the heritability of brain structures in

healthy people, in people with schizophrenia and pedigrees was carried out. In this article, evidence from literature on the heritability of brain structures in healthy monozygotic twins was examined and the heritability rates in studies with monozygotic and dizygotic twins concordant and discordant for schizophrenia were summarised in order to be able to estimate the contribution of genetic and environmental factors to brain structures. Examination of the contribution of genetic and environmental factors was also investigated in pedigree studies, in which the genetic component can be estimated more accurately as environmental factors are assumed to play a minor role in pedigree effects. In addition, the genes that may be involved in these brain structures in the different subgroups were investigated.

The following conclusions were drawn from the studies: the brain structures that were formed earlier in life and also the deeper structures were more genetically influenced than structures formed later in life, which are more environmentally influenced. The findings were similar for most of the brain structures across the different groups. However, there were also conflicting results in different studies on the same brain structures both in healthy people and in patients with schizophrenia. The brain changes in schizophrenia are present in about 50% of the patients that are included in these neuroimaging findings. As for the genes underlying these effects on brain structures, there are not enough studies showing evidence for effects of specific genes on specific brain structures.

The use of brain structures as an endophenotype may be valuable in deconstructing the genetics of brain traits in healthy people, people with schizophrenia and in pedigrees. Taking into account the limitations of neuroimaging as well of genetic epidemiological studies, and considering the problematic assumption that monozygotic twins share the (prenatal and postnatal) environment to the same degree as dizygotic twins, that most studies included rely on, the results of this review can only be described as helpful for further research in defining which brain structures might be more genetically influenced and represent genetic effects underlying the aetiology of schizophrenia. More research is necessary, and it is too early to state to what extent brain structural alterations represent the genetics of schizophrenia, let alone bipolar disorder, in a meaningful way.

In the *second* article, '*Murray et al. (2004) revisited: is bipolar disorder identical to schizophrenia without developmental impairment?*', the developmental factors in the overlap or non-overlap between the two disorders, i.e. schizophrenia and bipolar disorder, were investigated in a qualitative review. The search was carried out by examining the evidence from the literature in the past ten years and by revisiting the view by Murray et al., who published an article in 2004 which advocated the view that bipolar disorder was identical to schizophrenia without, however, expression of developmental impairment.

Most of the findings by Murray et al. (2004) are still relevant, according to our findings from the literature. An additional finding was that in the past ten years, more evidence has arisen that genetic risk for schizophrenia is expressed in part as neurocognitive impairments, whereas genetic risk for bipolar disorder is only mildly expressed with neurocognitive alterations. General population studies show that both disorders have phenotypes that are associated with psychometric risk states in healthy individuals and that these psychometric states are similarly highly comorbid with each other. One other finding was that exposure to an urban environment impacts on specific developmental associations with schizophrenia which is not observed in bipolar disorder, although we did find in one of our analyses with the NEMESIS data (Chapter 3, first article), that urbanicity specifically impacts on the psychotic

but not on the affective dimension of bipolar disorder, suggesting dimension-specific effects across diagnostic categories.

In the **third** article, '**Extended psychosis phenotype – yes: single continuum – unlikely**', an alternative theory opposing the categorical view of psychiatric disorder, in the sense of ill versus not ill (in contrast to the use of *continuum* as denoting a lack of contrast between disorder categories *within* psychotic illness), e.g. the continuum theory of psychosis, was investigated *conceptually* in an attempt to clarify whether a population psychosis continuum or, perhaps better described as *extended psychosis phenotype* exists and, if so, how this extended psychosis phenotype is distributed fully or quasi-continuous, and what determines whether some people experiencing psychotic experiences develop psychotic disorders later in life whereas others do not. Until recently, research on syndromal clustering of dimensions of psychosis was carried out almost exclusively in the population of people already attending mental health services, based on the assumption that symptoms observed in patients with psychotic disorder naturally did not exist outside mental health services. However, general population studies are showing that syndromal clusters of psychotic and affective symptoms not only exist in populations attending mental health services, but also are expressed as extended phenotypes in the general population (Stip & Letourneau, 2009). In order to be able to make a conceptual shift from studying clusters of psychosis dimensions in mental health services to the general population, it may not be productive to consider populations inside and outside the hospital as different at the level of symptoms *per se*, but at the level of whether or not *need for care* has developed. Not every person with a psychotic symptom will develop a clinical need, resulting in a visit to a general practitioner or to psychiatric services.

This subject is further investigated in the last article of chapter 4. We present in this article the first meta-analysis to ever attempt to estimate which people, given a certain level of expression of the extended psychosis phenotype in the general population (i.e. not in highly selected high-risk samples) will develop need for care, help-seeking behaviour and diagnostic status. Data were extracted from all published longitudinal studies in non-help-seeking general populations. We conclude that there are a number of variables predicting the transition of subclinical symptoms in general populations to clinical disorders. Not only the *load* of psychotic experiences is important, but also what type of coping the person develops, and the degree of persistence of these subclinical psychotic symptoms over time. We further suggested a new model for research across the psychotic spectrum, suggesting that there is a psychosis continuum, but not a single psychosis continuum.

In **Chapter 3**, studies concerning the affective domains of psychosis are presented. In the first two articles, NEMESIS data were analysed, in search for evidence for overlap (or non-overlap) between affective and non-affective psychosis. In the **first** article, '**Evidence that the urban environment specifically impacts on the psychotic but not the affective dimension of bipolar disorder**', urbanicity as an environmental risk factor for bipolar disorder was investigated, because reports on this issue have been inconsistent, whereas high rates of psychotic disorders have already been shown in numerous studies related to the urban environment. Our hypothesis was that any effect of urbanicity on the bipolar phenotype would be moderated by comorbid psychotic symptoms. The cumulative incidence of bipolar and psychotic symptoms and syndromes – assessed with the CIDI in relation to five levels of population density of place of residence – were examined. In addition, we examined the degree of comorbidity between broadly and narrowly defined bipolar phenotypes on the one hand and

the dichotomous presence of broadly (17.2%) and narrowly (3.8%) defined psychotic symptoms on the other, as a function of population density of place of residence.

Higher rates of bipolar disorder, however defined, were observed in more urbanized areas, as well as a strong interaction between comorbid psychosis and level of urbanicity, indicating that with greater degree of psychotic comorbidity, a greater effect size of the urban environment was observed. For bipolar disorder without psychosis, no effect of urbanicity was apparent. These results suggest differential environmental causal effects on affective and psychotic dimensions of bipolar psychopathology.

Given the fact that associations with urbanicity are thought to reflect the impact of an environmental exposure that interacts with genetic liability to produce illness (Van Os, 2003a, 2003b, 2004), these results should be examined in light of previous work in the field of both molecular genetics and genetic epidemiology that has shown that there is a substantial sharing of genetic risk between bipolar disorder and non-affective psychosis (Cardno et al., 2002; Berrettini W, 2003a, 2003b). This means that when two individuals have a similar amount of shared genetic liability for both bipolar disorder and schizophrenia, the one that becomes exposed to an urban environment may develop a more *psychotic illness*, whereas the one not exposed to an urban environment may develop a more *mania-only illness*, suggesting that within the bipolar spectrum the impact of urban environment on the occurrence of more psychotic illness may be mediated by a different pathway than the rate of more mania-only illness. These mechanisms of gene-environment interaction have also been described for other psychiatric disorders such as depression and anxiety, two conditions that have been shown to share genes that, however, produce differential outcomes depending on subsequent exposure to divergent environmental risk factors, some resulting in anxiety outcomes and other in depression (Kendler et al., 1987, 1992, Kendler, 1996).

In the *second* article, '***The impact of subclinical psychosis on the transition from sub-clinical mania to bipolar disorder***', the prevalence of subclinical psychotic and manic symptoms was investigated, in terms of how these subclinical population phenotypes co-vary with and impact on each other. Again, NEMESIS data were used and the degree of comorbidity between subclinical mania and subclinical psychosis was investigated. In addition, the impact of subclinical comorbidity on social impairment and on the transition from subclinical mania to onset of bipolar disorder was also investigated.

The lifetime prevalences of at least one manic and one psychotic symptom were 4.1% and 4.2%, respectively, but, after excluding the people with DSM-III-R diagnoses of bipolar disorder or psychotic disorder, these prevalences were 2.3% (subclinical mania) and 2.8% (subclinical psychosis). Regarding the question as to how these phenotypes co-vary with each other, it was found that individuals with subclinical mania had a 17% risk of subclinical psychosis, compared to 2.3% in those without ($p < 0.000$). Subclinical psychosis in individuals with subclinical mania was much more predictive of a future diagnosis of bipolar disorder. As for social impairment, there was a positive interaction between social impairment due to physical and psychological problems and subclinical psychosis, indicating that for a given level of subclinical mania, the coexistence of subclinical psychotic symptoms was more predictive of social impairment, although this statistical interaction was not significant.

Thus, the subclinical phenotypes of mania and psychosis are more prevalent than their clinical counterparts and cluster together. One of the mechanisms by which the clustering of subclinical mania and subclinical psychosis may be relevant for clinical outcomes is that pos-

sibly the formation of more toxic combinations of subclinical mania and subclinical psychosis may facilitate a higher transition to bipolar disorder. A better understanding of this pathway is crucial for the development of early intervention.

The study is important in showing that subclinical symptoms should not be neglected, since they result in higher transition rates from subclinical to clinical disorders; specifically the comorbidity of psychotic symptoms may be toxic in this regard. Subclinical phenotypes can be seen as intermediary phenotypes of a mood continuum that after exposure to additional risk factors may progress to a full-blown disorder (Hanssen et al., 2005), specifically in the presence of psychotic symptoms at the subclinical level.

In the *third* article, '**Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials**', the focus was on the maintenance treatment of depression, as a paradigm for sensitisation. Antidepressants are effective in the treatment of depression, but also in prevention of relapse after remission from an acute episode. It is unclear though, to what extent the prophylactic effect of antidepressants is moderated by the duration of the continuation phase, level of abruptness of antidepressants discontinuation, or the number of previous episodes. This study attempted to address these questions.

All published randomized, placebo-controlled, double-blind clinical trials available before May 2007 were identified that addressed the efficacy of continuation or maintenance treatment of major depressive disorder with either SSRIs or TCAs and included patients entering a maintenance phase after achieving remission from the acute phase.

The conclusions were that the overall reduction of relapse risk in the maintenance phase was highly significant for both SSRIs and TCAs over one year of follow-up of maintenance treatment. Treatment with an antidepressant results in approximately 70% reduction of risk of relapse, confirming previous findings by Loonen et al. (1991), Geddes et al. (2003) and Viguera et al. (1998). The prophylactic effect appeared to be constant over the length of the continuation phase. The major conclusion in this study was that recurrent episode patients experience less protection from antidepressants over the maintenance phase than single episode patients. This suggests that with increasing number of episodes, patients may develop a relative resistance against prophylactic properties of antidepressant medication. There was no difference between abrupt discontinuation of antidepressants versus gradual discontinuation on relapse rates, except for a particular subgroup of recurrent episode patients, for which the mode of discontinuation was important. In these patients, abrupt discontinuation may lead to a relapse, a problem that has been identified for lithium as well. This finding may be interpreted in the context of sensitisation or a kindling-like process, in which biochemical and physiological processes involved in the illness become progressively more easily triggered by the same circumstances or precipitants.

We develop the hypothesis that sensitisation, as a form of progressive behavioural sensitisation, would be evident in depressive disorder manifested by evidence of decreased response to treatment with an increasing number of depressive relapses. However, the sensitisation model may not only be applicable to depression. There is accumulating evidence that behavioural sensitisation may also be relevant for psychotic disorder and in particular for positive symptoms in psychotic disorders (Collip et al., 2010). In other words, sensitisation may be important for the affective pathway in psychotic disorder (Myin-Germeys & Van Os, 2007). Future studies should take this issue further, possibly focusing on both affective and

psychotic symptoms in psychotic disorder, also in relation to antidepressant treatment in this group.

In **Chapter 4**, we described to what extent findings in the literature and research in psychiatry on developmental and affective domains of psychosis are applicable to the prodrome. Research on the prodrome is important because it is known that disorders such as schizophrenia or bipolar disorder do not have a sudden onset. In many patients, the first episode is preceded by a lengthy pre-phase in which symptoms manifest themselves in attenuated form for prolonged periods, sometimes as long as years. These trajectories may be amenable to early intervention, in order to reduce the psychological, social and possibly biological disruption that can lead to poor outcome (Pantelis et al., 2003).

Although there are many studies on the prodrome, these may be biased to a degree due to the vagaries of the selection processes that underlie the *ultra-high-risk* samples. Moreover, there is considerable confusion about the meaning conveyed by the term *at risk mental state*.

In the *first* article, ***‘DSM-V and the ‘Psychosis Risk Syndrome’: Babylonian confusion’***, the focus is on whether DSM-V should consider the inclusion of a new category, called the *psychosis risk syndrome* – or possibly the related term *attenuated psychotic symptoms syndrome*. We make the point that this should not occur, since risk is not an appropriate term in this context because subjects already, by definition, have a need for care, and the predictive value in even ultra-high-risk samples is too low for use in clinical practice.

In the *second* article, ***‘The case of the missing evidence: what do subclinical psychosis spectrum experiences predict in unselected representative population samples? A systematic review enriched with new results’***, a meta-analysis on psychotic experiences in the general population is presented, with a specific focus on unselected general population samples with psychotic experiences that are at risk of making the transition to a clinical disorder. The yearly risk of conversion to a clinical psychotic outcome in exposed individuals (0.56%) was 3.5 times higher than for individuals without psychotic experiences (0.16%). Conversion to a clinical disorder increased with the number, certainty, frequency, persistence and degree of affective dysregulation of psychotic experiences. The major finding in this study was the discrepancy between the 10% conversion rate in the high-risk literature compared to the actual 0.56% conversion rate in unselected population-based samples. The explanation for the discrepancy lies in the sample enrichment strategies through community awareness campaigns and other selective inclusion methods by which people participating in these high-risk studies are selected, creating a very high density of risk. The high conversion rates of the high-risk early intervention studies thus are based on sample enrichment strategies, rather than on clinical high-risk criteria *per se*.

CHAPTER 6

Future directions

Future direction of diagnosis across the spectrum of psychosis

Given the results of the studies included in this thesis, we can conclude that a multidimensional approach to the broad range of psychotic disorders, whether it is the affective domain or non-affective psychotic (syndromal) domain, would be more useful (Van Os et al, Nature, 2010) than conceiving of these syndromes as categorical entities. Thus, psychotic disorders may be viewed as the variable expression of a general psychotic syndrome consisting of various symptom dimensions that cross-sectionally cluster together in different degrees and combinations in different people. These symptom dimensions may, longitudinally, differ within the same people over time.

In this multidimensional approach four main dimensions of symptoms characterize the general psychotic syndrome: affective dysregulation (depression, mania or anxiety), psychosis (delusions, hallucinations), negative symptoms (motivational impairment) and cognitive alterations. In the general population, low levels of these four dimensional phenotypes represent the behavioural expression of vulnerability (extended phenotype in Figure 2, prevalence of 10%-20%) for psychosis. Instead of estimating heritability rates for the diagnostic construct schizophrenia, from a scientific point of view it is more useful to investigate the heritability rates of these four symptom dimensions. The four symptom dimensions display moderately high heritability levels of their own, varying from 40% heritability rates for affective and psychosis domains to a range of 40%-60% of heritability rates for cognitive domains. For example, in the study by Chen and colleagues (2009), it was shown that in a sample of 278 subjects consisting of patients with schizophrenia, their non-psychotic siblings, healthy controls and their healthy full siblings, many clinical cognitive domains were impaired in patients with schizophrenia and their non-psychotic siblings compared to healthy controls and siblings of these controls. Negative symptoms, working memory, episodic memory and executive function were found to be significantly heritable in sibling pairs. Significant genetic correlations were observed between negative symptoms and the cluster of working memory, episodic memory and executive function. Similar findings on the heritability of cognitive functions were found by Antila and colleagues (2009). They found that the heritability of cognitive functions was generally similar irrespective of psychopathology in families of bipolar I disorder patients (bipolar families) and unaffected relatives with bipolar I disorder only in the family compared to another group of families with both bipolar I disorder and schizophrenia or schizoaffective disorder (mixed families).

The symptom domains, at subclinical level, show low levels of correlation in the general population as indicated by less overlap at the level of behavioural expression of vulnerability (heritability of 40%-60%) seen in Figure 2. The heritability of schizophrenia is around 80%-90%, however these high heritability rates are not purely due to genetic factors. Part of the high heritability rate is due to the effect of genetic and environmental interactions that give rise to more severe levels of phenotypic expression, which in turn contribute to the likelihood of clinical detection by psychiatric services, by passing the filters on the pathway to mental health care (see mental health care filter in Figure 2). The symptom dimensions contribute independently to the clinical detection by psychiatric services and give rise to clinical diagnostic descriptions such as schizophrenia that have a relatively low prevalence on its own. However, these four symptom dimensions are subject to comorbidity bias (Berkson's

bias), meaning that they are much more correlated and comorbid at the level of psychiatric services.

Current psychiatric diagnostic entities may not be as scientific or useful as we think. Ideally, a diagnosis in psychiatry should fulfil the following criteria (Van Os, 2010): the diagnostic construct of disease has: 1) some link with a measurable phenotype in nature, 2) is valid in combining aetiological, symptomatic, prognostic and treatment specificity, 3) is useful and 4) is acceptable to those who are invited to carry its label. These four elements do not apply to schizophrenia or bipolar disorder, or to any other psychiatric disorder (Bentall, 2004; Brockington, 1992; Kendell & Jablensky, 2003; van Praag, 1976). Psychosis is easy to identify, but it is not exclusive to schizophrenia, and it occurs across a range of diagnostic categories of psychotic disorders. And, more important, the psychotic symptoms that are known to characterize psychotic patients are also prevalent in the general population at a subclinical level and show characteristic patterns of clustering that strongly resemble the disease phenotype. Van Os and colleagues (2000) showed that in the general population, subclinical delusional experiences are strongly associated with subclinical hallucinatory experiences, and that similarly, subclinical positive psychotic experiences are associated with depressive symptoms and blunting of affect. The prevalence and incidence of positive psychotic experience is much higher than reported rates for the (clinical) psychotic disorder (Van Os et al., 2009). The same data exist with regard to symptoms pertaining to the bipolar spectrum (Angst, 2007).

Figure 2 Complexity of the psychotic disorder phenotype in aetiological research (Van Os et al, Nature, 2010)

This broader syndromal view of clustered dimensions, depicted in Figure 2, may be more useful for aetiological research as the impact of environmental influences in psychotic disorders appears to be dimensional rather than categorical. The subclinical expressions of these four symptom dimensions are also encountered in the non-diagnosed general population at a rate of 10%-20% (Van Os & Kapur, S, 2009; Dominguez et al., 2010) and are also associated

with the same demographic, familial and other risk factors as the clinical syndrome of schizophrenia and related psychotic disorders (Dominguez et al., 2010; Polanczyk et al., 2010; Van Os et al., 2009; Kelleher & Cannon, 2010). Therefore, this model is not only applicable to those who have permeated the filters of mental health care and thus are already in need for care, but also to those in the general population, who might show transient low levels of these dimensional phenotypes, representing the behavioural expression of vulnerability for the different dimensions of the psychotic range. The heritability levels of these four dimensions can be estimated taking into account the specific factors that impact this vulnerability, but also the non-specific commonalities, which are a result of the gene-environment interplay.

Research to date has shown that the cognitive alterations, psychosis (hallucinations and delusions) and affective dysregulations observed in psychotic disorders such as schizophrenia and bipolar disorder, are also encountered in common mental disorders, like anxiety disorders and depression. Differences between these groups are quantitative rather than qualitative (Hanssen et al., 2003; Weiser et al., 2008). The relative non-specificity of symptoms in psychiatric disorders extends to the level of familial aggregation (Van Os et al., 2010). For example, siblings of patients with common mental disorders also display cognitive alterations (Weiser et al., 2008) and brain changes (Boos et al., 2008), albeit to a lesser degree. Although a family risk of history of schizophrenia is associated with the strongest relative risk, almost any psychiatric disorder in first-degree relatives is associated with an increased risk for schizophrenia. This means, that in terms of attributable risk, 30% of schizophrenia in the general population can be attributed to psychiatric family history in general, compared to 6% that is attributable to a family history of schizophrenia specifically (Mortensen et al., 2010). This suggests that, in addition to possible specific factors impacting on liability to specific psychiatric disorders, shared genetic and environmental factors may also impact on broader neurodevelopmental alterations resulting in liability to broad dimensions of mental health (Argyropoulos et al., 2008).

Future directions high-risk and aetiological research across the spectrum

After decades of research, schizophrenia and related psychotic disorders are still among the most debilitating disorders in medicine. Research on the *psychosis risk syndrome* (or *attenuated psychotic symptoms syndrome*), known variably as *clinical high risk*, or *ultra-high risk mental state* was inspired by observations of chronic illness courses in most individuals, greater treatment responsiveness during the first episode, possible progressive gray matter decline during early disease stages, and retrospective accounts of prodromal or early illness signs and symptoms. Research on *psychosis risk syndrome* was mainly focused on evidence from research in high-risk groups selected for presence of need for care, and has a focus on prevention of deterioration of the already ongoing onset of psychosis in this subgroup of patients, who have already passed the filters on the pathway to mental health care. However, the examination of conversion rates in general population cohorts show only minimal yearly conversion risks, throwing doubt on the high-risk paradigm. Results from intervention

studies are encouraging, but only apply to highly selected and non-representative samples. Therefore, they cannot yet be generalised to general psychiatric care. The next phase of research on psychosis risk syndrome has moved to larger, multicentre projects to increase generalisability and to ensure that sufficiently large samples at true risk for psychosis are included. However, samples are still highly selected and artificial density of risk of conversion is brought about by non-replicable sample enrichment strategies. Thus, it may be misleading that much emphasis in these new studies is on identification of biomarkers for conversion to psychosis that mainly focus on neuroimaging and genetics because results are only valid in the uniquely selected sample in which they are produced, which precludes generalisation. None of these high-risk studies to date have shown replicated evidence for biological or non-biological causal factors. However, one positive note on high-risk research conducted to date is that it has shown that it is time to critically re-examine our diagnostic entities, the methodological approaches and consequences of sampling strategies in high-risk studies, and the need for *a priori* formulated hypotheses.

Future research therefore should attempt to integrate the genetic and epidemiological aspects of the psychosis spectrum in representative longitudinal general population samples followed over time. Genetic epidemiology should integrate the study of the relevant liability phenotypes with variables relating to the timing, severity and experience of environmental exposures within the same study design. This suggests that population cohort study approaches need be combined with clinical sample approaches, in order to investigate all syndromes across the entire non-clinical and clinical spectrum. This would represent a novel approach, as such work has not been undertaken before. Combining genome-wide-association studies with environmental-wide assessments and exploring the gene-environment wide-interactions (GEWIS) (Van Os & Rutten, 2009) may represent the next step in future study designs. From these studies, information on the genetic and environmental determinants of onset of psychosis in representative population samples, describing the trajectory from risk state to clinical outcome, may be produced, helping us to understand the true nature of psychosis and its disorders more thoroughly.

CHAPTER 7

Summary in Dutch

Nederlandse samenvatting

Inleiding

Deze thesis behandelt verschillende onderzoeken naar een mogelijke overlap van schizofrenie en bipolaire stoornis. We zijn uitgegaan van de klassieke diagnoses van schizofrenie (niet-affectieve psychose) en bipolaire stoornis (affectieve psychose), zoals geclassificeerd in de diagnostische handboeken DSM-IV en ICD-9 (**Hoofdstuk 1**). In de affectieve psychose staat de stemmingscomponent op de voorgrond, terwijl in de niet-affectieve psychose de cognitieve component de hoofdrol speelt. We hebben naar een eventuele overlap, of juist een gebrek daaraan, gezocht op een tweetal domeinen van de affectieve en niet-affectieve psychose, nl. het *ontwikkelings-* en *het affectieve* domein; verder hebben we gekeken hoe deze domeinen van invloed zijn op de *prodromale* fase van de twee stoornissen.

Bevindingen

In **hoofdstuk 2** begonnen we met het ontwikkelingsdomein van de affectieve en niet-affectieve psychoses, in het bijzonder keken we naar de diagnoses bipolaire stoornis en schizofrenie. We deden dit aan de hand van 3 artikelen.

Een theorie met brede consensus over de oorzaken van psychiatrische aandoeningen is, dat het ontstaan kan worden teruggevoerd op een multifactoriële aetiologie, d.w.z. dat er meerdere factoren bijdragen aan het ontstaan van de aandoening. Schizofrenie en bipolaire stoornis kennen een erfelijkheid van rond de 80%, maar onduidelijk is hierin de bijdrage van gen/omgevingsinteracties. De genetische contributie als oorzakelijke factor kan tot expressie komen in de ontwikkeling van het brein en worden onderzocht met beeldvormend onderzoek van de hersenen van patiënten met schizofrenie in vergelijking met (i) hun broers/ zusters/familieleden en (ii) gezonde controlepersonen.

Omdat de ontwikkelingsneurologische breinveranderingen het beste onderzocht zijn in de schizofrenie, hebben we in het **eerste** artikel van hoofdstuk 2, ***Heritability of structural brain traits: an endophenotype approach to deconstruct schizophrenia***, een literatuurstudie gedaan naar de erfelijkheid van breinstructuren in 1) gezonde personen, 2) personen met schizofrenie en 3) niet-menselijke primaten, om zo een conclusie te kunnen trekken over de invloed van genetische en omgevingsfactoren op breinstructuren. Daarnaast hebben we gekeken of er genen zijn die bij de ontwikkeling van specifieke breinstructuren betrokken zijn.

We kwamen tot de volgende conclusies:

- 1) De breinstructuren die vroeg in het leven ontwikkeld zijn, of die diep in het brein liggen, ondervinden meer invloed van genetische factoren dan breinstructuren die later in het leven gevormd zijn en meer worden beïnvloed door omgevingsfactoren.
- 2) In de gepubliceerde onderzoeken zijn tot op heden geen specifieke genen gevonden die coderen voor specifieke breinstructuren; er is nog maar weinig onderzoek verricht op dit gebied.
- 3) Ondanks de beperkingen van neuroimaging en genetisch onderzoek, kunnen de bevindingen tot nu toe als leidraad dienen voor verder onderzoek naar genetische oorzaken die aan de basis van schizofrenie liggen.

In het **tweede** artikel, *Murray et al. (2004) revisited: is bipolar disorder identical to schizophrenia without developmental impairment*, hebben we gekeken naar een mogelijke overlap (of juist gebrek daaraan) van ontwikkelingsfactoren bij enerzijds schizofrenie en anderzijds bipolaire stoornis. De volgende conclusies konden worden getrokken:

- 1) De bipolaire stoornis is in vele opzichten “identiek” aan schizofrenie, maar mist, of vertoont in veel mindere mate, de ontwikkelingsneurologische beperkingen die de schizofrenie kenmerken zoals beschreven door *Murray et al, 2004*.
- 2) Uit de onderzoeken van de afgelopen 10 jaar komt naar voren dat het genetische risico op schizofrenie onder meer tot expressie komt als neurocognitieve beperking, terwijl dat bij de bipolaire stoornis veel minder het geval is.
- 3) Urbanisatie (leven in de grote stad) als omgevingsfactor heeft invloed op het voorkomen van de ontwikkelingsneurologische stoornis schizofrenie, maar niet op het voorkomen van bipolaire stoornis.

In het **derde** artikel, *Extended psychosis phenotype-yes: single continuum-unlikely*, is de zogenaamde continuümtheorie van psychosen onderzocht en is getracht een conceptueel model te maken van een dergelijk psychosecontinuüm (in de zin van overlap met de normale mentale gesteldheid in de algemene populatie; ook wel *extended psychosis continuum* genoemd): wat maakt dat sommige mensen over het continuüm bewegen van lage waarden naar de hogere, klinische relevante expressiewaarden van psychose? Hiertoe werd onder andere een meta-analyse uitgevoerd (zie hieronder).

De conclusies die getrokken werden uit dit onderzoek zijn:

- 1) Er zijn meerdere variabelen die de overgang van subklinische symptomen in de algemene bevolking naar een klinische stoornis kunnen verklaren.
- 2) Niet alleen de hoeveelheid psychotische ervaringen, en hun frequentie, zijn belangrijk, maar ook wat voor soort mechanismen iemand ontwikkelt om hiermee om te gaan, alsmede de mate van persistentie (duur) van de klachten over de tijd.
- 3) Op basis van de huidige gegevens in de literatuur valt nog niet met zekerheid te zeggen of er werkelijk sprake is van een lineair continuüm, of dat er toch mogelijk kwalitatieve verschillen optreden op het uiterste einde van het continuüm.

In **hoofdstuk 3** zijn affectieve (stemmings-) domeinen van psychose onderzocht aan de hand van 3 artikelen. In de eerste twee artikelen zijn data van de NEMESIS-studie geanalyseerd en is er onderzoek gedaan naar evidentie van overlap (of gebrek aan overlap) tussen affectieve en niet-affectieve psychoses.

In het **eerste** artikel, *Evidence that the urban environment specifically impacts on the psychotic but not on the affective dimension of bipolar disorder*, is onderzoek gedaan naar wonen in de stad als omgevingsrisicofactor bij bipolaire stoornissen.

De conclusie van de analyses was dat urbaniteit invloed heeft op het voorkomen van bipolaire stoornis, maar alleen in samenhang met psychotische comorbiditeit: het voorkomen van bipolaire stoornis zonder psychose is niet afhankelijk van de mate van stedelijkheid van de omgeving. Bij gelijke genetische kwetsbaarheid kan blootstelling aan urbaniteit dus meer schade aanrichten op het ontwikkelingsneurologisch domein.

In het **tweede** artikel, *The impact of subclinical psychosis on the transition from subclinical mania to bipolar disorder*, is de prevalentie van subklinische psychotische en manische symptomen onderzocht, met name hoe deze subklinische symptomen covariëren en op welke manier ze elkaar beïnvloeden.

De conclusies waren:

- 1) Subklinische manie in aanwezigheid van subklinische psychotische symptomen is meer voorspellend voor een toekomstige diagnose van bipolaire stoornis (is dus meer “toxisch” voor het beloop).
- 2) Er is een suggestieve positieve interactie tussen het optreden van sociale beperkingen in het kader van medisch-psychiatrische aandoeningen en subklinische psychose; de aard van de interactie was dat voor een gegeven niveau van subklinische manie, de (co-) aanwezigheid van subklinische psychotische symptomen meer voorspellend is voor het optreden van sociale beperkingen.

In het **derde** artikel, *Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials*, is via de methode van de meta-analyse het fenomeen van de progressieve sensitisatie bij affectieve dysregulatie nader onder de loep genomen. Het onderzoek richtte zich op de onderhoudsbehandeling van depressies. Antidepressiva zijn effectief in behandeling van acute depressies en in het voorkomen van terugval na een acute fase (‘relapse’). De vraag van het onderzoek was met name of de hoeveelheid eerdere depressieve periodes de beschermende effecten van antidepressiva kunnen beïnvloeden, wat compatibel is met het idee van progressieve sensitisatie: de kans om depressief te worden naar aanleiding van een zelfde hoeveelheid stress wordt met het verstrijken van de tijd steeds groter omdat het individu gesensitiseerd is. De conclusie van de meta-analyse was inderdaad dat patiënten die eerdere depressieve periodes achter de rug hebben, minder profiteren van het profylactisch (beschermend) effect van antidepressiva dan patiënten die een eerste periode van depressie doormaken. Dit kan worden verklaard door ‘sensitisatie’ of ‘kindling-like’ processen: door de ontstane gevoeligheid worden de biochemische en fysiologische processen die tot de ziekte leiden gemakkelijker in gang gezet. Gezien het feit dat affectieve dysregulatie een kerncomponent is van psychose, verwachten we dat deze sensitisering ook een rol speelt bij psychose.

In **hoofdstuk 4** wordt aan de hand van 2 artikelen beschreven in welke mate de bevindingen uit de literatuur over de ontwikkelings- en affectieve domeinen van psychoses, toe te passen zijn op de prodromale fase. Onderzoek van de prodromale fase is erg belangrijk, omdat stoornissen als schizofrenie of bipolaire stoornissen meestal niet een plotselinge start of ontstaan kennen, maar vaak een lange prodromale fase hebben, waarin vroege interventie mogelijk is. Er is veel onderzoek gedaan naar deze prodromale fase, maar de onderzoeken geven mogelijk een vertekend beeld (bias) vanwege een idiosyncratische selectie van ‘ultra-high risk’ populaties, waardoor de voorspellende waarde meer wordt bepaald door de selectieve samenstelling van de onderzochte groep dan door ‘ultra high risk’- criteria, met name *attenuated psychotic symptoms*. Echter wat nu de voorspellende waarde van *attenuated psychotic symptoms* in de algemene populatie is, blijft onbekend.

In het **eerste** artikel, *DSM-5 and the 'Psychosis Risk Syndrome': Babylonian confusion*, wordt de DSM-V (in opzet) nader bekeken, met name wat betreft de eventuele inclusie van een *psychosis risk syndrome* (of mogelijk de daaraan verwante term *attenuated psychotic symptoms syndrome*). We tonen aan dat dit mogelijk verkeerd zou zijn, met name vanwege de boven beschreven *selective sampling* in de onderzoeken en het verkeerde gebruik van het woord "risk" in *psychosis risk syndrome*.

In het **tweede** artikel, *The case of the missing evidence: what do subclinical psychosis spectrum experiences predict in unselected representative population samples? A systematic review enriched with new results*, wordt een meta-analyse uitgevoerd met betrekking tot psychotische ervaringen in niet-geselecteerde representatieve populaties uit de algemene bevolking, en de voorspellende waarde van deze ervaringen voor het ontstaan van een psychotische stoornis. De conclusies waren dat:

- 1) het jaarlijkse risico op het ontwikkelen van een psychotische stoornis bij mensen met een of meer subklinische psychotische ervaringen (0,56%) 3,5 keer hoger is dan voor mensen zonder een psychotische ervaring,
- 2) het risico op transitie van subklinische psychotische ervaring naar psychotische stoornis toeneemt met aantal, frequentie, persistentie en mate van affectieve dysregulatie van de psychotische ervaringen,
- 3) de hoofdbevinding van de studie is de discrepantie tussen het 10% jaarlijkse transitierisico uit de *ultra high risk*- literatuur en het 0,56% transitierisico in ongeselecteerde algemene bevolkingsonderzoeken. De verklaring voor deze forse discrepantie ligt ons inziens in de manier van *selective sample enrichment* die wordt toegepast in de *ultra-high risk*- onderzoeken maar onterecht wordt toegeschreven aan psychopathologische '*ultra-high risk*'-criteria.

Toekomstige ontwikkelingen

Naar aanleiding van onze publicaties en literatuurgegevens kan geadviseerd worden om de psychotische stoornis, zowel affectieve als niet-affectieve, multidimensioneel te benaderen; dit vanwege de beperkingen die een categorale indeling van psychiatrische stoornissen met zich meebrengt voor de dagelijkse klinische praktijk, voor wetenschappelijk onderzoek in de psychiatrie en voor de hanteerbaarheid van deze diagnoses voor patiënten en familieleden. Daarbij kan worden uitgegaan van verschillende symptoomdimensies, die cross-sectioneel in verschillende mate en in verschillende combinaties aanwezig zijn in verschillende individuen, zoals voorgesteld door Van Os en collega's in een recente publicatie (Nature, 2010). In dit multidimensionele model kan uitgegaan worden van in ieder geval vier symptoomdimensies in het psychosesyndroom: affectieve dysregulatie (depressie, manie, angst), psychose (wanen, hallucinaties), negatieve symptomen (o.a. verminderde motivatie) en cognitieve veranderingen. In de algemene bevolking zijn lage gradaties van deze vier symptoomdimensies ook aanwezig, die beschouwd kunnen worden als de expressie van genetische en niet-genetische kwetsbaarheid voor psychose (prevalentie van rond de 10-20%). In plaats van ons vast te bijten op de erfelijkheid van grote en vage diagnostische entiteiten zoals schizofrenie, waarbij onduidelijk is welk deel van het erfelijkheidspercentage werkelijk door genetische factoren wordt bepaald en welk deel door gen/omgevingsinteractie, is het misschien beter om de

erfelijkheid van deze vier symptoomdimensies apart te bepalen. De symptoomdimensies zelf tonen matig tot hoge erfelijkheidspercentages, variërend van 40% erfelijkheid voor affectieve dimensies tot 40-60% erfelijkheid voor cognitieve dimensies.

Toekomstige onderzoekslijnen zouden de genetische en epidemiologische aspecten van het psychosespectrum moeten integreren; genetische epidemiologie zou het relevante fenotype (of de symptoomdimensie) moeten koppelen aan variabelen van *timing*, ernst en invloed van omgevingsfactoren, in een en dezelfde studieopzet. Dat betekent dat populatiecohortonderzoeken gecombineerd zouden kunnen worden met klinische onderzoeken om zo alle syndromen van het klinische en niet-klinische spectrum bij elkaar te brengen. Op deze manier zou het moleculair genetisch onderzoek (zoals *Genome-wide association studies* [GWAS] en de speurtocht naar zeldzame varianten met grote of kleine effecten) gecombineerd kunnen worden met onderzoek naar omgevingsfactoren, en gen/omgevingsinteracties in kaart kunnen worden gebracht.

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Dankwoord

Het is erg moeilijk om één van de coryfeeën in psychiatrie en onderzoekswereld te bedanken... ik heb het over mijn promotor prof. dr. J. van Os. Waarmee moet ik beginnen... met zijn bodemloze statistische en wetenschappelijke kennis? Met de vele wetenschappelijke publicaties en jaren achtereenvolgend tot medisch specialist van het jaar benoemd te worden? Of hoe hij stigmatisering in de psychiatrie, en de bijdrage van onze diagnostische systemen daaraan, bespreekbaar maakt? Hij is een van de meest inspirerende hoogleraren voor de GGZ professionals, hij brengt wetenschap dicht bij de klinici.

Jim, ik geloof dat ik één van je 'enfants terribles' (of misschien de enige) ben geweest, maar ik dank je voor je betrokkenheid en uithoudingsvermogen dit proefschrift tot een goed einde te brengen. Wat mij het meest opgevallen is, dat jij mij en mijn promotie nooit opgegeven hebt, ondanks het feit dat ik bij momenten door allerlei teleurstellingen niet verder wilde..... en nog steeds vraag ik me af of ik het verdiend heb en of mij al deze eer toekomt.

Ik dank de leden van de leescommissie: prof. dr. M. de Vries, dr. Ph. Delespaul, dr. F. Peeters, prof. dr. D. Wiersma en prof. dr. W.A. Nolen.

Prof. Nolen, beste Willem, ik wil je in het bijzonder bedanken, omdat ik van jou de kans heb gekregen om aan onderzoek te proeven tijdens mijn arts-assistentenschap en mijn eerste artikel, een meta-analyse over onderhoudsbehandeling van depressie, met je te schrijven. Ook ben je gaandeweg de promotie continu betrokken geweest en heb je met een aantal artikelen mee gepubliceerd. Ik heb zeer veel van je geleerd: ik dank je hiervoor!

Prof. Wiersma wil ik bedanken voor zijn enthousiasme in het laatste traject van de promotie om het tot een afronding te brengen.

Lex Wunderink, mijn eerste (ja, ik heb er vele gehad!) A-opleider: Lex, ik dank je voor de kansen die je me gegeven hebt: te beginnen met de mogelijkheid om met de A-opleiding van start te gaan! Van jou heb ik vooral geleerd om goed psychiatrisch onderzoek en goede diagnostiek te doen; altijd in beweging te blijven en jezelf te ontwikkelen... ook jij doet veel dingen tegelijkertijd en gaat op nieuwe uitdagingen af.

Een dankwoord richt ik ook graag tot Peter Turpijn, voorzitter van Mediant, alsmede Henk van den Berg, lid van de Raad van Bestuur, voor de jarenlange ondersteuning en hulp bij het tot stand brengen van mijn promotie en het faciliteren daarin. Peter, ik kan je niet genoeg bedanken voor je eindeloze energieke en motiverende houding; Henk, ik wil je bedanken voor je voortdurende ondersteuning, de inspiratie en de coaching die ik van je heb gekregen, niet alleen als beginnend psychiater, maar ook in mijn huidige baan als manager behandelingen, en daarnaast gedurende mijn hele promotietraject. Zelfs toen ik een jaar in de USA zat, bleef je me adviezen geven en steunen bij alle perikelen rondom promotie. Ook was het

nodig dat je de laatste maanden tijdens elke managementvergadering zowat als vast agendapunt mijn promotietraject aan de orde liet komen, om me continu met de afronding ervan bezig te houden, voor het geval dat ik teveel met andere zaken bezig was.

De samenwerking met jullie ervaar ik als zeer prettig en zeer dynamisch.

Dank ook aan de leden van het managementteam van Mediant voor hun ondersteuning gedurende mijn promotietraject: Paul Deursen, manager Bedrijfsvoering, bij Acute en Curatieve Zorg, voor voor de fantastische samenwerking met veel humor en daadkracht! Willem Snelleman, Hans Agelink en tot recent Hesie Chung, managers behandelzaken, Jurrien Smit, Marcel Hooch Antink, Gabriëlle Parel, Vincent van Antwerpen, Frans van de Pol, Annelies ter Huurne, Arie Holkers, Yvette Loves, Janet Poels, Ger Geuke, Wynand Koekkoek, allen lid van het managementteam bij Mediant, dank ik voor hun samenwerking. Peter Dingemans wil ik bedanken voor alle steun en begeleiding bij de laatste fase van mijn promotieonderzoek; Peter, dank voor alle uitleg en de voorbereidingen voor mijn promotie!

Bovendien wil ik mijn collega's bij Acute en Curatieve Zorg, de team- en programmanagers bedanken voor het geduld dat ze hebben uitgeoefend ondanks alle drukte en de weinige tijd die er was voor overleg of patiëntencontacten. Met name de collega's van crisis-voordeurteam en bemoeizorg zijn zeer begripvol geweest in deze fase en hebben naast de dagelijkse bezigheden steeds hun interesse getoond voor mijn promotieonderzoek. Er was afgelopen jaar zelfs weinig tijd over om de krant te lezen, maar dankzij jullie was ik toch op de hoogte van de interviews die mijn promotor had gegeven in allerlei dagbladen.

De secretaresses van het circuitmanagement en A&CZ wil ik bedanken, met name Bibiane, Sandra en Petra, voor al hun hulp en inzet in de laatste fase van mijn promotietraject, ik was zeer blij met jullie ondersteuning. De secretaresses van het crisis-voordeurteam heb ik soms, misschien wel -erg -vaak, tot wanhoop gedreven met voortdurende wijzigingen van afspraken en aanpassingen in de agenda, maar zonder het eeuwige geduld van Jeanne, Juliette, Ingrid en Tineke was werken aan mijn promotie het afgelopen jaar niet mogelijk geweest.

Aan de UM heb ik zeer veel hulp gehad van Elsa Misdom met het realiseren van dit proefschrift; Elsa, dank voor al je hulp!

In het bijzonder dank ik Ellemieke Nederlof, psychiater en vriendin, niet alleen voor alle steun en aanmoediging voor mijn onderzoek, maar ook voor de leuke sociale contacten. Ellemieke, ik wil je enorm bedanken voor je steun en hulp en ik ben zeer vereerd dat je mijn paranimf wilt zijn. Ik hoop dat we nu wat rustiger tijden tegemoet gaan, al is het de vraag of wij in staat zijn ons bezig te houden met maar één of twee dingen en niet met tig dingen tegelijkertijd. Ik dacht altijd dat ik na de promotie in een groot gat, ook wel 'post-promotie depressie' genoemd, zou vallen, omdat ik dan wellicht veel te veel tijd over zou houden. Maar, als ik zie hoe druk jij nog steeds bent na je promotie, en hoe we ons continu nieuwe dingen op de hals halen, dan maak ik me daar niet meer zo druk over... tegen die tijd heb ik niet eens meer tijd om depressief te worden!

Chantal Theunissen wil ik bedanken voor de leuke en ontspannen momenten, waarbij we over totaal andere zaken dan werk en onderzoek konden praten. Chantal, super, om je na zoveel jaren weer terug te zien en dat je mijn paranimf wilt zijn; ik was gelukkig net op tijd,

om in je paranimf- agenda, die bijna volgeboekt is voor het voorjaar, nog een dag te kunnen claimen voor mijn promotie!

Ik wil verder Fred Dreef en zijn vrouw Janine bedanken voor de gekkigheid, humor en gezellige gesprekken... dank Fred! Dankzij jouw humor kon ik dingen beter relativeren en soms zodanig dat ik een paar maanden voor het afronden zowat alles opgaf om meer van het leven te kunnen genieten... al duurde dat maar een paar seconden, het was wel geweldig! Een zorgeloos bestaan, helemaal overtuigd van de zinloosheid van ons bestaan!

Lieve Serap, hoe vaak hebben we onze afspraken niet uitgesteld vanwege de zoveelste deadline... het gaat binnenkort echt lukken om af te spreken! En geweldig, dat je temidden van alle drukte, stress en slapeloze nachten mij opbelde, om me uit te nodigen voor een trektocht door het Midden-Oosten en de zijderoute naar China! Misschien dit jaar dan?

Isik, jij was mijn eerste leermeester in de psychiatrie en hebt me, tijdens mijn co-schappen, laten zien wat voor een geweldig vak psychiatrie is! Nog altijd leg ik mensen uit dat ik niet de enige Koerdische psychiater in Nederland ben en dat jij de eerste was!

Verder wil ik alle vrienden die altijd betrokken, steunend zijn geweest bedanken voor hun betrokkenheid; Diederik ten Back, Tekleh Zandi, Pieter de Nijs, Albert Meyer en natuurlijk Agnieszka Ederveen, dank voor alles!

Lieve Nicole, we gaan nu vaker uit!

... en nu even met z'n allen omschakelen naar een andere taal: Rozelin Aydina, benim Der-simli bilim arkadasima tesekkurluk etmek istiyorum... sen, Turkiyeden ta buralara geldin, bilimle ugrasmak icin, oysa ben burada, bu rahatliklar icinde bazen sikayetleniyorum, Sana cok saygi duyuyorum, tabii adinin Rozelin olmasida herseyi daha anlamlı yapıyor; biliyorsun, benim dunyalarca sevdegim yegenimin adida Rozelin!

Dear Prof. N. Freimer, I would like to thank you for giving me the opportunity to work at your lab at the UCLA and learn the basics of science and be very critical, even about the biological findings, which most researchers and clinicians seem to be accepting as conclusive. It was a wonderful year and I did learn a lot during that year!

My dear Ania Jansinska, how can I thank you for the wonderful time we have spent together at the UCLA and in Los Angeles/California! I miss you a lot and miss our visits to botanical gardens, to the opera and into the nature! You're probably the only scientist I know who has two PhDs and I admire your relentless focus on good methodology, analyses and also your modesty. Well, I hope we can meet soon in California or in your homeland Poland.

Dear Emery and JD; thanks for all the fun we had in LA! Hope to visit you guys soon! Debra, querida amiga, muchas gracias por todo! Ojala, encontramos en verano en Sueca....of all places!

En last but not least... wat zou ik zijn zonder mijn familie, en daarbij bedoel ik mijn grote familie, dus niet alleen mijn broer, mijn twee zusjes en mijn moeder en vader, maar ook mijn tantes, ooms, neefjes, nichtjes en oma. Bij Koerden is het niet gebruikelijk familie te bedanken voor het feit dat ze er voor je zijn, dat is zoiets waardevols en tegelijkertijd vanzelfsprekends, dat je dat niet eens ter discussie of ter sprake kunt brengen door ze te bedanken... het is ergens ook 'not done'... en toch ga ik het wel een beetje doen.

Zoals dat hoort in een groot Koerdisch gezin is iedereen erg betrokken bij elke fase van je leven en zo ook mijn familie. Ze hebben me gesteund vanaf het begin tot het eind. Al was het soms moeilijk te begrijpen waar ik mee bezig was, jullie zijn er altijd voor mij geweest. Niet alleen tijdens mijn promotietraject, maar vanaf het begin dat ik naar de universiteit ging tot en met het afronden van het specialisme psychiatrie, tot het promotieonderzoek.

Ook de bezorgde momenten dat jullie af en toe me zelfs adviseerden om 'mijn hersenen rust te geven'.

Ercan dayi ve Fatos yengeye tesekkurler! Insallah, gelecek sefer Dersime geldigimde siz-inle rahat rahat oturup oradaki doganin guzelliginin tadina varirim. Bu sefer bilgi sayarimi getirmiyecem!

Murat dayi, cher oncle, et Sidar, Berivan, Serkan et ma cherie Meral, Paris n'est pas très loin, mais j'ai toujours manque du temps... mais après juin nous allons nous voir souvent, et surtout à Paris, comme d'habitude!

Lieve Thea en Asmen, Yasar dayi is niet meer bij ons, maar hij is mijn grootste inspirator geweest voor de psyche van de mens en zo ook van grote invloed op mijn keuze om psychiatrie te doen!

Mijn andere ooms en tantes en mijn oma wil ik bedanken voor al hun steun, ook mijn neefjes en nichtjes en hun partners: Serda en Siska en Nino, Laser, Murat, Seval, Ozgur, Ozge, Aynur teyze, Ayten teyze en Pierre, Unal dayi en Songul, met jullie geniet ik van de familiemomenten... na al die jaren is het nog steeds amazing om te zien met hoeveel mensen we soms in een kleine woonkamer passen bij zulke gelegenheden... hoe doen we dat toch?

Mijn zusje Meral wil ik bedanken voor alle hulp die ik de afgelopen jaren heb gekregen om dit promotieonderzoek af te kunnen ronden. Er is geen wereldstad waar we naar afgereisd zijn waar we het niet over mijn promotieperikelen hebben gehad. Je eeuwige steun om vooruit te kijken, ondanks tegenslagen, is geweldig! Zonder jou had ik het waarschijnlijk niet gered, je bent een grote inspiratiebron geweest.

Mijn zusje Safak dank ik voor de bemoedigende woorden, de rationaliteit waarmee je naar de zaken kijkt en de nuchterheid waarmee je dingen aanhoorde en zorgvuldig je adviezen gaf. Ik heb er vijf jaar over gedaan om hier iets van te bakken en intussen ben jij in de afgelopen jaren moeder geworden. Jij en Kurtulus, mijn zwager, geweldig dat jullie je dochtertje, mijn schatje Rozelin Sarya, regelmatig aan mij toevertrouwen in de weekenden (met mijn moeder op de achtergrond weliswaar)... tja, heb weinig maternale instincten, maar ben volgens mij wel een leuk maatje voor Rozelin! En als ik eens afdwaalde tijdens het spelen, omdat ik aan werk of onderzoek dacht, dan kreeg ik een klap in mijn gezicht van Rozelin om mijn aandacht weer bij het spelletje te houden! Kijk, dat zijn nou momenten waar je dankbaar voor bent, dat zo'n kleintje van 3 jaar je even terug in de realiteit brengt.

Mijn broer Akansel wil ik bedanken voor de rust en kalmte en laat ik het zeggen, toch de structuur, die je steeds bij mij, je tegenpool, wist aan te brengen. Telkens als ik in paniek raakte en het niet meer zag zitten, wist jij mij gerust te stellen en met je zakelijke kijk op dingen tot logische keuzes te brengen... En als ik eens weer radicale beslissingen had genomen, dan was jij er altijd om snel wat 'damage control' te doen. Je bent er altijd voor mij geweest en je bent een enorme steun voor me, maakt niet uit in welke stad ik woon, of in welk land ik me op dat moment bevind of in welke fase van mijn leven. De tijden die ik met jou, je vrouw Dagmar en de kinderen, lieve Miro, Amber en Sofie heb kunnen doorbrengen, dat zijn geweldige momenten! Mijn vader wil ik bedanken voor de inspiratie die ik van hem

heb gekregen en voor de discipline. We hebben weinig tijd om elkaar te zien, maar van jou heb ik veel geleerd, met name niet opgeven, risico's durven nemen, vallen en opstaan en gaan voor je ambities...

Mijn lieve moeder, waar moet ik beginnen... ergens denk ik dat jij vandaag ook promoveert, dat er ook een last van jou afvalt, omdat je de hoeveelheid stress die ik heb gehad de afgelopen jaren net zo goed doorgemaakt hebt. Sevgili annecigim, Derman hanim, sensiz hic bir yere kavusamazdim!

Curriculum vitae

Nil Kaymaz was born on 2 July 1972 in Mazgirt, East Turkey (Kurdish section). She completed her pre-university education in the Netherlands at the Christelijke Streeklyceum in Ede, Gelderland. After that, she studied medicine in Belgium, the first three years at the Free University of Brussel and the last four years at Ghent University. She did part of her clinical rotations at the Vall d'Hebron University Hospital in Barcelona, Spain. In 1999, Nil completed her medical studies and began working as a junior doctor in the adolescent clinic at the Sophia Children's Hospital in Rotterdam. Subsequently, she worked as a junior doctor at Midden-Brabant Mental Healthcare (GGZ) agency in Tilburg, the Netherlands. In 2000, she worked as a junior doctor at Grote Rivieren, an organization for mental health care in Dordrecht, the Netherlands, to begin her specialization in psychiatry. She completed her education in psychiatry in 2005 and then went to work as a psychiatrist/team psychiatrist at Altrecht Mental Healthcare agency in Utrecht. In the same year, she was awarded a Mozaïek grant from The Netherlands Organization for Scientific Research (NWO) and she began her postdoctoral research. Since 2005, Nil has been following the Master's programme in Epidemiology given by the Free University of Amsterdam/Institute for Health and Care Research (EMGO). In 2008, she carried out research on neuroimaging for one year at the University of California in Los Angeles (UCLA) in the United States, where she also lectured college students in psychopathology and neuroimaging. In 2009, after returning to the Netherlands, she started working at Arkin in Amsterdam as a psychiatrist/psychiatrist administrator in long-term care.

During the winter of 2009-2010, she moved to a post at the Mediant Mental Healthcare agency in Enschede, the Netherlands, where she is currently employed as treatment manager of the curative division and as psychiatrist with the critical time intervention team.

Publications

1. Kaymaz N, Lataster T, Lieb R, Wittchen H-U, Van Os J, Drukker M. The case of the missing evidence: what do subclinical psychosis spectrum experiences predict in unselected representative population samples? A systematic review enriched with new results. Submitted, 2010.
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