A dynamic model of the onset of clinical psychosis from an epidemiological perspective

Citation for published version (APA):

Domínguez Barrera, M. D. G. (2009). *A dynamic model of the onset of clinical psychosis from an epidemiological perspective*. [Doctoral Thesis, Maastricht University]. Datawyse / Universitaire Pers Maastricht. <https://doi.org/10.26481/dis.20091217md>

Document status and date:

Published: 01/01/2009

DOI:

[10.26481/dis.20091217md](https://doi.org/10.26481/dis.20091217md)

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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- The final published version features the final layout of the paper including the volume, issue and page numbers.

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A Dynamic Model of the Onset of Clinical Psychosis
from an Epidemiological Perspective

ISBN 978 90 5278 896 8

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Printed by Datawyse / Universitaire Pers Maastricht

Cover illustration: *Multitud*, by Luis Gutiérrez Dubón. <http://www.dubon.es>

A Dynamic Model of the Onset of Clinical Psychosis from an Epidemiological Perspective

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. mr. G.P.M.F. Mols,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op donderdag 17 december 2009 om 16:00 uur

door

María de Gracia Domínguez Barrera
geboren op 9 november 1974 te Pamplona

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South Limburg Mental Health Research and Teaching Network PhD Series

The research presented in this thesis was conducted at the School of Mental Health and Neuroscience, Department of Psychiatry and Neuropsychology of Maastricht University, Psychiatric Hospital Vijverdal.

ITHACA, by K. Kavafis

When you set out on your journey to Ithaca,
 hope that the road is long,
 full of adventure, full of discovery.
 Laistrygonians, Cyclops,
 angry Poseidon -- do not fear them:
You will never find such as these on your way,
as long as you keep your thoughts raised high,
 as long as a fine emotion touches
 your spirit and your body.
 Laistrygonians, Cyclops,
the fierce Poseidon -- you will never encounter them,
 unless you bring them alone inside your soul,
 unless your soul sets them up in front of you.

 Hope that the road is long.
 That the summer mornings are many, when,
 with such pleasure, with such joy
you will enter harbours you are seeing for the first time;
 may you stop at Phoenician markets,
 and purchase fine merchandise,
mother-of-pearl and coral, amber and ebony,
 sensual perfumes of all kinds,
 as many sensual perfumes as you can;
 and may you visit many Egyptian cities,
 to learn and learn from their scholars.

 Always keep Ithaca in your mind.
 Arriving there is what you are destined for.
 But do not hurry the journey at all.
 Better if it lasts for years;
and to anchor at the island when you are old,
wealthy with all you have gained on the way,
 not expecting Ithaca to make you rich.

Ithaca has given you the marvellous journey.
 Without her you would have never set out.
 She has nothing left to give you now.

And if you find her poor, Ithaca won't have fooled you.
 Wise as you will have become, so full of experience,
you will have understood by then what these Ithacas mean.

Paranimfen

Nicole Geschwind

Anne Fett

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CHAPTER 1

INTRODUCTION

INTRODUCTION: CONTENTS

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The work presented in this thesis starts from a theoretical model of the development of psychosis, which posits interactive mechanisms by which the individual's bio-psychosocial environments contribute to the development of major psychiatric disorders. This thesis specifically examines how the psychosis phenotype exists in nature and the dynamic process driving psychosis expression from an epidemiological perspective.

Firstly, this introductory chapter describes the concept of psychosis as a clinical construct, providing a comprehensive literature review of clinical psychosis, the symptomatic presentation which has replicated associations with psychometric expression of psychosis.

In the second part, this introduction will turn to the epidemiological perspective, presenting the development of epidemiological research in recent years and postulating the hypothesis of the present thesis.

Psychosis in Clinical Settings

Schizophrenia, the Paradigm of Psychotic Disorders

Schizophrenia is an enigmatic mental disorder, which ranks among the world's top ten causes of long-term disability (Murray & Lopez, 1996), with a high economic cost extending beyond the health care system to public sector bodies, lost income due to unemployment, leisure (Van Os & Kapur, 2009). The concept of schizophrenia is based on the work of Kraepelin, who emphasised the long-term deteriorating course of the syndrome that was later characterized by the coexistence of (i) core cognitive impairment (Kraepelin, 1919), (ii) the "Bleulerian blend" of negative symptoms (Bleuler, 1950), such as apathy, social withdrawal, difficulties in thinking straight (loosening of associations), incongruous or flattened affect, loss of goal-directed behaviour or ambivalence due to conflicting impulses, and retreat into an inner world (autism); and (iii) the cluster of "Schneiderian First Rank Symptoms" (Schneider, 1959) including auditory hallucinations, delusional ideas of persecution, conspiracy, thought interference and passivity phenomena. According to DSM-IV (American Psychiatric Association, 1994) and ICD-10 (World Health Organization, 1990b), a diagnosis of schizophrenia is established when this syndrome interferes with social and occupational functioning, in terms of impaired functioning in work, school, parenting, self-care, independent living, interpersonal relationships and leisure time, so that individuals result in need for care and, consequently, reach patient status.

The Group of Psychotic Disorders

Not only ‘schizophrenia’ but another five mental disorders are identified in the DSM-IV group of non-affective psychotic disorders, named ‘schizoaffective disorder’, ‘schizophreniform disorder’, ‘delusional disorder’, ‘brief psychotic disorder’ and ‘psychotic disorder not otherwise specified’. When affective and substance-induced psychoses are considered, four more diagnostic categories are described: ‘bipolar disorder’ with psychotic features, ‘major depressive disorder’ with psychotic features, ‘alcohol-induced’ and other ‘substance-induced psychotic disorders’. Together with ‘psychotic disorders due to other medical conditions’, these 10 psychotic categories share a phenomenological manifestation: the presence of positive psychotic symptoms. Delusions and hallucinations are thus not exclusive to schizophrenia and psychotic disorders occur across a range of diagnostic categories. Differential diagnosis between these different categories of psychotic disorder is based on duration, symptom patterns, dysfunction, associated substance use, “bizarreness” of delusions and presence of depression or mania. However, the resulting psychotic diagnostic categories show overlap in genetic liability (Kendler & Diehl, 1993) and with bipolar disorder (Craddock & Owen, 2007), suggesting a broad underlying liability that expresses across the different categories.

Generations of psychiatrists have been taught that schizophrenia affects 1% of the adult population in the world (American Psychiatric Association, 1994). A systematic review of studies considering the diagnostic category of schizophrenia in isolation revealed a lifetime prevalence and incidence of 0.30% – 0.66% and 10.2 – 22.0 per 100,000 person-years, respectively (Easton & Chen, 2006; McGrath, Saha, Chant, & Welham, 2008). Rates vary 3-fold depending on the diagnostic definition of schizophrenia that is used: a ‘narrow’ definition including patients with longer illness duration, younger age and more negative symptoms has lower rates than a ‘broad’ definition with less specific criteria (Castle, Wessely, & Murray, 1993). However, when a broad definition of psychotic disorder was examined, including diagnostic categories such as ‘delusional disorder’, ‘brief psychotic disorder’ and ‘psychotic disorder not otherwise specified’, a lifetime prevalence rate of psychotic categories of 2.3% was obtained (Perala et al., 2007), rising to 3.5% if bipolar disorder and substance-induced psychotic disorder were included.

Schizophrenia is a polythetic disease showing marked clinical heterogeneity in symptoms, determinants, course, and prognosis across individuals (van Os & Kapur, 2009). The cause of psychotic disorders is unknown, but evidence suggests that multiple susceptibility genes (Harrison & Owen, 2003), each with small effect, and acting in concert with (van Os & Marcelis, 1998) environmental influences e.g. obstetric complications (M. Cannon, Jones, & Murray, 2002), social-environmental factors, such as urbanicity (Krabbendam & van Os, 2005), migration (Cantor-Graae

& Selten, 2005), cannabis use (D'Souza et al., 2004), social disadvantage (Morgan et al., 2008) and trauma (Morrison, Frame, & Larkin, 2003) contribute. Definitions of schizophrenia with emphasis on negative symptoms and persistence of symptoms (associated with poorer outcome) have higher incidence rates for men (Roy, Maziade, Labbe, & Merette, 2001), whereas for broader definitions which include affective symptoms and brief presentations (associated with better outcome, including fewer hospital admissions and better social functioning) the gender ratio is closer to unity (Castle et al., 1993). Similarly, the course and outcome of schizophrenia is characterized by largely unexplained (van Os & Allardyce, 2009) heterogeneity rather than uniformly poor outcome, with a systematic review of follow-up studies showing poor outcome in less than 50% of patients and good outcome in less than 50% of patients in one year time (Menezes, Arenovich, & Zipursky, 2006).

Phenomenological Heterogeneity of Psychotic Disorders

While psychotic disorders have manifestly similar clusters/dimensions of positive psychotic symptoms, the psychotic diagnostic categories encapsulate patients with markedly different clinical features. In fact, evidence has shown that quantitatively different psychopathology define the diagnostic phenotype in psychotic disorder (Dikeos et al., 2006; Grube, Bilder, & Goldman, 1998; McGorry, Bell, Dudgeon, & Jackson, 1998). Researchers have tried to reduce heterogeneity by defining subtypes of the disorder. e.g. 'positive' and 'negative' symptom clusters. Clinical scales such as the *Brief Psychiatric Rating Scale* (Overall & Gorham, 1962), the *Scale for the Assessment of Negative Symptoms* (N.C. Andreasen, 1981) and the *Scale for the Assessment of Positive Symptoms* (N.C. Andreasen, 1984), the *Positive and Negative Syndrome Scale for schizophrenia* (Kay, Fiszbein, & Opler, 1987) as well as the *Signs and Symptoms of Psychotic Illness* (Liddle, 1992) were developed for the quantitative measurement of such symptoms domains. This provides a two syndromic framework (typologies) (N. C. Andreasen & Olsen, 1982; Carpenter, Heinrichs, & Wagman, 1988; Crow, 1980; Kay, 1990), which have been integrated into classification systems proposing subtypes within the diagnostic categories (Allardyce, Gaebel, Zielasek, & van Os, 2007).

Over the last three decades the development of intense computational procedures, such as exploratory factor analysis has allowed studies to identify psychopathological dimensions, which are groups of symptoms which co-occur more often than would be expected by chance alone. An individual can then be defined by how high or low they score on the different continuously scored latent dimensions, which may co-exist (Allardyce, Suppes, & Van Os, 2007). A meta-analysis of 10 studies of clinical schizophrenia (published prior to 1994) based on exploratory factor analyses of symptom ratings confirmed a three factor solution: 1)

the ‘positive’ or reality distortion, 2) ‘negative’ or psychomotor poverty, and 3) the ‘disorganized’ dimension (Grube et al., 1998). When measures of affective symptomatology are considered, a five factor solution is found adding the depressive and the manic or excitement dimensions (Dikeos et al., 2006; Good et al., 2004; Lindenmayer, Grochowski, & Hyman, 1995; van Os, Gilvarry et al., 1999). The 5-dimensional model is found across the full spectrum of functional psychotic disorders including affective disorders (Lindenmayer et al., 2004; van Os, Gilvarry et al., 1999) and has reasonable internal validity (Dikeos et al., 2006; Lindenmayer et al., 2004). Models which split psychotic and affective symptoms on separate dimensions fit the data best (Dikeos et al., 2006; Serretti & Olgiati, 2004), though there may be conflation of the disorganised and negative dimensions, in first onset samples (McGorry et al., 1998).

The five dimensional model (Figure 1) describes (i) the ‘positive’ dimension including symptoms of delusions, ideas of reference, unusual thought content, hallucinations, grandiosity and suspiciousness/persecution; (ii) the ‘negative’ dimension including those of alogia, affective flattening, avolition, apathy, anhedonia, asociality, social withdrawal, stereotyped thinking and motor retardation; (iii) the ‘disorganized’ dimension distinguishing conceptual disorganization, positive formal thought disorder, difficulty in abstract thinking, derailment, tangentiality, incoherence, illogicality, circumstantiality, associative loosening, inattention/distractibility, disorientation, inappropriate affect, bizarre behavior, mannerisms and posturing; (iv) the ‘depressive’ dimension consisting of observed depression, hopelessness, self-depreciation, feelings of guilt, guilty ideas of reference, early wakening, suicidal ideation, anxiety and active social avoidance; and (v) the ‘manic/excitement’ dimension comprising pressured speech, excessive activity, thoughts racing, elevated mood, increased sociability, reduced need for sleep, reckless activity, irritable mood, increased self-esteem and grandiose delusions.

Figure 1. The Five Dimensional Model of the Psychosis Phenotype

Note: 5-D: 5 Dimensional; Positive: Positive Dimension; Negative: Negative Dimension; Disorganized: Disorganized Dimension; Depressive: Depressive Dimension; Manic: Manic Dimension

Associations among Psychosis Dimensions: A Narrative Review

Research Question

Although studies including the whole spectrum of functional psychotic disorders produced similar factor solutions, there is likely to be proportional variation in the dimensional profiles across different diagnostic groups, as individuals diagnosed with schizophrenia score higher in the positive, negative and disorganized factors, while patients with affective diagnoses score higher in the manic and depressive dimensions and lower in the negative and positive ones. This suggests a quantitative variation in symptom dimension scores across psychotic categories rather than qualitative differences, in which establishing differential patterns of psychosis dimension's overlap might yield further insight in the underlying mechanisms of heterogeneity in psychosis. Therefore, a narrative review of the correlations among psychopathological dimensions in subjects with a lifetime history of psychosis is presented.

Searching for Factor Intercorrelation Matrixes in Clinical Psychosis

Articles were identified through literature search based on expert advice and cross-reference search. Using a start date of 1977, the following psychiatric classification systems were included: DSM-III, DSM-III-R and DSM-IV (American Psychiatric Association, 1980, 1987, 1994), *Research Diagnostic criteria* (Spitzer, Endicott, & Robins, 1978), *Schedule for Affective Disorders and Schizophrenia* (Endicott & Spitzer, 1978) and ICD-9 and ICD-10 (World Health Organization, 1977, 1990b).

The following criteria guided the inclusion of studies: i) the sample consisted of patients with a lifetime history of affective and/or non-affective psychosis using a recognized criterion-based diagnostic system; ii) the study used standardized and reliable clinical scales; iii) the study conducted factor analysis with the oblique rotation method; iv) the study reported the data obtained from the factor intercorrelations matrix among psychosis dimensions; iv) the study was published as an original article in a peer-reviewed, English language journal. Given that no analytical procedures were applied, possibly overlapping samples was allowed.

The following clinical scales were used in the studies: the *Brief Psychiatry Rating Scale* (Overall & Gorham, 1962), the *Scale for the Assessment of Negative Symptoms* (N.C. Andreasen, 1981), the *Scale for the Assessment of Positive Symptoms* (N.C. Andreasen, 1984), the *Multidiagnostic Instrument for Psychosis* (McGorry, Copolov, & Singh, 1990; McGorry, Singh et al., 1990) and the *Operational Checklist for Psychotic Disorders* (McGuffin, Farmer, & Harvey, 1991).

The majority of factor analysis has employed the orthogonal rotation method to make the factors more interpretable. This procedure assumes that the factors are independent. However, oblique rotation methods allow the determination of inter dimension correlations, which has theoretical and empirical face validity. Furthermore, if substantial correlations are demonstrated among the factors, the intercorrelations matrix may be factor analyzed (using a varimax rotation) to obtain a second-order factor structure.

Few and Inconsistent Findings

Seven studies used rotational methods which allowed intercorrelations among psychopathological dimensions in psychosis. These studies are listed in Table 1, along with the sample sizes and the main sample characteristics, the clinical scales that were used, the statistical procedure applied, the factor solution obtained and the results of the factor intercorrelations matrixes.

Disparity of Findings Leads to an Inconclusive End

Examination of intercorrelations among psychosis dimensions in clinical samples shows inconsistent patterns of associations. Disparity in methodology was observed among the studies, which differed in their selection of measurement instruments, and inclusion of affective psychopathological indicators, which has previously been shown to influence the factor solution (Peralta & Cuesta, 2001). Furthermore, studies tended to examine samples with different duration of disease with varying proportions of stage of disorder. Half of the studies looked exclusively at schizophrenia patients whereas the other half broadened the diagnostic concept including the whole spectrum of functional psychotic disorders. Similarly, different statistical procedures were applied. The factor solutions obtained varied from a 4-5 factor solution in most of studies to a 12 factor solution in one of them. Variability of findings in terms of factor composition may be due to the methodological disparity to the degree that an analytic synthesis of these studies could not be applied. Although psychopathological dimensions of psychosis appear to be obviously intercorrelated for both clinicians and researchers, the precise pattern of overlap can not be derived from the factor analysis literature up to date and remains uncertain.

Table 1. Intercorrelations among Psychosis Dimensions

Study	Sample characteristic	Clinical Scale	Type of analysis	Factor-solution	Factor Intercorrelations Matrix																																				
Brekke, 1994	<i>n</i> =193 RDC Schizophrenia and Schizoaffective disorder Community-based care 73% men Age: 33 y. Illness duration: 11 y.	BPRS	CFA Correlations between de factors were allowed to covary	Positive Negative Disorganization Depression	<table><tr><td></td><td>1</td><td>2</td><td>3</td><td>4</td></tr><tr><td>1</td><td>1</td><td></td><td></td><td></td></tr><tr><td>2</td><td>0.19</td><td>1</td><td></td><td></td></tr><tr><td>3</td><td>0.29</td><td>0.38</td><td>1</td><td></td></tr><tr><td>4</td><td>0.34</td><td>0.15</td><td>0.20</td><td>1</td></tr></table>		1	2	3	4	1	1				2	0.19	1			3	0.29	0.38	1		4	0.34	0.15	0.20	1											
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Peralta, 1994	<i>n</i> =253 DSM-III-R Schizophrenia Acute inpatient unit 67% men Age: 36 y. Illness duration: 10.6 y.	SANS SAPS	CFA	Positive Negative Disorganization Relational	<table><tr><td></td><td>1</td><td>2</td><td>3</td><td>4</td></tr><tr><td>1</td><td>1</td><td></td><td></td><td></td></tr><tr><td>2</td><td>-0.36</td><td>1</td><td></td><td></td></tr><tr><td>3</td><td>-0.24</td><td>0.39</td><td>1</td><td></td></tr><tr><td>4</td><td>-0.20</td><td>0.57</td><td>0.23</td><td>1</td></tr></table>		1	2	3	4	1	1				2	-0.36	1			3	-0.24	0.39	1		4	-0.20	0.57	0.23	1											
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Dollfus and Everitt, 1998	<i>n</i> =135 DSM-III-R Schizophrenia Inpatient unit (acute or stabilized) 49.6% men Age: 41 y. Illness duration: 11.1 y.	SANS SAPS	CFA	Positive Negative Disorganization Relational	<table><tr><td></td><td>1</td><td>2</td><td>3</td><td>4</td></tr><tr><td>1</td><td>1</td><td></td><td></td><td></td></tr><tr><td>2</td><td>-0.01</td><td>1</td><td></td><td></td></tr><tr><td>3</td><td>0.15</td><td>0.57</td><td>1</td><td></td></tr><tr><td>4</td><td>0.00</td><td>0.83</td><td>0.43</td><td>1</td></tr></table>		1	2	3	4	1	1				2	-0.01	1			3	0.15	0.57	1		4	0.00	0.83	0.43	1											
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	inpatient unit 65.8% males Age: 24.4 y. Illness duration: 0.25 y.		approach of Harris & Kaiser																																						
Peralta, 1999	n=660 DSM-III-R Functional Psychotic Disorder Acute inpatient unit 58.2% men Age: 36 y. Illness duration: 9.0 y.	SAPS SANS	PCA Oblique rotation (OBLOMIN procedure)	Poverty of affect/speech Thought disorder/innappropriate affect Schneiderian delusions Social dysfunction Religious delusions Paranoid delusions Bizarre behavior Non-auditory hallucinations Auditory hallucinations Manic thought disorder Attention Delusions of jealousy	* Due to space constrain, see the correspondent matrix table attached at the last row.																																				
Allardyce, 2007	n=464 DSM-III-R Functional psychosis First episode psychosis 45% men Age: 36 y.	OPCRIT	EFA Tetrachoric correlation matrix Promax rotation (oblique)	Hallucinations Delusional Disorganised Depression Manic	<table><tr><td></td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td></tr><tr><td>1</td><td>1</td><td></td><td></td><td></td><td></td></tr><tr><td>2</td><td>-0.29</td><td>1</td><td></td><td></td><td></td></tr><tr><td>3</td><td>0.32</td><td>-0.26</td><td>1</td><td></td><td></td></tr><tr><td>4</td><td>-0.36</td><td>0.27</td><td>-0.32</td><td>1</td><td></td></tr><tr><td>5</td><td>-0.29</td><td>0.34</td><td>0.13</td><td>0.21</td><td>1</td></tr></table>		1	2	3	4	5	1	1					2	-0.29	1				3	0.32	-0.26	1			4	-0.36	0.27	-0.32	1		5	-0.29	0.34	0.13	0.21	1
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6	-0.19	-0.10	0.13	-0.10	-0.01	1						
7	0.11	0.25	0.03	0.18	-0.02	-0.02	1					
8	0.00	-0.02	0.17	-0.01	0.11	0.03	0.01	1				
9	0.01	0.02	0.31	0.01	0.06	0.12	-0.06	0.14	1			
10	-0.13	0.24	0.02	-0.14	0.11	-0.05	-0.15	-0.01	-0.05	1		
11	0.24	0.23	0.01	0.15	0.04	-0.08	-0.06	-0.01	-0.07	0.12	1	
12	-0.06	0.03	-0.08	-0.02	0.00	0.00	0.05	0.02	0.04	0.02	0.02	1

Note: n: Sample size; DSM: Diagnostic Statistical Manual; RDC: Research Diagnosis Criteria; y.: Years; BPRS: Brief Psychiatry Rating Scale; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; MIP: Multidiagnostic Instrument for Psychosis; OPCRIT: The Operational Checklist for Psychotic Disorders; CFA: Confirmatory Factor Analysis; EFA: Exploratory Factor Analysis; PCA: Principal Component Analysis

Associations between Psychosis Dimensions and Intermediary Phenotypes: Neurocognition

Clinical heterogeneity can be further reduced by examining intermediate phenotypes, which are considered to be more proximal to the pathophysiological processes than the symptoms and may further allow the development of hypotheses regarding the pathoplastic effects of liability to psychosis. Investigations in relatives of psychotic patients have defined intermediary phenotypes as heritable traits (Goldman et al., 2008; Greenwood et al., 2007) which underlie the illness, such as neurocognitive functioning, structural MRI brain volume measures, neurophysiological information processing traits and sensitivity to stress (Boos, Aleman, Cahn, Hulshoff Pol, & Kahn, 2007; Bramon et al., 2005; Dickinson, Ramsey, & Gold, 2007; Touloupoulou et al., 2007). Intermediate phenotypes are thus heritable biomarkers, lying along the causal pathway from gene to disorder, at a more proximal position to the gene than the manifest symptoms.

In particular, neurocognitive impairment is well-known as a core feature of schizophrenia, characterized by a generalized cognitive impairment with especially pronounced deficits in the domains of memory, attention, executive functioning – including reasoning, concept formation, executive control and problem solving, verbal fluency, working memory, basic language processes and IQ (Aleman, Hijman, de Haan, & Kahn, 1999; Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Heinrichs & Zakzanis, 1998; Lee & Park, 2005; Pelletier, Achim, Montoya, Lal, & Lepage, 2005). Meta-analysis of family studies (Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Szoke et al., 2005) has demonstrated that cognitive deficiencies in relatives of schizophrenic patients parallel the deficits found in patients, and are especially pronounced in the domains of memory, executive functioning, verbal fluency, working memory and attention, in the small to moderate range. These familiar associations provide support for certain cognitive deficiencies as putative endophenotypes for schizophrenia (Lee & Park, 2005; Sitskoorn et al., 2004).

Previously published reviews of cognitive impairment suggest that dimensions of psychopathology are not associated with neurocognitive deficits in non-affective psychotic disorder (Green, 1996), however there is some evidence suggesting subtle and contrasting associations (Kerns & Berenbaum, 2002; Nieuwenstein, Aleman, & de Haan, 2001) that may yield important clues to differential underlying cerebral alterations. Hundreds of studies have examined the association between psychosis psychopathology and neurocognition. Two meta-analyses (Kerns & Berenbaum, 2002; Nieuwenstein et al., 2001) have been performed in this field. While informative, these meta-analyses were not complete, in that only non-affective dimensions and performance on few neuropsychological tests were examined. The advantage of a systematic approach including affective and non-affective measures

of psychopathology and all measures of neurocognition in psychotic disorder would allow examining meaningful contrasts across the whole spectrum of common manifest symptoms.

A Consilience Model for Clinical Psychosis

The past decade has seen the development of inter-disciplinary working with mutual exchange and integration of ideas from the different branches of neuroscience, with the majority of psychiatric disorders now being studied from both a brain & behavioural perspective, and models being proposed which integrate cognitive theory, phenomenology, ethiological based and pathophysiological into a single model of psychotic processes (Broome et al., 2005; Garety, Bebbington, Fowler, Freeman, & Kuipers, 2007; van der Gaag, 2006).

In the last Lancet seminar dedicated to Schizophrenia, van Os & Kapur (2009) formulated a consilience model for clinical psychosis incorporating the recent advances of genetics, epidemiology, imaging, cognitive sciences and psychopharmacology. This model postulates that there is a clear genetic vulnerability to schizophrenia – however, what one inherits is not the illness but altered brain development, shared in part with developmental disorders such as autism and in part with affective disorders such as bipolar disorder. In most who carry this vulnerability it only leads to subtle alterations in cognition, interpersonal style, some suspiciousness or affective dysregulation and mild functional impact. But, in some who are vulnerable – perhaps when combined with environmental insults indexed by urbanicity, cannabis and immigration – it leads to abnormal dopamine release. This abnormal dopamine release leads to an aberrant assignment of salience – thereby leading to the clinical expression of psychosis which brings these patients to attention.

In this model (Figure 2), psychotic psychopathology is differentially associated to differential distributed genetic liabilities to psychosis; (i) psychotic symptoms, shared by all diagnostic categories along the psychosis spectrum, occupy a central position in the model, as the result of gene-environment interactions integrating the neurobiological mechanism of dopamine sensitization and the cognitive process of aberrant salience attribution; (ii) developmental features such as interpersonal style and negative symptoms, associated with the intermediary phenotype of neurocognitive impairment, are the phenomenological expression of altered brain development; and (iii) affective dysregulation associated with affective genetic risk leads to the expression of reality distortion through the altered mechanism of aberrant salience attribution. To date, the epidemiological prediction of this model has not been tested.

Figure 2. A Syndromal Consilience Model of Schizophrenia and related Psychotic Disorders; bringing together affective and non-affective dimensions of psychopathology, (GxE: gene-environment interaction). (Published in Lancet, 2009)

Psychosis from an Epidemiological Perspective

Mapping Epidemiological Research on Psychosis in the General Population

Psychiatric epidemiological research has developed three frameworks in terms of participants' samples: (i) clinical samples, (ii) high-risk populations, and (iii) the general population, representing alternative perspectives for the common interest of tracing the ontogenesis, development and course of psychosis. These three perspectives diverge in their target populations, the operational definition of outcomes, the variety of instruments specifically designed for each one, the different framing in terms of time and the contribution that each alternative represents.

Since the earliest psychosis research, a categorical diagnosis was developed which required -fulfilling inclusion criteria according to standardized diagnostic classifications- to be identified as a participant in a clinical sample. Once the diagnosis was established, the whole range of determinants (including symptom severity evaluated by clinical scales, i.e. the *Positive and Negative Syndrome Scale* (PANSS) (Kay, Fiszbein, & Opler, 1987) and the *Brief Psychiatric Rating Scale* (BPRS) (Overall & Gorham, 1962) from the natural course of the disease to the development of chronic impairment was examined. Therefore, scientific conclusions from clinical psychosis research would concern severe cases in need of

treatment, so that one would understandably conceptualize psychosis as a discrete disease entity, as a categorical construct, distinct from normality. This, however, may not reflect the true distribution of psychosis at the population level.

High-risk populations defined groups of ‘high-risk individuals’ who fulfilled criteria for ‘prodromal syndromes’ (Hafner & Maurer, 2006; Miller et al., 2003). Prodromal syndromes are operationally defined by characteristics which are highly correlated with the onset of the disease, including sociodemographic features, genetic risk, exposure to environmental risk factors, clusters of symptoms well-known to precede the onset (the so-called prodromal symptoms) (Jackson, McGorry, & Dudgeon, 1995), personality features and secondary functional impairment which will lead to clinical relevance over time. Research on High-risk populations comprises the change over time of clinically relevant characteristics assessed at frequent intervals, and resulting in high rates of transition to “psychotic disorder” over a 3- to 12- month periods (van Os & Delespaul, 2005). Protocols for identification of high-risk populations which have demonstrated high positive predictive power (T. D. Cannon et al., 2008) can be developed yielding screening protocols, i.e. the *Comprehensive Assessment of At Risk Mental State* (Yung et al., 2005) and the *Structure Interview for Prodromal Syndromes* (Miller et al., 2003), and resulting in target groups for early intervention (Hafner et al., 2004). Given the recently reported possibility of early intervention in the course of prodromal psychotic states in ultra-high risk samples (McGorry et al., 2002), the importance of risk prediction approaches at the level of mental health services has become established (T. D. Cannon et al., 2008).

Although most research on predictors of transition to psychosis is based on clinical and high-risk samples, a third perspective faces up to investigate psychosis in large cohort studies at the level of the population. Population-based studies aim to bridge the gap between the general population and the early intervention clinic (McGorry, 2002; McGorry et al., 1995; van Os & Delespaul, 2005). They offer the opportunity to measure psychometric risk of psychotic experiences (which can be assessed with self-reported instruments, i.e. the *Self-report Symptom Checklist-90-R* (L.R. Derogatis & Cleary, 1977), the *Community Assessment of Psychic Experiences* (Stefanis et al., 2002) and the *Composite International Diagnostic Interview* (World Health Organization, 1990a)), with the potential of examining their population distribution, identifying turning points and relevant factors in the course of the very earliest expressions of psychosis and how these may develop into clinical correlates (McGorry, Yung, Bechdolf, & Amminger, 2008). In addition, a prospective longitudinal evaluation in the general population has the capacity to examine occurrence estimates of psychometric expression and to examine their clinical correlates over time. This requires the availability of a large number of subjects to develop prediction models of a relatively low frequency outcome.

Population-based Work on Psychotic-Like Experiences

Although psychosis has been commonly considered a rare phenomenon outside the range of normal human experience, the type of liability distribution expected for disorders with multifactorial interactive aetiologies would be continuous (Johns & van Os, 2001; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009) and many mental disorders have accordingly been shown to exist along a spectrum which includes subclinical expressions, evidenced by, for example, relatively high rates of expression of bipolar spectrum symptoms, subthreshold depressive states and social restriction associated with autism (Akiskal & Vazquez, 2006; Angst & Cassano, 2005; Constantino & Todd, 2003).

Similar findings have been reported for psychosis (Johns & van Os, 2001). The clinical psychosis phenotype has not only been shown to be more prevalent than previously thought (Perala et al., 2007) but also is expressed at levels below its clinical manifestation (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Stefanis et al., 2002; van Os, Hanssen, Bijl, & Ravelli, 2000; Yung et al., 2003). Furthermore attenuated psychopathology has been recognized and these symptoms tend to cluster in individuals and are classified as ‘schizotypal’ or ‘schizoid’ traits. A systematic review of the general population surveys suggests that the experiences associated with psychotic categories, such as paranoid delusional thinking and auditory hallucinations, are observed, in an attenuated form, in 5-8% of respondents who have never been diagnosed with any psychotic disorder (van Os et al., 2009). Subclinical psychotic experiences are typically expressed during adolescence and in young adulthood and are usually transitory (Poulton et al., 2000). Such subclinical expressions may be the manifest expression of an underlying liability for psychotic disorders (Lataster, Myin-Germeys, Derom, Thiery, & van Os, 2009), analogous to higher recorded blood pressure associated with a higher probability for developing future, cardiovascular disease, which shows an exposure gradient effect.

There may be continuity between the observed clinical and subclinical phenotypes since (i) similar associations with demographic factors, in particular the negative association with age and the positive association with single marital status and social disadvantage (Johns & van Os, 2001; Peters, Joseph, & Garety, 1999; van Os et al., 2000; Verdoux et al., 1998), (ii) sharing of environmental risk factors such as cannabis (Fergusson, Horwood, & Swain-Campbell, 2003; Henquet et al., 2005) and strong dose-response effects of the urban environment on both phenotypes (Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2006), (iii) sharing of cognitive and motor deficits (Krabbendam, Myin-Germeys, Hanssen, & van Os, 2005; Voglmaier et al., 2000), (iv) sharing of risk genes (Stefanis et al., 2004) and familial co-clustering of the clinical and the subclinical expression (Kendler & Diehl, 1993).

Longitudinal research further shows a link between psychotic experiences in adolescence and increased probability of having a psychotic disorder later in life. Since the seminal study by Chapman and colleagues (Chapman et al., 1994), there has been replication from 2 birth cohorts (Poulton et al., 2000; Welham et al., 2009) and 2 representative general population cohorts (M. Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005; Werbeloff, Drukker, & Dohrenwend, 2009) that low grade psychotic experiences, such as delusional thinking and mild hallucinatory experiences may precede the diagnosis of psychotic disorder, including clinical diagnosis of schizophrenia requiring hospital admission, by many years. In particular, Poulton and colleagues demonstrated that more than 25% of participants with low grade psychotic experiences at age 11 years developed a clinical psychotic disorder by age 26 years (Poulton et al., 2000). However, an equally important conclusion of that study was that the great majority of children with expression of psychotic experiences would never develop a psychotic disorder – psychosis was only a transitory developmental state for most. Similar conclusions were reached in adult population cohorts, with transition rates of around 10% (Chapman et al., 1994; M. Hanssen et al., 2005). Cougnard and colleagues (2007) suggested that transition from transitory to persistent psychotic experiences may be due to exposure of additional environmental risk factors during significant developmental critical periods; possible environmental risk factors were cannabis use, childhood trauma and urban environment (Cougnard et al., 2007). Many questions remain, however, with regard to the hypothesized continuity over time from subclinical to clinical psychotic states.

Psychometric Assessment with Self-report Instruments

The main instruments used for the assessment of psychometric expression in the general population are self-report questionnaires, such as the *Self-report Symptom Checklist-90-R* (SCL-90-R) (L.R. Derogatis & Cleary, 1977), the *Community Assessment of Psychic Experiences* (CAPE42) (Stefanis et al., 2002) and the *Composite International Diagnostic Interview* (CIDI) (World Health Organization, 1990a)).

The SCL-90-R is regarded as a comprehensive self-report symptom inventory, multidimensional in nature, and oriented toward the measurement of psychopathology in community samples of physical illnesses (Rossler et al., 2007) and also in psychiatric illness respondents (L. R. Derogatis, Rickels, & Rock, 1976). The SCL-90-R covers a broad range of psychiatric symptoms comprising 90 items, each rated on a five-point scale of distress, which are grouped along nine primary symptom dimensions plus three global indices of pathology. Two symptom dimensions are relevant for psychosis: the six-items ‘Paranoid Ideation’ and the ten-items ‘Psychoticism’ dimensions, developed in a fashion to represent the construct

as a continuous dimension of human experience, including the spectrum of psychotic experiences as paranoid behaviour and first-rank symptoms of schizophrenia.

The CAPE is a psychometric assessment of psychic experiences in a dimensional scale designed for use in the community. It is a 42-item self-report instrument for assessing the frequency of clinical symptoms and severity of symptom-related distress in the general population (Konings, Bak, Hanssen, van Os, & Krabbendam, 2006; Stefanis et al., 2002; van Os et al., 2002). It evaluates three major clusters of symptoms seen in severe mental illness: positive, negative and depressive. The positive symptom dimension comprises 16 items related to delusional experiences and four items to hallucinatory experiences. Each item is rated with a 4-point Likert scale (0 to 3) to indicate symptom frequency (“Never”, “Sometimes”, “Often” and “Nearly always”) and a 4-point scale to indicate degree of distress experienced due to the symptom, if present (“Not distressed”, “A bit distressed”, “Quite distressed” and “Very distressed”).

The CIDI is a comprehensive, fully standardized diagnostic interview and assesses symptoms, syndromes, and diagnoses of various mental disorders in accordance with the definitions and criteria of the ICD-10 and DSM-IV, along with information about onset, duration, severity of symptoms and psychosocial impairment. The CIDI has been primarily designed for use in epidemiological studies of mental disorders and can also be used for clinical purposes, but can be administered by trained lay people. It is divided into 16 sections: one sociodemographic section, 12 sections consisting of 288 symptom questions regarding groups of mental disorders (including as ‘Somatoform and dissociative’, ‘Phobic and other anxiety’, ‘Depressive and dysthemic’, ‘Manic and bipolar affective’, ‘Schizophrenia and other psychotic’, ‘Eating’, ‘Dementia and other cognitive’, ‘Post-traumatic stress’, as well as ‘Tobacco’-, ‘Alcohol’-, and ‘Substance-related’ disorders) and three final sections containing concluding questions, interviewer observations and interviewer ratings.

A comparison of positive psychotic experiences measured across the different instruments and emphasizing delusional and hallucinatory items is depicted in Table 2. A distinction is noted between the self-reported questionnaires SCL-90-R and CAPE 42 on the one hand, and the CIDI diagnostic interview on the other. In addition, two well-known clinical scales (the PANSS and the BPRS), specifically designed for measuring symptom severity in psychiatric patients, were included to allow comparison with a clinical, symptom-based measure. Comparing their formulation of psychosis items, self-reports on psychotic experiences can be regarded, if not as clear-cut psychotic symptoms, as a subclinical expression of psychotic experiences.

Table 2. Comparison of Delusional and Hallucinatory Items along Psychometric Instruments

Self-reported instruments			Self-reported instruments by diagnostic interview	Clinical scales
Instrument	Symptom check list – 90-Revised (SCL-90-R) (L. R. Derogatis et al., 1976)	Community Assessment of Psychic Experiences (CAPE 42) (Stefanis et al., 2002)	Composite International Diagnostic Interview (CIDI) (World Health Organization, 1977)	Brief Psychiatric Rating Scale (BPRS) (Overall & Gorham, 1962)
Description	A 90 item self-reported questionnaire for measurement of psychopathology in community, medical and psychiatric respondents	A 40-item self-report instrument, developed for assessing the frequency of clinical symptoms, and severity of symptom-related distress, in the general population	Self-reported experiences in a comprehensive fully standardized diagnostic interview to assess symptoms, syndromes and diagnoses of various mental disorders. Primarily designed for use in epidemiological studies of mental disorders, also used for clinical purposes.	A clinical scale developed to evaluate the psychiatric status of patients
Measure of Psychotic experiences	Two subscales: Paranoid Ideation subscale (6 items) and the Psychoticism subscale (10 items)	Items referring to the positive symptom dimension	G-section (including delusions and hallucinatory items)	Items referring to symptoms of delusions and hallucinations
Rating system	Each item is scored in 5 levels, from ‘not-at-all’ (0) to ‘extremely’ (4). A total score for each subscale can be obtained summarizing the included items.	Each item is scored in 4 levels, from ‘never’ (0) to ‘nearly always’ (3). A total score per dimension by adding up the number of positive answers to the frequency question.	Each item is dichotomously scored as present (1) or absent (5).	Each item is scored in 8 levels, from ‘not-assessed’ (0) to ‘extremely-severe’ (7).
Items of Delusional-like Experiences	‘Paranoid Ideation’ subscale: 8 - Feeling others are to blame for most of your troubles	‘Do you ever feel as if’ 2 - ‘. . . people seem to drop hints about you or say things with a double meaning?’	‘Have you ever’ G1 - ‘. . . believed people were spying on you, or following you?’	11 - Suspiciousness: Mistrust, belief others harbor malicious or discriminatory intent.

Self-reported instruments		Self-reported instruments by diagnostic interview	Clinical scales
(cont.) Items of Delusional-like Experiences	18 - Feeling that most people cannot be trusted	5 - '... things in magazines or on TV were written especially for you?'	15. Unusual thought content: Unusual, odd, strange, bizarre thought content. P6 - Suspiciousness / Persecution: Unrealistic and exaggerated ideas of persecution, as reflected in guardedness, a distrustful attitude, suspicious Pervigilance, or frank delusions that others mean one harm. Basis for rating: thought content expressed in the interview and its influence on behaviour.
	43 - Feeling you are watched or talked about by others	6 - '... some people are not what they seem to be?'	
	68 - Having ideas or beliefs that others do not share	7 - '... you are being persecuted in some way?'	
	76 - Others not giving you proper credit for your achievements	10 - '... there is a conspiracy against you?'	
	83 - Feeling that people will take advantage of you if you let them	11 - '... you are destined to be someone very important?'	
		13 - '... you were a very special or unusual person?'	
		15 - 'Do you ever think that people can communicate telepathically?'	
		17 - '... electrical devices such as computers can influence the way you think?'	
		20 - 'Do you believe in the power of witchcraft, voodoo or the occult?'	
		22 - '... people look at you oddly because of your appearance?'	
		24 - '... the thoughts in your head are being taken away from you?'	G2 - Was there ever a time when you believed people were following you? G3 - '... believed that you were being secretly tested or experimented on?'
		26 - '... the thoughts in your head are not your own?'	
		28 - 'Have your thoughts ever	G4 - '... believed that someone was plotting against you or trying to hurt you or poison you?'
			G7 - '... believed that someone was reading your mind?'
			G8 - '... er believed you could actually hear what another person was thinking, even though he or she was not speaking?'
			G9 - Have you ever believed that others could hear your thoughts?'
			G10 - Have you ever been convinced that strange thoughts, or thought that were not your own, were being put directly into your mind?'
			G11 - 'Have you ever been convinced that someone or

Self-reported instruments		Self-reported instruments by diagnostic interview	Clinical scales
(cont.) Items of Delusional-like experiences	been so vivid that you were worried other people would hear them? 30 – ‘Do you ever hear your own thoughts being echoed back to you?’ 31 – ‘... you are under the control of some force or power other than yourself?’	something could take or steal your thoughts out of your mind?’ G13- Have you ever believed that you were being sent special messages through television or the radio, or that a program had been arranged just for you alone?	
Items of Hallucinatory- like experiences	‘Psychoticism’ subscale: 7 - The idea that someone else can control your thoughts 16 - Hearing voices that other people do not hear 35 - Other people being aware of your private thoughts 62 - Having thoughts that are not your own 77 - Feeling lonely when you are with people 84 - Having thought about sex that bother you a lot 85 - The idea that you should be punished for your sins 87 - The idea that something serious is wrong with your body 88 - Never feeling close to another person 90 - The idea that something is wrong with your mind.	G17 – Have you ever seen something or someone that others who were present could not see – that is, had a vision when you were completely awake? G18 - ‘Have you more than once heard things other people couldn’t hear, such as a voice?’ G20 – Have you ever been bothered by strange smells around you that nobody else seemed to be able to smell, perhaps even odours coming from your own body? G21 – Have you ever had unusual feelings on your skin or inside your body – like being touched when nothing was there or feeling something moving inside your body?	P3 – Hallucinatory behaviour: Verbal report or behavior indicating perceptions which are not generated by external stimuli. These may occur in the auditory, visual, olfactory, or somatic realms. Basis for rating: Verbal report and physical manifestations during the course of interview as well as reports of behaviour by primary care workers or family. 12. Hallucinatory behavior: Perceptions without normal external stimulus correspondence.

During the development of these measures of subclinical psychotic symptoms, attention has been paid to the potential measurement bias inherent in self-reported instruments. There is nevertheless a substantial literature on the (predictive or other forms of) validity of self-reported psychotic symptoms, assessed with CIDI, SCL-90-R and other instruments (van Os et al., 2009). For example, one study validated self-reported psychotic symptoms against a clinical interview with the BPRS in a sample of psychotic patients, concluding that self-reported scores reflect clinical experience of psychosis (van Os, Verdoux et al., 1999). Reliability and validity of the SCL-90-R were established previously (L.R. Derogatis & Cleary, 1977). A recent, 20-year longitudinal cohort study on psychotic symptoms also showed high predictive validity of the SCL-90-R psychosis items used in the current sample in terms of deficiencies in social achievement and functioning (Rossler et al., 2007). Validity and reliability of the CAPE 42 as a self-report instrument for the measurement of psychotic experiences in community samples has also been established (Konings et al., 2006). With regard to the CIDI, designed for use by trained interviewers who are not clinicians, it has shown high interrater (kappa>0.70) (Cottler, Helzer, Mager, Spitznagel, & Compton, 1991; Reed, Gander, & Pfister, 1998; Wittchen, 1994; Wittchen et al., 1991). Poulton et al presented strong evidence for predictive validity of CIDI self-reported psychotic symptoms (Poulton et al., 2000). Similarly, Hanssen confirmed that the probability of having a psychotic disorder increased in a dose-response fashion with the level of self-reported psychotic experiences in the general population (M. S. Hanssen, Bijl, Vollebergh, & van Os, 2003).

Clinical Relevance versus Categorical Diagnosis

Since the earliest clinical research on psychosis, a categorical diagnosis was considered the cut-off point to be identified as a case. While diagnosis is considered important in clinical research, it may be neither the best outcome measure nor the first step in examining the dynamic process from mental wellbeing to clinical states at a population level as it introduces a bias towards unfavourable outcomes. The diagnosis of psychotic disorders is in part understanding the onset of need for care (formal or informal) and can be assessed within the context of frequency of subclinical psychotic experiences, distress, an individual's preoccupation and how the process influences behaviour (van Os, 2009). Impairment secondary to psychotic experiences in terms of help-seeking behaviour and dysfunction makes individuals reach the status of clinical relevance. Individuals who seek professional help because of their psychotic-like experiences will invariably obtain a "formal" diagnosis, however individuals suffering from dysfunctional repercussions of psychotic experiences –i.e. dysfunction work, relationships, daily functioning and levels of distress- who do not take the initiative to seek for professional help may not reach a "formal" diagnosis. Impairment considering both, help-seeking

behaviour and secondary dysfunction, is therefore a broader concept than categorical diagnoses of psychoses in general population samples (Poulton et al., 2000).

It is true, however, that the quality of the assessment of psychosis-related impairment in population-based studies ought to ensure (i) the quality of the assessment of psychotic experiences, (ii) the guarantee that impairment is truly secondary to those psychotic experiences, and (iii) the possibility of under/overestimating impairment. Since this is a somewhat controversial topic, it is extremely important to clarify the hazards of measuring clinical relevance of psychosis in terms of impairment at a population level. On the one hand, help-seeking behaviour may lead to an underestimation of true positives in the case of individuals who do not seek for help in spite of suffering from true clinical psychotic symptoms. On the other hand, dysfunction may lead to an overestimation of true positives in the case that individuals self-report secondary dysfunction only based on subjective level of distress. Finally, development of impairment is certainly necessary before any diagnosis of psychotic disorder can be made, and thus represents the first step that needs explaining and predicting in tracking the ontogenesis of psychotic disorder in the general population.

An Epidemiological Prediction of the Clinical Psychosis Model

The above population-based work has focused on experiences resembling positive psychotic symptoms and it is not known if and how the role of other attenuated symptom domains. Earlier general population surveys in Greece and the Netherlands have shown a high degree of overlap between psychotic experiences and affective symptoms below the threshold for clinical disorder (Krabbendam et al., 2004; Krabbendam, Myin-Germeys, Hanssen, de Graaf et al., 2005; Stefanis et al., 2002). It has also been suggested that experiences resembling negative symptoms are also expressed in attenuated form in otherwise “healthy” individuals (Maric et al., 2004).

Research in clinical samples cannot examine the degree variable clinical characteristics and other variables are due to illness or treatment effects. Similarly, clinical research cannot determine the degree to which the processes underlying symptom dimensions in psychotic patients may be universal, representing quantitative variations of normal human mentation (van Os & Kapur, 2009) or determine if and how interacting processes underlying phenomenology, from a perspective of risk, may contribute to the onset of clinical psychosis. Therefore, epidemiological research on such psychopathological phenomena may be productive, particularly when a longitudinal perspective allows for the clarification of the direction of effects and the relationship with onset of clinical psychosis.

Aims of the Thesis

The overall aim of this thesis was to describe the evolution of the psychotic process from mental wellness to onset of clinical psychosis within the general population.

1) To investigate the association between symptom dimensions and the intermediary phenotype of neurocognition in clinical psychosis by examining the correlations of the psychopathological dimensions and their relationship with neurocognition (an indirect measure of psychosis liability). Establishing differential patterns of cognitive performance among the different psychopathological dimensions may provide insight regarding the underlying mechanisms of heterogeneity. Since hundreds of studies had examined the association between psychosis psychopathology and neurocognition producing controversial findings, a systematic review of associations between psychopathological dimensions and neurocognition in subjects with a lifetime history of non-affective psychosis was conducted (**chapter 2**). The advantage of a systematic approach including affective and non-affective measures of psychopathology and all measures of neurocognition in psychotic disorder would allow examining meaningful contrasts. Previous work suggested that negative symptoms are, and positive/affective symptoms are not associated with measures of neurocognition (van Os & Kapur, 2009), which may be compatible with two contrasting and possibly even mutually exclusive pathways to psychosis (Myin Germeys, Krabbendam, Jolles, Delespaul, & van Os, 2002). Thus, differential patterns of neurocognition were hypothesized between the positive/affective dimensions on the one hand and the negative/disorganization dimensions on the other.

Meta-analysis is a standard method for aggregating, summarizing and drawing inferences. Associated regression methods provide the best available statistical tools for dealing with heterogeneity in the direction and strength of the association between variables. A clear set of rules is used to search for studies and to determine which studies will be included or excluded from the analysis. The results of the systematic review are based in the statistical synthesis of the data, in which the weights assigned to each study are based on mathematical criteria that are specified in advance, so that a transparent, objective and replicable framework is given for its discussion. Meta-analysis, as it is the case for the present thesis, is not only a way of synthesizing controversial information but also is part of the research process. Meta-analysis can play a role in designing new research formulating novel hypothesis based on aggregate rather than individual findings.

2) To test the dynamic process of psychosis expression through to the onset of clinical psychosis in a large representative sample of the general population followed longitudinally by examining (i) the quantitative variation of psychometric

expressions of the psychosis phenotype (included in chapters 3, 4 and 5), (ii) the hypothesis of continuity over time from abnormal persistence of commonly transitory psychotic-like experiences to clinically relevant psychosis (chapter 3), and (iii) if and how interacting processes underlying psychopathological dimensions (the associations of which were obtained in our first aim), from a perspective of risk, may contribute to the onset of clinical psychosis (chapters 4 and 5).

To this purpose, the analyses were carried out using the prospective, observational Early Developmental Stages of Psychopathology (EDSP) study which consists on a large, general population sample of 3021 adolescents and young adults, in Munich, Germany. The EDSP study, primarily designed to examine the incidence and developmental risk factors for psychopathology, collected data on the prevalence, incidence, risk factors, comorbidity and course of mental disorders (Lieb, Isensee, von Sydow, & Wittchen, 2000; Wittchen, Perkonig, Lachner, & Nelson, 1998). The overall design of this cohort study was longitudinal and prospective, consisting of a baseline and three follow-up surveys, covering a time period up to ten years.

Chapter 3 examined the degree to which positive measures of psychopathology are universal -that is, represent quantitative variations of normal human mentation- and whether subclinical psychotic experiences with a greater tendency to persist over time would have a greater probability to become clinically relevant in terms of dysfunction and need for care (impairment). The hypotheses of greater persistence resulting in a greater probability of transition from subclinical to clinical psychosis characterized by impairment are tested.

Chapter 4 examined the degree to which affective measures of psychopathology are universal - that is, represent quantitative variations of normal human mentation- and if and how interacting attenuated positive and affective measures of psychopathology, from a perspective of risk, may contribute to the onset of clinical psychosis. Hypotheses were derived from evidence from clinical patient populations indicates that affective dysregulation is strongly associated with reality distortion (Myin-Germeys & van Os, 2007; van Os & Kapur, 2009), suggesting that a process of misassignment of emotional salience may underlie this connection. In order to test the epidemiological predictions of this model, the link between affective dysregulation, emotional salience misattribution and psychosis was examined, taking the advantage of a longitudinal perspective allowing to clarify the direction of effects and to study the relationship with onset of impairment. It was hypothesised that (i) level of affective dysregulation, in the form of depression or (hypo)mania symptoms (regardless of the presence of formal mood disorder) in the general population, would be strongly and linearly associated with experience of reality distortion, expressed as psychotic experiences, (ii) presence of

affective dysregulation would be associated with persistence of reality distortion over time and (iii) affective dysregulation would be associated with impairment in the context of reality distortion.

In **chapter 5**, we examined the degree to which negative measures of psychopathology are universal - that is, represent quantitative variations of normal human mentation- and if and how interacting attenuated positive and negative measures of psychopathology, from a perspective of risk, may contribute to the onset of clinical psychosis. Hypotheses were derived from the suggestion that cognitive/negative symptoms associated with schizophrenia may represent alterations in brain development associated with distributed genetic risk, influencing a hypothesized final common pathway of neurotransmitter dysregulation resulting in the onset of positive psychotic symptoms, particularly when combined with environmental exposures, such as cannabis, developmental trauma and urbanicity (van Os & Kapur, 2009). It was hypothesized that: (i) subclinical expressions of positive and negative symptoms are distributed in the general population and occur more often together than predicted by chance, (ii) positive symptoms are associated with environmental risks and negative features with indices of developmental impairment, (iii) negative symptoms predict psychotic experiences over time but not the other way round and, finally, (iv) “co-morbid” expression of positive and negative experiences are associated with impairment and risk for patient status.

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CHAPTER 2

ARE PSYCHOTIC PSYCHOPATHOLOGY AND NEUROCOGNITION ORTHOGONAL? A SYSTEMATIC REVIEW OF THEIR ASSOCIATIONS

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Abstract***Objective and Method***

A systematic review (58 studies, 5009 individuals) is presented of associations between psychopathological dimensions of psychosis and measures of neurocognitive impairment in subjects with a lifetime history of nonaffective psychosis.

Results

Results showed that negative and disorganized dimensions were significantly but modestly associated with cognitive deficits (correlations ranging from $-.29$ to $-.12$). In contrast, positive and depressive dimensions of psychopathology were not associated with neurocognitive measures. The patterns of association for the 4 psychosis dimensions were stable across neurocognitive domains and independent of age, gender and chronicity of illness. In addition, significantly higher correlations were found for the negative dimension in relation to verbal fluency ($p: .005$) and for the disorganized dimension in relation to reasoning and problem solving ($p: .004$) and attention/vigilance (p -value: $.03$).

Conclusions

Psychotic psychopathology and neurocognition are not entirely orthogonal, as heterogeneity in nonaffective psychosis is weakly but meaningfully associated with measures of neurocognition. This association suggests that differential latent cerebral mechanisms underlie the cluster of disorganized and negative symptoms versus that of positive and affective symptoms.

Key words

Meta-analysis, Systematic Review, Psychosis Dimensions, Cognitive Disorders, Neurocognition

Introduction

Measures of psychopathology define the diagnostic phenotype in nonaffective psychotic disorder (Dikeos et al., 2006; Grube, Bilder, & Goldman, 1998; Lindenmayer, Grochowski, & Hyman, 1995; McGorry, Bell, Dudgeon, & Jackson, 1998). Cognitive impairment is an important feature of psychotic disorder (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Heinrichs & Zakzanis, 1998) that reflects developmental impairment and expression of genetic risk (Nuechterlein & Dawson, 1984; Sitskoorn, Aleman, Ebisch, Appels, & Kahn, 2004; Strauss, Buchanan, & Hale, 1993; Szoke et al., 2005). Although it has been suggested that cognitive impairment is not associated with dimensions of psychopathology in nonaffective psychotic disorder (Green, 1996), there is evidence suggesting subtle and contrasting associations (Kerns & Berenbaum, 2002; Nieuwenstein, Aleman, & de Haan, 2001) that may yield important clues to differential underlying cerebral alterations.

Two meta-analyses have been performed in this field. The meta-analysis by Nieuwenstein et al (2001) provided a quantitative review of the relations between three dimensions of schizophrenia symptoms (negative and positive dimensions, the latter subdivided into disorganization and reality distortion) and performance on 2 neuropsychological tests related to executive function and vigilance: the *Wisconsin Card Sorting Test* (WCST; 16 studies) and the *Continuous Performance Test* (CPT; 6 studies), respectively. Negative symptoms were significantly associated with impairments in both domains of cognitive functioning. Disorganization showed a significant association with worse WCST performance but not with CPT performance. Although significant, the effect sizes were small to modest in magnitude. General scores for all positive symptoms and separate scores for reality distortion symptoms were not associated with either WCST or CPT performance. Moderator analyses indicated that neither age, nor gender, nor duration of illness affected the overall effect sizes. Another meta-analysis, reported by Kerns and Berenbaum (2002), was focused exclusively on formal thought disorder and examined which of four specific cognitive domains would be associated with this psychopathological measure. Kerns and Berenbaum concluded that impaired executive functioning (26 studies) and impaired semantic memory (8 studies) were consistently associated but that increased spreading activation (5 studies) and impaired language production (5 studies) were not. Although informative, these meta-analyses were not complete, in that many other studies in nonaffective psychosis have assessed associations between domains of neurocognition and psychopathology (in particular, depression) that they did not cover.

The advantage of a systematic approach that includes affective measures of psychopathology and all measures of neurocognition is that such an approach

allows examination of meaningful contrasts. Previous work (Myin Germeys, Krabbendam, Jolles, Delespaul, & van Os, 2002) has suggested that negative symptoms are and positive/affective symptoms are not associated with measures of neurocognition, and this finding may be compatible with two contrasting and possibly even mutually exclusive pathways to psychosis. Therefore, establishing differential patterns of cognitive performance among the different psychopathological dimensions may yield further insight into the underlying mechanisms of heterogeneity of psychosis. Thus, differential patterns of neurocognition were hypothesized between the positive/affective dimensions on the one hand and the negative/disorganization dimensions on the other.

Method

Data Sources and Literature Search

Articles were identified through a literature search in MEDLINE and PsychINFO, the latter of which also references unpublished works such as those found in Dissertations Abstracts. The search covered the period from January 1977 to April 2008. We used a start date of 1977 and included the following psychiatric classification systems: *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1980, 1987, 1994); *Research Diagnostic Criteria* (Spitzer, Endicott, & Robins, 1978), *Schedule for Affective Disorders and Schizophrenia* (Endicott & Spitzer, 1978) and *International Classification of Diseases* (World Health Organization, 1977, 1990). The keywords were *psychosis* or *schizophrenia*, combined with *neuropsychol** or *neurocogn**, combined with *positive* or *negative* or *disorg** or *depressive*. The search produced 3,098 articles. References provided by relevant meta-analyses (Kerns & Berenbaum, 2002; Nieuwenstein et al., 2001) and included in the retrieved articles were examined and yielded an additional 31 articles. We contacted the authors of the 15 unpublished dissertation abstracts that were potentially eligible for inclusion in order to retrieve the necessary data. One author responded and referred to a later publication in which all relevant data were reported. Therefore, the abstracts of 3,129 articles were examined for possible inclusion in the analysis.

Criteria for Inclusion and Exclusion

The following criteria guided the inclusion of studies in the meta-analysis: (a) the sample consisted of patients with a lifetime history of nonaffective psychosis according a recognized criterion-based diagnostic system; (b) the study used standardized and reliable clinical scales and neuropsychological tasks; (c) the study reported all the correlations between symptom dimensions and neuropsychological performance; (d) the study was published as an original article in a peer-reviewed,

English-language journal. Studies that included groups of patients with special characteristics that possibly affected neuropsychological performance (e.g., geriatric patients or patients with childhood psychosis) were excluded.

Overlapping of Samples

The studies that fulfilled the inclusion criteria were examined for possibly overlapping samples. Authors whose studies were performed in the same departments or areas were contacted and were asked to provide the relevant information. Any overlap was dealt with in one of three different ways: (a) Of the studies with complete overlap in samples and clinical/cognitive measures, the study with the smaller sample size was excluded. This was the case for Good et al. (2004) versus Heydebrand et al. (2004); Docherty and Gordinier (1999) versus A. S. Cohen and Docherty (2004), and J. Addington and Addington (1998) versus J. Addington & Addington (1997). (b) Of the pairs of studies with overlap in samples but without overlap in the examined associations between cognitive domains and psychopathological dimensions, both studies were included, but the size of the smallest sample from each pair was subtracted from the total number of individuals who contributed to the meta-analysis. This was the case for Woodward, Ruff, Thornton, Moritz, & Liddle (2003) versus Woodward, Thornton, Ruff, Moritz, and Liddle (2004) and O'Leary et al. (2000) versus Torres, O'Leary, & Andreasen (2004). (c) Of the pairs of studies in which the degree of overlap in the samples was uncertain, all the studies were initially included in the analysis, and sensitivity analysis were conducted in which the studies with the smallest samples of each pair were excluded. This was the case for Braff et al. (1991) versus Perry and Braff (1998) and Himelhoch, Taylor, Goldman, and Tandon (1996) versus Tandon et al. (2000).

Psychosis Dimensions

Four psychosis dimensions (positive, negative, disorganized and depressive) were a priori considered to be of interest. Each had been reliably established as a constellation of symptoms of psychosis in previous work (Dikeos et al., 2006; Grube et al., 1998; Lindenmayer et al., 1995; McGorry et al., 1998). The positive dimension included delusions, ideas of reference, unusual thought content, hallucinations, grandiosity and suspiciousness/persecution. The negative dimension included alogia, affective flattening, avolition, apathy, anhedonia, asociality, social withdrawal, stereotyped thinking and motor retardation. The disorganized dimension included conceptual disorganization, positive formal thought disorder, difficulty in abstract thinking, derailment, tangentiality, incoherence, illogicality, circumstantiality, associative loosening, inattention/distractibility, disorientation, inappropriate affect, bizarre behavior, mannerisms and posturing. The depressive dimension consisted of observed depression, hopelessness, self-depreciation,

feelings of guilt, guilty ideas of reference, early wakening, suicidal ideation, anxiety and active social avoidance.

The following clinical scales were used in the studies: the *Scale for the Assessment of Negative Symptoms* (SANS; Andreasen, 1981), the *Scale for the Assessment of Positive Symptoms* (SAPS; Andreasen, 1984), the *Positive and Negative Syndrome Scale* (PANSS; Kay, Fiszbein, & Opler, 1987), *Symptoms and Signs of Psychotic Illness* (SSPI; Liddle, 1992), the *Brief Psychiatry Rating Scale* (BPRS; Overall & Gorham, 1962), *Community Adjustment Form* (CAF; Test et al., 1991), the *High Royds Evaluation of Negativity Scale* (HEN; Mortimer, McKenna, Lund, & Mannuzza, 1989), the *Calgary Depression Scale* (CDS; D. Addington, Addington, & Schissel, 1990), the *Hamilton Rating Scale for Depression* (HRSD; Hamilton, 1960), positive symptoms from the *Present State Examination interview* (PSE; Wing, Cooper, & Sartorius, 1974), the *Scale for the Assessment of Thought, Language, and Communication* (TLC; Andreasen, 1979), the *Manchester Scale* (Krawiecka, Goldberg, & Vaughan, 1977), the *Positive and Negative and Disorganized Symptoms Scale* (PANADSS; Andresen & Moritz, 2000) and the *Comprehensive Assessment of Symptoms and History* (CASH; Andreasen, 1987).

Cognitive Domains

The neuropsychological tests used in the studies were divided into 9 categories that measure approximately the same cognitive construct (Table 1). The classification was based on the MATRICS consensus (Buchanan et al., 2005), which proposed 6 neurocognitive constructs: reasoning and problem solving, speed of processing, attention/vigilance, working memory (verbal), verbal learning and memory, and visual learning and memory. The result of factor analytic studies, these 6 separable neurocognitive factors were replicable across studies and are thought to represent fundamental dimensions of cognitive deficit in schizophrenia (Nuechterlein et al., 2004).

Three other neurocognitive domains were included in the analysis on the basis of evidence of cognitive impairment in specific domains, as reported in previous meta-analyses. IQ was included as a measure of general intelligence (Fioravanti et al., 2005; Heinrichs & Zakzanis, 1998). In accordance with the discussion in the review by Nuechterlein et al (2004), verbal fluency was examined as a separate factor, given previous meta-analyses that reported substantial impairment of verbal fluency in schizophrenia (Heinrichs & Zakzanis, 1998; Johnson Selfridge & Zalewski, 2001). Finally, the construct of executive control was added and assessed with the *Stroop Color–Word* interference (Stroop, 1935). This test is thought to reflect executive functioning (Derrfuss, 2005), which is substantially impaired in schizophrenia (Johnson Selfridge & Zalewski, 2001).

Table 1. Cognitive Domains, Tests and Parameters

Cognitive domain	Cognitive tests	Test parameters
IQ	Wechsler Adult Intelligence Scale and Revised (Wechsler, 1955,1981) Wechsler Adult Intelligence Scale- Third Edition (Wechsler, 1997)	Full-scale IQ
Reasoning and problem solving	Wisconsin Card Sorting Test (Heaton, 1981) Nelson's Modified Card Sorting Test (Nelson, 1976)	Number or percentage of categories completed Number or percentage of perseverative errors
Executive control	Stroop Colour-Word Test interference (Stroop, 1935)	Number of incongruent words read (number of correct responses) Number of incongruent errors made
Verbal fluency	Either words from a certain category or words beginning with a certain letter	Number of words generated from either a certain category or beginning with a certain letter
Speed of processing	Digit symbol Substitution Test (Wechsler, 1955) Trail Making Test Parts A and B (Reitan, 1958) Stroop Color-Word Test (Stroop, 1935)	Number of symbols correctly copied Time in seconds to complete the task Colors (time in seconds to complete) Names (time in seconds to complete)
Attention/vigilance	Continuous Performance Test (Nuechterlein & Dawson, 1984) and its variations (e.g. Letter-Number Span)	Number or percentage of omissions Number or percentage of commissions Response sensitivity (d'- A')
Verbal working memory	Digit Span Backward (Wechsler, 1955) Letter-Number Span (Gold, 1997)	Total number of digits recalled Number of correct sequences
Verbal learning and memory	California Verbal Learning Test (Delis, 1987) Rey Auditory Verbal Learning Test (Rey, 1964) Wechsler Memory Scale-Revised (WMS-R; Wechsler, 1987), Paired – Associate Learning subtest Hopkins Verbal Learning Test (Brandt, 1991) Story recall (the Logical Memory subtest from the WMS-R; Wechsler, 1987)	Total number of correct responses on either immediate or delayed recall
Visual learning and memory	Benton Visual Retention Test (Benton, 1992) WMS-R visual memory (Wechsler, 1987) Rey-Osterrieth Complex Figure (Rey, 1941)	Total number of items on either immediate or delayed recall

First, data on estimated IQ were reported by 14 studies. Of these studies, 13 were based on full scale of the *Wechsler Adult Intelligence Scale* (WAIS; Wechsler, 1955) or the *Wechsler Adult Intelligence Scale-Revised* (WAIS-R; Wechsler, 1981) and 1 was based on a short form of the *Wechsler Adult Intelligence Scale-Third Edition* (WAIS-III; Wechsler, 1997). We did not include IQ estimates that were based on 1 or 2 subtests of the WAIS.

Second, reasoning and problem solving was assessed by 30 studies that used the *Wisconsin Card Sorting Test* (WCST; Heaton, 1981) and 3 studies that used *Nelson's Modified Card Sorting Test* (Nelson, 1976). Many studies reported two WCST parameters, namely, number of categories achieved and number of perseverative errors; these data were pooled into a combined effect size, as factor analyses have indicated that these variables load on a single factor of perseveration (Nuechterlein et al., 2004).

Third, the construct of executive control was assessed by 10 studies with the *Stroop Color-Word* interference (Stroop, 1935).

Fourth, verbal fluency, either words from a certain category or words beginning with a certain letter, was assessed in 23 studies.

Fifth, speed of processing was assessed using the *Digit Symbol Substitution Test* (Wechsler, 1955) in 8 studies, the *Trail Making Test* Parts A and B (Reitan, 1958) in 19 studies, and the *Stroop Color-Word* name and colour lists (Stroop, 1935) in 3 studies.

Sixth, attention/vigilance was measured by 18 studies that used a *Continuous Performance Test* (CPT; Nuechterlein & Dawson, 1984) and its variations. Several studies reported more than one CPT parameter; these were combined into one measure of accuracy. Reaction time variables for the CPT were not used.

Seventh, verbal working memory was assessed with the *Digit Span Backward* (Wechsler, 1955) in nine studies and with the *Letter-Number Span* (Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997) in two studies.

Eighth, verbal learning and memory was assessed with (a) word list learning tasks (the *California Verbal Learning Test*, Delis, Kramer, Kaplan, & Ober, 1987 [5 studies]; the *Rey Auditory Verbal Learning Test*, Rey, 1964 [4 studies]; the Associate Learning subtest from the *Wechsler Memory Scale-Revised* [WMS-R], Wechsler, 1987 [5 studies]; or the *Hopkins Verbal Learning Test*, Brandt, 1991 [3 studies] or (b) story recall (the Logical Memory subtest from the WMS-R, Wechsler, 1987 [8 studies]). Both immediate and delayed recall were included,

given that the results from factor analysis revealed that both loaded on the same factor (Nuechterlein et al., 2004).

Ninth, visual learning and memory was measured with the *Benton Visual Retention Test* (Benton, 1992; three studies), the Visual Reproduction subtest from the WMS-R (Wechsler, 1987; five studies), or the *Rey Osterrieth Complex Figure* (Rey, 1941; six studies); again, immediate and delayed measures were included.

No combined effect sizes were calculated for other possible domains, such as language, reasoning, visuoperceptual and visuospatial functions, or for performance on a single composite cognitive score because of lack of data and/or substantial heterogeneity between the tests used to assess these domains.

Statistical Analysis

The relevant results from the included studies were quantified in terms of correlations. Because higher scores reflected worse performance for some measures and lower scores reflected worse performance for other measures, all correlations were recoded such that a negative correlation indicated an association between higher levels of symptomatology and worse cognitive performance. Before the meta-analytic methods were applied (as discussed below), the correlations were transformed with Fisher's r-to-z transformation. The results from the meta-analyses were back-transformed into the raw correlation metric whenever possible (e.g., estimated mean correlations, confidence interval bounds). Data extraction and calculations of effect sizes were performed independently by Maria de Gracia Dominguez and Claudia J. P. Simons, who reached consensus in case of discrepancies. All analyses were carried out using the statistical software packages R and S-plus.

Four steps were performed for the analyses. First, we conducted 36 individual meta-analyses that examined the correlation between the four psychosis dimensions and the nine cognitive domains. Only analyses based on five or more observations were considered. When multiple correlation coefficients were reported for one cognitive domain-psychosis dimension combination within a single sample, these coefficients were first averaged into one r value. We used a random-effects model to account for heterogeneity among the population correlations and to obtain unconditional inferences about the distribution of population correlations (Hedges & Vevea, 1998). For each of these individual meta-analyses, we report k (number of studies), $\hat{\mu}_p$ (estimated average correlation in the population distribution), 95% confidence interval (CI) for μ_p , p (p value for the test $H_0 : \mu_p = 0$) and I^2 (percentage of the total variability in the observed correlation coefficients due to

heterogeneity). Values of I^2 equal to 0 indicate the absence of heterogeneity, in which case the random-effects model simplifies to a fixed-effects model. In that case, $\hat{\mu} = \hat{\rho}$, where $\hat{\rho}$ denotes the estimated true (homogeneous) correlation.

As part of this step, we also examined the data for the presence of publication bias. In general, publication bias occurs whenever the results obtained from the published literature are not representative for all of the research that has been conducted on a particular topic. One of the most problematic forms of publication bias is the over- or underrepresentation of particular findings based on their statistical significance. As a result, the estimate of the true correlation can become severely biased. In the absence of this form of publication bias, we would expect to see a more or less symmetric (inverted) funnel when plotted the observed correlations against their corresponding sample sizes (a so-called funnel plot). However, when studies with nonsignificant findings are suppressed from the published literature, the plot can become asymmetrical, and this leads to an association between the correlations and the corresponding sample sizes. The regression test for funnel plot asymmetry examines whether such an association is present in the data; the presence of an association would be indicative of publication bias and would call the findings into doubt (Sterne & Egger, 2005).

Regression tests for funnel plot asymmetry were conducted for each of the 9 x 4 meta-analyses. We also examined funnel plots for asymmetry in terms of the correlations between all of the cognitive domains and each psychopathological dimension (i.e., one funnel plot for each dimension). Because the same sample could contribute multiple correlations to the funnel plot in this case, dependencies are present. We decided not to model these dependencies, as doing so would have required us to obtain information (or estimates) of the $9(8)/2 = 36$ intercorrelations between the nine cognitive dimensions. Therefore, the results from the regression test for funnel plot asymmetry for those four funnel plots have to be treated with some caution.

Second, three variables (two sociodemographic and one clinical) were a priori chosen to be included in the analyses as moderators, as these variables have been reported as factors that influence the relationship between cognition and symptoms and therefore may account for at least some of the heterogeneity observed in the meta-analyses. Specifically, the three moderators were (a) chronicity of illness (in years), (b) mean age, and (c) percentage of men. It was hypothesized that studies that included more chronically ill or older or male subjects would show stronger associations between cognition and symptoms (Dikeos et al., 2006; Murray et al., 2005; Schultz et al., 1997; Simonsen et al., 2007). We examined a fourth moderator for the positive dimension that indicated whether the positive subscale included any symptoms of disorganization, as this was done in the older studies in particular.

Inclusion of symptoms of disorganization in the positive subscale was expected to increase the correlations with the cognitive domains (Liddle & Morris, 1991; Nieuwenstein et al., 2001).

We used a mixed-effect model was used to examine the influence of the moderators on the average correlation within each psychosis dimension–cognitive domain combination. The amount of residual heterogeneity was estimated with the method of moments estimator based on the basis of weighted least squares (Raudenbush, 1994). Because information about some of the moderator values within the studies was missing, we decided to examine each moderator individually (instead of including all moderators simultaneously within a single model). Results are expressed in terms of the estimated regression coefficient $\hat{\beta}$ and indicate by how much the average correlation (in the transformed units) is estimated to change with a 1-unit increase in the moderators. For age and chronicity of illness, 1 unit means 1 year; for men, 1 unit means 1%; and for positive-disorganized, 1 unit means going from (0) positive symptoms to (1) positive and disorganized symptoms. The corresponding 95% CI for the true regression coefficient is given also. Because the r-to-z transformation is nonlinear, one cannot easily back-transform the slope of the regression coefficient into the raw correlation metric.

Third, within each of the cognitive domains, we examined whether the average correlation coefficient differed between the negative and disorganized dimensions, in order to further clarify the controversial issue of differential patterns of cognitive impairment related to both (Liddle, 1987; Nieuwenstein et al., 2001). Because numerous samples/studies contributed correlations between a particular domain and both dimensions, we had to account for the dependencies between multiple correlations from a single sample. We estimated the covariance between two r-to-z transformed correlations from a single sample using Equation 10 given by Steiger (1980) and replaced parameters with their corresponding sample estimates where necessary. In doing so, we had to estimate the correlation between the two dimensions on the basis on the previous literature (none of the studies reported these correlations). For this analysis, the correlation between the negative and the disorganized dimension was estimated at .39 (Peralta, Cuesta, & de Leon, 1994). Sensitivity analyses were conducted using two other assumed correlation values (i.e., .20 and .60).

Fourth, in order to deal with potential overlap in the samples in the three previous steps of the statistical analyses, we conducted sensitivity analyses that excluded the smallest studies of each pair with an uncertain degree of overlap, as discussed before.

Results

Of the 3129 studies produced by the search, 187 were considered eligible for inclusion. Of these, 129 were excluded, because (a) the study examined associations with single symptom items (3.1% of the total number of studies not included); (b) the study split the subject sample into groups on the basis of their score on the different clinical scales (27.9%) or on the basis of their cognitive performance (6.2%) and reported the associations with these groups; (c) the study reported only correlations that were statistically significant (24%); (d) the study used neuropsychological tasks that were not used in any of the other included studies or that could not be classified under one of the cognitive domains (24%); (e) the study reported global cognitive or psychopathology scores (2.3%); (f) the study sample completely overlapped with a larger study that was included (2.3%); or (g) the authors did not reply to the request to provide additional data (10.1%).

The literature search thus yielded 58 studies that evaluated psychosis dimensions and cognitive performance in patients with a lifetime history of nonaffective psychosis, according to standardized neuropsychological instruments. These studies are listed in Table 2, along with the sample sizes and the main sample characteristics. In total, 5,009 individuals with a diagnosis of non-affective psychosis contributed to this meta-analysis. The patients were 72.7% men (reported by 57 articles). The mean age of the patients ranged from 19.1 to 51.9 years (reported by 55 articles). Mean chronicity of illness ranged from 4.8 to 28.9 years (reported by 37 articles). The mean age of illness onset ranged from 18.6 to 26.23 years (reported by 18 articles). The mean years of education ranged from 9.9 to 13.7 (reported by 39 articles). A total of 58% of the subjects were inpatients (reported by 44 articles). Of the patients, 94% were diagnosed with schizophrenia, 3% with schizoaffective disorder, and 3% with delusional and other psychotic disorders (reported by 55 articles). Other variables, such as level of symptoms, dosage of antipsychotic medication, percentage of patients on typical versus atypical medication, and number of prior psychotic episodes, may be relevant for the association between symptoms and cognition but were reported by too few studies. A table with all data points is not reported due to space constraints.

Table 2. Studies Included in the Meta-Analysis and Its Descriptive Variables

	<i>n</i>	Men (%)	Age (years)	Education (years)	Chronicity of illness	In-patients (%)	SF	SA	Del & others	Clinical scale	IQ Scale
J. Addington & Addington (1997)	59	67.8	33	11.5	10.5	100	100	0	0	PANSS	
J. Addington & Addington (1999)	80	67.5	36	12		100	100	0	0	PANSS	
J. Addington et al. (1991)	38	65.8	30.9	11.5		100	100	0	0	SANS	WAIS
Basso et al. (1998)	62	72.6	32.26	13.68	9.82	14.51	100	0	0	SANS/SAPS	WAIS
Baxter & Liddle (1998)	55	71.4	37.8		16.6	100	100	0	0	SSPI	NART/Quick t.
Bell, et al. (1994)	147	95.2	42	12		18.4	67.3	32.6	0	PANSS	Slosson
Bell & Mishara (2006)	267	87	43.1	12.9	20.5	0			0	PANSS	WAIS
Berman et al. (1997)	30	96.66	50.6	12.3		100	100	0	0	PANSS	WAIS
Bozikas et al. (2004)	56	71	37.45	10.37	10.31	0	100	0	0	PANSS	
Braff et al. (1991)	40	75	29.7	13.3		0	100	0	0	SANS/SAPS	WAIS
Brebion et al. (1997)	31	74	35.3	12.1	12.3	100	100	0	0	PANSS	
Brekke et al. (1995)	40	62.5	33.2	12.5		0	57.5	42.5	0	BPRS/CAF	
Bryson et al. (1999)	120	95.8	43.46	12.57		0	78.33	21.7	0	PANSS	WAIS-R
Cameron et al. (2002)	52	76.92	37.5		14.9	0	100	0	0	PANSS	NART
Chen et al. (1996)	176	59.8	40.5		15.1	100	100	0	0	HEN	WAIS
A. S. Cohen & Docherty (2004)	38	70	35.6	12.5		0	100	0	0	BPRS	SILS
A. S. Cohen & Docherty (2005)	76	61.64	36	12.4		0	100	0	0	SAPS	SILS
R. M. Cohen et al. (1998)	13	100	32.6		13.2	100	100	0	0	SANS	
Collins et al. (1997)	58	77.58	34.1	12.47	14.24	0	100	0	0	PANSS/CDS	
Donohoe et al. (2006)	32	66			15.63	0	100	0	0	PANSS	NART
Eckman & Shean (2000)	51	62.74	40.9	11.1		100	100	0	0	SANS/SAPS	
Ehmann et al. (2004)	37	86.48	30	11.24		100	75.67	24.32	0	PANSS	WAIS-R
Franke et al. (1992)	73	63.01	32.5	9.9	4.8	100	100	0	0	SANS/SAPS	
Guillem et al. (2001)	27	59.25	38.1				100	0	0	SAPS/SANS	

	<i>n</i>	Men (%)	Age (years)	Education (years)	Chronicity of illness	In-patients (%)	SF	SA	Del & others	Clinical scale	IQ Scale
Hammer (1995)	65	87.69	28.28			100	100	0	0	SANS/PSE	WAIS-R
Heydebrand et al. (2004)	307	75.89	25				53.42	9.44	37.13	PANSS	
Himelhoch et al. (1996)	47	75	29.4	13.3	7.44	100	100	0	0	SANS/BRPS	
Holthausen et al. (1999)	50	68	25				64	0	36	PANSS	
Ihara et al. (2003)	43	51.16	44.2	12.46	15.25		100	0	0	PANSS	NART
Ito et al. (1997)	49	61.2	40.9	11.6	17	97.75	100	0	0	BPRS	
Keefe et al. (2006)	1,332	74	40.56	12.1	14.43		100	0	0	PANSS	
Krishnadas et al. (2007)	25	64	40.16	9.08	11.32	0	100	0	0	SANS/HRSD	
Less-Roitman et al. (1997)	30	100	43.13	12.25	20.55		100	0	0	BPRS	WAIS
Liddle & Morris (1991)	40	65.11	51.9		28.9	100	100	0	0	SANS/Manchester	
Lucas et al. (2004)	53		19.1	10.8			77	2	21	PANSS/CDS	WAIS-III
Mahurin et al. (2006)	84	90			12.8	100	100	0	0	BPRS	
Minzenberg et al. (2003)	57	74	40.2	13.2	19.6	0	100	0	0	PANSS/CASH	WAIS-R
Moritz, Andresen et al. (2001)	47	66	31.8	11	6.7	100	100	0	0	PANADSS	
Moritz, Heeren et al. (2001)	25	64	30.8	11.1	6.5		100	0	0	PANADSS	
Nelson et al. (1990)	46	78.3				100	100	0	0	Manchester	
Norman et al. (1997)	87	65.5	33.3		5.9		100	0	0	SANS/SAPS	
Nuechterlein et al. (1986)	40	85	22.3	12.3		100			0	BPRS	
O'Leary et al. (2000)	126	67.2	31.2	13.1	10.5	100	100	0	0	SANS/SAPS	WAIS-R
Pandurang (1994)	41	73	30.2	12.34		100	100	0	0	CASH	
Perry & Braff (1998)	71	60.6	34.2	12.3	12.9	81.7	100	0	0	SANS/SAPS	
Ragland et al. (1996)	30	56.7	31		9.3		100	0	0	BPRS/SANS/SAPS	
Rocca et al. (2005)	78	59	36.1		11.6	0	100	0	0	PANSS/CDS	
Rocca et al. (2006)	70	66	40.8		15.5	0	100	0	0	SANS/SAPS	
Rosse (1993)	27	96.3	38.5		14.8		100	0	0	SANS	

	<i>n</i>	Men (%)	Age (years)	Education (years)	Chronicity of illness	In-patients (%)	SF	SA	Del & others	Clinical scale	IQ Scale
Rund et al. (2004)	207	58	28.1	12			27.05	12.56	60.39	PANSS	WAIS-R
Sanfilipo et al. (2002)	47	100	38.8	13.1	15.2	40.32	100	0	0	BPRS/SANS	
Simon et al. (2003)	38	60.53	24				100	0	0	PANSS/CDS	NART
Strauss et al. (1993)	50	76	34	12.5	12.5	0	90	10	0	BPRS/TLC	WAIS-R
Tandon et al. (2000)	19	63.33	29	12.8	8	100	100	0	0	BPRS/SANS	WAIS-R
Torres et al. (2004)	107	68.22	30.9	13.2	9		100	0	0	SANS/SAPS	WAIS-R
Voruganti et al. (1997)	52	65.07	32.4		9.2	0	100	0	0	PANSS	
Woodward et al. (2003)	36	75	35.6	12.8	10.22	100	100	0	0	SSPI	K-BIT
Woodward et al. (2004)	68	70.58	35.84	12.31	9.92	100			0	SSPI	NART

Note. Data for age, education, and chronicity are in mean years. SF = percentage of subjects diagnosed with schizophrenia in the sample; SA: percentage of subjects diagnosed with schizoaffective disorder in the sample; Del & others: percentage of subjects diagnosed with delusional disorders and other nonaffective disorders in the sample; PANSS = Positive and Negative Syndrome Scale (Kay et al., 1987); SANS = Scale for the Assessment of Negative Symptoms (Andreasen, 1981); SAPS = Scale for the Assessment of Positive Symptoms (Andreasen, 1984); SSPI = Symptoms and Signs of Psychotic Illness (Liddle, 1992); BPRS = Brief Psychiatry Rating Scale (Overall & Gorham, 1962); CAF = Community Adjustment Form (Test et al., 1991); HEN = High Royds Evaluation of Negativity Scale (Morimer et al., 1989); CDS = Calgary Depression Scale (D. Addington et al., 1990); PSE = Present State Examination (Wing et al., 1974); HRSD = Hamilton Rating Scale for Depression (Hamilton, 1960); Manchester = Manchester Scale (Krawiecka et al., 1977); CASH = Comprehensive Assessment of Symptoms and History (Andreasen, 1987); PANADSS = Positive and Negative and Disorganized Symptoms Scale for Schizophrenia (Andresen & Moritz, 2000); TLC = Scale for the Assessment of Thought, Language, and Communication (Andreasen, 1979); WAIS = Wechsler Adult Intelligence Scale (Wechsler, 1955); NART = National Adult Reading Test (Nelson & O'Connell, 1978); Slosson = Slosson Intelligence Test (Slosson, 1963); WAIS-R = Wechsler Adult Intelligence Scale—Revised (Wechsler, 1987); SILS = Shipley Institute of Living Scale (Zachary, 1986); WAIS-III = Wechsler Adult Intelligence Scale—Third Edition (Wechsler, 1997); K-BIT = Kaufman Brief Intelligence Test (Kaufman & Kaufman, 1990).

Meta-analyses of Correlations between Cognitive Domains and Psychosis Dimensions

Results for the meta-analyses are shown in Table 3 (for visual representation, see Figure 1). Both the negative and the disorganized dimensions were significantly and negatively correlated with the majority of the nine cognitive domains, with averaged correlations in the order of -.29 to -.12. The largest effect sizes (estimated correlation higher than -.2) were for verbal fluency, verbal learning and memory, and IQ in the negative dimension and for attention/vigilance, visual learning and memory, and IQ in the disorganized domain. The correlations with the positive dimension were neither large nor significant, except for a negative correlation with the domain of speed of processing ($\hat{\mu}_p = -.089$; 95% CI = -.164, -.012), which indicated that worse performance was associated with a higher level of symptoms. For the analysis of the depressive dimension, none of the correlations were either large or significant; however, five or more observations were available for only three cognitive domains.

Figure 1. Meta-analyses of Correlation Coefficients between Four Psychosis Dimensions and Nine Neurocognitive Domains in Nonaffective psychosis.

Note: Boldface values indicate associations between psychosis dimensions and neurocognitive domains for which the correlation was statistically significant. CI = 95% confidence interval.

Table 3. Four x Nine Meta-analyses of Correlation Coefficients Between Psychosis Dimensions and Neurocognitive Domains

Cognitive domain		Positive	Negative	Disorganized	Depressive
IQ	k	10	13	6	1
	$\hat{\mu}_\rho$	0.024	-0.244	-0.205	
	CI	-0.063, 0.111	-0.333, -0.151	-0.327, -0.076	
	p	0.591	0	0.002	
	I ²	26	52	45	
Reasoning and problem solving	k	27	33	15	6
	$\hat{\mu}_\rho$	-0.013	-0.14	-0.197	0.074
	CI	-0.066, 0.041	-0.197, -0.081	-0.336, -0.048	-0.024, 0.171
	p	0.639	0	0.009	0.137
	I ²	37	58	81	0
Executive control	k	9	10	7	3
	$\hat{\mu}_\rho$	0.082	-0.131	-0.089	0.059
	CI	-0.017, 0.179	-0.265, 0.008	-0.202, -0.026	-0.264, 0.369
	p	0.103	0.063	0.130	0.725
	I ²	6	56	20	73
Verbal fluency	k	20	23	13	4
	$\hat{\mu}_\rho$	-0.035	-0.291	-0.092	-0.056
	CI	-0.101, 0.031	-0.356, -0.224	-0.208, 0.027	-0.199, 0.089
	p	0.292	0	0.128	0.446
	I ²	17	42	61	0
Speed of processing	k	20	23	13	5
	$\hat{\mu}_\rho$	-0.089	-0.167	-0.171	-0.097
	CI	-0.164, -0.012	-0.241, -0.09	-0.275, -0.062	-0.256, 0.068
	p	0.023	0	0.002	0.250
	I ²	46	53	56	46
Attention/vigilance	k	11	15	6	2
	$\hat{\mu}_\rho$	-0.012	-0.134	-0.277	0.154
	CI	-0.054, 0.03	-0.191, -0.076	-0.392, -0.154	-0.023, 0.257
	p	0.969	0	0	0.087
	I ²	0	26	34	0
Verbal working memory	k	9	10	5	3
	$\hat{\mu}_\rho$	-0.013	-0.07	-0.117	-0.113
	CI	-0.144, 0.118	-0.174, 0.036	-0.247, 0.018	-0.303, 0.085
	p	0.843	0.194	0.09	0.263
	I ²	37	19	0	5
Verbal learning & memory	k	17	20	13	3
	$\hat{\mu}_\rho$	-0.021	-0.214	-0.169	0.126
	CI	-0.096, 0.054	-0.279, -0.146	-0.27, -0.064	-0.035, 0.281
	p	0.578	0	0.001	0.123
	I ²	47	54	59	0
Visual learning & memory	k	9	13	6	3
	$\hat{\mu}_\rho$	-0.005	-0.126	-0.206	0.029
	CI	-0.089, 0.079	-0.202, -0.047	-0.331, -0.074	-0.147, 0.203
	p	0.91	0.001	0.002	0.749
	I ²	0	29	42	0

Note: Boldface values indicate associations between psychosis dimensions and neurocognitive domains for which the correlation was statistically significant. CI = 95% confidence interval.

Regression Test for Funnel Plot Asymmetry

None of the regression tests for funnel plot asymmetry were significant for the 36 pairs of psychosis dimensions and cognitive domains, except for the combination of depressive dimension and visual learning and memory ($p = .014$). However, only three observations were included in this analysis, so this result should be treated with some reservation. The funnel plots for each symptom dimension combine all cognitive domains are shown in Figure 2. None of the regression tests for asymmetry were significant for these four plots ($ps = .145-.927$).

Effect of Moderator Variables

Substantial heterogeneity was found in the correlations between psychosis dimensions and cognitive domains. However, none of the three variables included as possible moderators could account for the observed heterogeneity. The effect of gender on the average correlation was not significant for any of the meta-analyses (all $\hat{\beta}$ values between -.037 and .017, all ps between .054 and .996). Likewise, age did not influence the strength of the associations between the cognitive domains and symptom dimensions (all $\hat{\beta}$ values between -.288 and .020, all ps between .127 and .983), except for the association of the depressive dimension and speed of processing ($\hat{\beta}=.020$, ps = .047), the strength of which became weaker with increases in the average age of the sample. Heterogeneity in the correlations between cognitive domains and symptom dimensions could not be attributed to differences in the chronicity of the illness (all $\hat{\beta}$ values between -.049 and .150, all ps between .055 and .977), except for the association of the disorganized dimension and IQ ($\hat{\beta}=.037$, ps = .022), the strength of which became weaker with increases in the average duration of the illness. However, these two findings are inconsistent with the general pattern of results and may constitute Type I errors. Finally, inclusion of symptoms of disorganization in the positive subscale led to a stronger correlation only with respect to IQ ($\hat{\beta}=-.157$, ps = .033; all other $\hat{\beta}$ values between -.134 and .110, all other ps between .131 and .849). Again, this isolated result is not consistent with the findings for the other eight cognitive domains.

Differential Correlation Coefficients for Cognitive Impairment: Negative Versus. Disorganized Dimension

The negative dimension showed a significantly stronger correlation with verbal fluency (p = .005), whereas the disorganized dimension showed stronger correlations with reasoning and problem solving (p = .004) and attention/vigilance (p = .03). The correlation coefficients did not differ significantly between the two dimensions for the other six cognitive domains. The sensitivity analysis (i.e., assuming different values for the strength of the association between negative and disorganized symptoms) corroborated these results.

Sensitivity Analyses to Account for Sample Overlap

The sensitivity analysis (i.e., those excluding the smaller studies of each pair with an uncertain degree of overlap in the samples) corroborated all of the results in the three previous steps of the analyses.

Discussion

Findings

Psychopathological heterogeneity in nonaffective psychosis was weakly but differentially related to distinct patterns of neurocognitive function (Figure 1): negative and disorganized dimensions were modestly but meaningfully associated with impairment in the majority of neurocognitive domains. Associations were in the expected direction but smaller and nonsignificant for the domains of executive control and verbal working memory for both dimensions and for verbal fluency in relation to the disorganized dimension. Thus, cognitive impairment in psychosis (Aleman, Hijman, de Haan, & Kahn, 1999; Fioravanti et al., 2005; Heinrichs & Zakzanis, 1998; Johnson Selfridge & Zalewski, 2001; Lee & Park, 2005; Pelletier, Achim, Montoya, & Lal, & Lepage, 2005) does not appear to be entirely orthogonal to psychopathology. In addition, significantly higher correlations were found for the negative dimension in relation to verbal fluency and for the disorganized dimension in relation to reasoning and problem solving and to attention/vigilance. In contrast, positive and depressive dimensions were not consistently associated with the neurocognitive measures examined, with the exception of a significant correlation found for the positive dimension in relation to speed of processing.

The patterns of association for the four psychosis dimensions were stable across neurocognitive domains and were independent of age, gender and chronicity of illness. These findings in relation to the negative and positive symptoms agree with a more limited previous meta-analysis (Nieuwenstein et al., 2001), whereas the findings with regard to the disorganized dimension were in agreement with a meta-analysis that focused on formal thought disorder (Kerns & Berenbaum, 2002). The results further suggest that distinguishing multiple domains of cognitive functioning in schizophrenia is useful, even though the deficit is to a large extent generalized and may even be accounted for statistically by a single-factor model (as suggested by the CATIE trial, Keefe et al., 2006). Differential patterns of cognitive performance among the different psychopathological dimensions were found. These patterns may indicate some meaningful contrasts suggestive of differential latent cerebral mechanisms underlying the cluster of disorganized and negative symptoms on the one hand and that of positive and affective on the other.

Do Patterns of Psychopathology-Neurocognition Associations in Nonaffective Psychosis Match Evidence of Differential Underlying Patterns of Cerebral Dysfunction?

Functional brain imaging studies have demonstrated that different patterns of altered cerebral activity, possibly reflective of clinical heterogeneity, occur in schizophrenia. Early studies (Ebmeier et al., 1993; Heaton, 1985; Liddle, Friston,

Frith, & Frackowiak, 1992; Liddle, Friston, Frith, Hirsch et al., 1992; Nelson, 1976; Weinberger & Berman, 1988; Weinberger, Berman, & Illowsky, 1988; Weinberger, Berman, & Zec, 1986) have tended to concur on findings suggesting that (a) psychomotor poverty is associated with prefrontal cortex and parietal cortex underactivity, especially on the left, and with overactivity of the caudate nuclei bilaterally; (b) the disorganization syndrome is associated with decreased perfusion in the right ventral prefrontal cortex and contiguous insula and with increased perfusion in the right anterior cingulate; and (c) reality distortion is associated with overactivity in the left medial temporal lobe and left lateral frontal lobe and underactivity in the left lateral temporal lobe, adjacent parietal cortex, and posterior cingulate cortex. Later brain imaging studies in schizophrenia (Lawrie & Abukmeil, 1998; Lieberman et al., 2001) confirmed that negative (Andreasen, Paradiso, & O'Leary, 1998; Sanfilippo et al., 2000; Schroder et al., 1996) and disorganization symptoms (Crider, 1997; Liddle, Friston, Frith, Hirsch et al., 1992) are associated with alterations in frontal lobe functioning, whereas auditory hallucinations produced normal activation of the left prefrontal cortex but exhibited less activation of the left middle temporal gyrus and supplementary motor area (Lennox, Park, Medley, Morris, & Jones, 2000; McGuire et al., 1995; Shergill, Brammer, Williams, Murray, & McGuire, 2000; Shergill, Bullmore, Simmons, Murray, & McGuire, 2000). Recently, abnormal connectivity has been postulated as the central functional cerebral abnormality in schizophrenia (Josin & Liddle, 2001; Menon, Anagnoson, Glover, & Pfefferbaum, 2001). This possibility would indicate that the core abnormality may be a disruption of functional connectivity between frontal cortex and other cerebral sites that gives rise to distributed cortical and subcortical deficits that may be associated with differential behavioural expression, such as variation in symptom dimensions and cognition.

At the level of neurotransmission, different patterns involving several interconnected limbic, cortical and subcortical structures have been implicated in schizophrenia. The dopamine (DA) hypothesis has been extended to include both cortical and subcortical components. An overactivity in neurotransmission from DA cell bodies (D2 receptors), located in the ventral tegmental area of the midbrain, may result in the development of positive symptoms. A hypodopaminergic state in the prefrontal cortical terminal fields of the mesocortical DA neurons (D1 receptors) has been hypothesized to underly cognitive impairment and negative symptoms of schizophrenia and may in turn contribute to the disinhibition of subcortical DA function (Duncan, Sheitman, & Lieberman, 1999; Kellendonk et al., 2006). Moreover, alterations in prefrontal connectivity involving glutamate transmission at N-methyl-D-aspartate (NMDA) receptors has been proposed. This hypothesis suggests that the DA imbalance in schizophrenia (striatal excess and cortical deficiency) may be secondary to NMDA hypofunction in the prefrontal cortex and its connections (Laruelle, Kegeles, & Abi-Dargham, 2003).

Negative and Disorganized Dimensions Versus Positive and Affective Dimensions: Does Clinical Research Suggest Two Pathways in Psychosis?

There is evidence that intermediary phenotypes associated with genetic risk of psychosis may fall into two broad groups: one associated with cognitive impairment and negative and disorganized symptom dimensions and one associated with altered sensitivity to stress expressed as increased levels of affective and positive psychotic symptoms following exposure to small stressors in the flow of daily life (Myin-Germeys & van Os, 2007). Thus, increased emotional reactivity correlates negatively with cognitive impairment in patients with schizophrenia (Myin-Germeys et al., 2002). The two intermediary phenotypes of stress sensitivity and cognitive impairments may therefore constitute separate and even mutually exclusive pathways to psychosis associated with partly different expression of psychopathology.

Another area of research that may help understand the pathways of differential expression of psychopathology is social cognition (Blakemore & Frith, 2004; Freeman, Garety, & Kuipers, 2001; Frith, 2004; Kuipers et al., 2006). Positive psychotic symptomatology has been associated with impaired social cognition, such as alterations in self-monitoring (Bentall, 1990; Johns et al., 2001), a probabilistic reasoning bias referred to as jumping-to-conclusions (Garety & Freeman, 1999; Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001; van Dael et al., 2006), and mentalizing deficits (Versmissen et al., 2007). Where examined, research suggests that the association between altered social cognition and symptoms is weakest for the negative and disorganization dimensions (van Dael et al., 2006). These observations tend to agree with our finding that positive and affective symptoms were not associated with neurocognition, whereas negative and disorganized dimensions were. Recent analyses support this view and show that, in patient samples, alterations in social cognition are largely independent of measures of neurocognition (van Hooren et al., submitted).

Conclusion: Different Underlying Pathophysiological Processes Associated with Different Intermediary Phenotypes May Account for a Substantial Part of Psychopathological Heterogeneity in Nonaffective Psychosis

Findings at different levels of neuroscientific and neurocognitive research have suggested some evidence of meaningful contrasts in the underlying patterns of cerebral dysfunction in relation to the psychopathological heterogeneity of psychosis. Neuroimaging, neuropharmacological and neurocognitive findings concur in that weak but systematic patterns of associations are found with dimensions of psychopathology. These associations fit in the simplistic but heuristically useful two-pathway model of psychosis, in which the exophenotypes of negative and disorganized symptoms are associated with the intermediary

phenotype of neurocognitive impairment and the positive and affective dimensions are not. This reduction may explain at least some of the psychopathological heterogeneity in nonaffective psychosis and may be refined in future studies, to the extent that they become nosologically useful.

Methodological issues

First, four rather than five psychosis dimensions were analyzed, although evidence suggests that a five-factor solution that includes a manic symptom dimension may yield a better fit (Dikeos et al., 2006; Grube et al., 1998; Lindenmayer et al., 1995; McGorry et al., 1998; Serretti, De Ronchi, Lorenzi, & Berardi, 2004; Serretti et al., 2001). However, because only four studies reported the manic/excitement dimension, there were too few data for an informative synthesis. Second, only non-affective psychotic disorder was considered in the inclusion criteria for study selection. The reason for this was that although rather similar patterns of cognitive impairment have been found in the affective domain of psychosis (Fioravanti et al., 2005; Krabbendam, Arts, van Os, & Aleman, 2005) and rather similar psychopathological dimensions have been identified in affective and nonaffective psychosis (Peralta et al., *Biol Psychiatry*, 1997), associations between psychopathological dimensions and neurocognition have been examined to only a substantial degree in nonaffective psychotic disorders. Third, some of the included cognitive tests may vary in terms of sensitivity, and this variance may be problematic in view of the generalized cognitive deficit in schizophrenia (Chapman & Chapman, 1978). That is, the difference between performance of patients with schizophrenia and healthy controls will be greater for tasks with higher reliability and variance, regardless of differences in true ability. Such variation may result in different likelihoods of correlating with other parameters, such as symptom dimensions. This problem can be solved only by using tasks that are matched on the relevant psychometric characteristics. This is a limitation that should be acknowledged by each systematic review that summarizes and combines different cognitive tests. Fourth, because all subjects in the selected studies were younger than 51.9 years of age, no conclusions can be made regarding the impact of aging for each psychopathology dimension-cognition combination. Fifth, many other moderator variables may be of relevance; however, due to underreporting, they could not be examined in more detail (e.g., clinical scales scores, pharmacological treatment, previous history of symptoms, genetic vulnerability, hemisphere correlation, and comorbidity). Sixth, exclusion of a number of studies was necessary because of incomplete information, resulting in sample restriction.

Author note

Preparation of this article was supported by grants and financial support: Maria de Gracia Dominguez, Marie Curie Early Stage Research Training Fellowship of the European Community's Sixth Framework Program under contract number "MEST-CT-2005-020589"; Jim van Os, research support by Eli Lilly, GSK, Organon, BMS, AstraZeneca, and speaker support by Eli Lilly, BMS, Lundbeck, Organon, Janssen-Cilag and AstraZeneca; Lydia Krabbendam, VIDI-grant from the Netherlands Organization for Scientific Research (NWO).

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CHAPTER 3

EVIDENCE THAT ONSET OF CLINICAL PSYCHOSIS IS AN OUTCOME OF PROGRESSIVELY MORE PERSISTENT SUBCLINICAL PSYCHOTIC EXPERIENCES: AN 8-YEAR COHORT STUDY

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Abstract***Objective***

This study examined the hypothesis that developmental expression of psychometric risk in the form of subclinical psychotic experiences in the general population is usually transitory, but in some instances may become abnormally persistent and progress to a clinical psychotic state.

Method

A prospective cohort study was conducted in a general population sample of 845 adolescents, aged 14-17 years, in Munich, Germany (Early Developmental Stages of Psychopathology Study). Expression of psychosis was assessed four times (T0-T3) over a period of 8.4 years. Transition from subclinical psychosis at T0-T2 to clinical psychosis in terms of impairment at T3 was examined as a function of the level of prior persistence of subclinical psychosis (present never, once, twice or thrice).

Results

The more subclinical psychosis persisted over the period T0-T2, the greater the risk of transition to clinical psychosis at T3 in a dose-response fashion (subclinical psychosis expression once over T0-T2: OR=1.5 (95%CI: 0.6-3.7), post-test probability (PP)= 5%; twice: OR=5.0 (95%CI: 1.6-15.9), PP=16%; at all three measurements: OR=9.9 (95%CI: 2.5-39.8), PP=27%). Of all clinical psychosis at T3, more than a third (38.3%) was preceded by subclinical psychotic experiences at least once and a fifth (19.6%) at least twice.

Conclusions

Consequently, a significant proportion of psychotic disorder may be conceptualized as the rare poor outcome of a common developmental phenotype characterised by persistence of psychometrically detectable subclinical psychotic experiences. This may be summarized descriptively as a psychosis proneness-persistence-impairment model of psychotic disorder.

Key words

Epidemiology, General Population, Psychosis Onset, Adolescence, Transition to Clinical Relevance, Subclinical Psychosis.

Introduction

Psychosis is commonly considered a rare phenomenon outside the range of normal human experience, giving rise to significant disability. However, the type of distribution expected for disorders of multifactorial interactive aetiologies is continuous (Johns & van Os, 2001; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009) and many mental disorders have accordingly been shown to exist along a spectrum including subclinical expressions, evidenced by, eg, relatively high rates of expression of bipolar spectrum symptoms, subthreshold depressive states and social restriction associated with autism (Akiskal & Vazquez, 2006; Angst & Cassano, 2005; Constantino & Todd, 2003; Judd & Akiskal, 2003).

Similar findings have been reported for psychosis (Johns & van Os, 2001). The clinical psychosis phenotype has not only been shown to be much less rare than previously thought (Perala et al., 2007) but is also thought to be expressed at levels well below its clinical manifestation (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Stefanis et al., 2002; van Os, Hanssen, Bijl, & Ravelli, 2000; Yung et al., 2003). Apart from strong evidence of phenomenological continuity in form and structure (Johns & van Os, 2001), continuity between clinical and subclinical phenotypes is further suggested by: (i) similar associations with demographic factors, in particular the negative association with age and the positive association with single marital status and social disadvantage (Johns & van Os, 2001; Peters, Joseph, & Garety, 1999; van Os et al., 2000; Verdoux et al., 1998), (ii) transitions over time from the subclinical to the clinical (Chapman et al., 1994; M. Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005; Poulton et al., 2000), (iii) familial co-clustering of the clinical and the subclinical (Kendler & Diehl, 1993), (iv) strong dose-response effects of the urban environment on both phenotypes (Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2006), (v) sharing of cognitive and motor deficits (Krabbendam, Myin-Germeys, Hanssen, & van Os, 2005; Voglmaier et al., 2000), (vi) sharing of risk genes (Stefanis et al., 2004) and of environmental risk factors such as cannabis (Fergusson, Horwood, & Swain-Campbell, 2003).

Many questions remain, however, with regard to the hypothesized continuity over time from subclinical to clinical psychotic states. The seminal study by Poulton and colleagues demonstrated that more than 25% of participants with low grade psychotic experiences at age 11 years developed a clinical psychotic disorder by age 26 years (Poulton et al., 2000). However, an equally important conclusion of the study was that the great majority of children with expression of psychotic experiences would never develop a psychotic disorder –psychosis was only a transitory developmental state for most. Similar conclusions were reached by other, less lengthy follow-up studies in adult population cohorts, with transition rates of around 10% (Chapman et al., 1994; M. Hanssen et al., 2005). Cougnard et al (2007)

recently suggested that one of the reasons why most developmental expression of psychosis remains transitory is that exposure to additional environmental risks over development, such as cannabis use, childhood trauma and urban environment (Cougnard et al., 2007), is necessary in order for subclinical psychosis to first become persistent and, second, to deteriorate into a clinical psychotic state (Figure 1). However, to date, no evidence has been presented suggesting that abnormal persistence of a common and normally transitory developmental subclinical psychosis phenotype is the precursor state of clinical deterioration.

In the current paper, it was examined whether subclinical psychotic experiences with a greater tendency to persist over time would have a greater probability to become clinically relevant in terms of dysfunction and need for care (impairment). The hypothesis of greater persistence resulting in greater probability of transition from subclinical to clinical psychosis characterised by impairment was tested using a prospective, observational study in a large, general population sample of adolescents followed over a period of more than 8 years.

Figure 1. Study Design

Note. The study hypothesis was that level of persistence of subclinical psychosis (T0-T2 psychosis persistence) over a period of 3.5 y, that previous work showed is associated with exposure to environmental risk factors (Cougnard et al., 2007), impacts on the risk of transition to T3 psychotic impairment approximately 5 y later. Psychosis persistence (defined as presence of the 10% highest score of psychotic experiences of the symptom check list-psychosis subscale): never, sporadic (once), recurrent (twice), persistent (thrice) over the period T0-T2. Psychotic impairment: a variable scored “0” in subjects with psychotic experiences who scored “0” on both help seeking and dysfunction associated with the symptom and “1” in subjects scoring “1” on either or both of help seeking and dysfunction.

Method

Sample

Data came from the Early Developmental Stages of Psychopathology (EDSP) Study, which collected data on the prevalence, incidence, risk factors, comorbidity and course of mental disorders in a random, representative population sample of adolescents and young adults in the general population. The baseline sample, following ethics committee approval, was randomly drawn, in 1994, from the respective population registry offices of Munich and its 29 counties, to mirror the distribution of individuals expected to be 14-24 years of age at the time of the baseline (T0) interview in 1995. The base population were all those born between June 1, 1970 and May 31, 1981, registered as residents in these localities and having German citizenship. These registers can be regarded as highly accurate because (1) each German is registered by his town, (2) they are regularly updated, (3) in the interest of scientific studies, any number of randomly drawn addresses with a given sex and age-group can be obtained, and (4) strict enforcement of registration by law and the police applies. More details on the sampling, representativeness, instruments, procedures and statistical methods of the EDSP Study sample have previously been presented (Lieb, Isensee, von Sydow, & Wittchen, 2000; Wittchen, Perkonig, Lachner, & Nelson, 1998).

Study Design

The overall design of this cohort study is longitudinal and prospective, consisting of a baseline (T0) and 3 follow-up surveys, covering a time period of on average 1.6 years (T0-T1, $SD=0.2$), 3.5 years (T0-T2, $SD=0.3$) and 8.4 years (T0-T3, range 7.3-10.5 years, $SD=0.7$).

Because the primary goal of the study was to examine the incidence and developmental risk factors for psychopathology, the younger group (14-15 y), presumed to have the highest incidence density, were sampled at twice the rate of persons aged 16-21 years, and the oldest group (22-24 y) was sampled at half this rate. For the same reason, subjects aged 14-17 years at baseline were examined at the 4 time points, and subjects aged 18-24 years were assessed only 3 times.

The present study is based on a subset of EDSP Study respondents, namely, the younger cohort (aged 14-17 y at baseline) only (T0, $n=1395$, response rate:75%), thus ensuring an adolescent population at risk of developing psychotic experiences and subsequent transition to clinically relevant psychotic states over 4 assessment periods. Response rates for the younger cohort were respectively 88% at T1 ($n=1228$), 83% at T2 ($n=1169$) and 73% at T3 ($n=1022$). After description of the study to the subjects, written informed consent was obtained.

Instruments

The Self-report Symptom Checklist-90-R

At all time points, participants completed the self-report *Symptom Checklist-90-R* (SCL-90-R), a comprehensive self-report symptom inventory, multidimensional in nature, and oriented to screen for a broad range of psychological problems and psychopathology in community respondents and respondents with somatic and psychiatric disorders. It contains 90 items, scored on a 5-point severity scale, measuring 9 primary symptom dimensions named ‘somatization’, ‘obsessive-compulsive’, ‘interpersonal sensitivity’, ‘depression’, ‘anxiety’, ‘hostility’, ‘phobic anxiety’, ‘paranoid ideation’ and ‘psychoticism’. Reliability and validity of the SCL-90-R were established previously (Derogatis & Cleary, 1977). The time frame is the past 2 weeks.

The Munich-Composite International Diagnostic Interview

Participants were also assessed using the computerized version of the *Munich-Composite International Diagnostic Interview* (DIA-X/M-CIDI) (Wittchen & Pfister, 1997), an updated version of the World Health Organization’s CIDI version 1.2 (World Health Organization, 1990). The DIA-X/M-CIDI is a comprehensive, fully standardized diagnostic interview and assesses symptoms, syndromes, and diagnoses of various mental disorders in accordance with the definitions and criteria of the *International Classification of Diseases*, Tenth Revision, and *Diagnostic and Statistical Manual of Mental Disorders* (Fourth edition), along with information about onset, duration, severity of symptoms, and psychosocial impairment. The CIDI has been primarily designed for use in epidemiological studies of mental disorders and can also be used for clinical purposes. It is divided into 16 sections: 1 sociodemographic section, 12 sections assessing 288 symptoms of groups of mental disorders (including ‘somatoform and dissociative’, ‘phobic and other anxiety’, ‘depressive and dysthymic’, ‘manic and bipolar affective’, ‘schizophrenia and other psychotic’, ‘eating’, ‘dementia and other cognitive’, ‘post-traumatic stress’, as well as ‘tobacco’, ‘alcohol’, and ‘substance-related’ disorders), and 3 final sections containing concluding questions, interviewer observations and interviewer ratings.

The instrument, designed for use by trained interviewers who are not clinicians, has shown high interrater ($k > 0.70$) (Cottler, Helzer, Mager, Spitznagel, & Compton, 1991; Wittchen et al., 1991) and test-retest reliability (Reed, Gander, & Pfister, 1998; Wittchen, 1994). However, the assessment of psychosis with CIDI by lay interviewers is not considered reliable (Anthony et al., 1985; Wittchen, 1994). Therefore, in the EDSP Study, trained and experienced clinical interviewers at the level of psychologist, who were allowed to probe with follow-up clinical questions, conducted the interviews in the respondents’ homes.

At baseline, the DIA-X/M-CIDI lifetime version was used. At each of the follow-up assessments, participants applied the interval version, which covers the period of assessment from the last interview until the next. However, data on the G-section concerning psychosis and its clinical relevance were only collected at time point 2 (lifetime version) and time point 3 (interval version).

Construction of SCL-Psychosis Subscale

The 2 symptoms dimensions relevant for psychosis of the SCL-90-R, the so-called paranoid ideation and psychoticism subscales, were used to assess persistence of psychotic experiences over the period T0-T3. The 2 scales include self-reports on psychotic experiences which can be regarded, if not as clear-cut psychotic symptoms, as a subclinical expression of psychotic experiences. The 6-item paranoid ideation subscale represents paranoid behavior fundamentally as a disordered mode of thinking, including the cardinal characteristics of projective thought, hostility, suspiciousness, grandiosity, centrality and fear of loss of autonomy (items 8, 18, 43, 68, 76, and 83). The 10-item psychoticism subscale was developed in a fashion to represent the construct as a continuous dimension of human experience, including items indicative of a withdrawn, isolated, schizoid lifestyle, and first-rank symptoms of schizophrenia, such as hallucinations and thought broadcasting (items 7, 16, 35, 68, 77, 84, 85, 87, 88, and 90). The severity scale of each symptom was scored from ‘not-at-all’ (0) to ‘extremely’ (4). The psychoticism and paranoia scales are strongly correlated (in the current sample, mean correlation over T0-T3 was .7) and the items in the scales have high predictive validity for future deficiency in social achievement and functioning (Rossler et al., 2007).

Therefore, conform previous research in this sample (Henquet et al., 2005; Spauwen et al., 2006), psychoticism and paranoia ideation subscales were combined into one Psychosis scale (hereafter: ‘SCL-psychosis subscale’) by summing their scores. The resulting SCL-psychosis subscale thus was a continuous score displaying a half-normal distribution at all time points (T0-T3). Previous research has shown that instruments assessing psychotic experiences dimensionally typically display a half-normal distribution (van Os et al., 2009).

Assessment of Persistence of Psychotic Experiences over the Period T0-T2

In order to examine the hypothesis relating to persistence over time, a discrete variable indicating presence or absence of psychosis across interview waves was, per definition, necessary. For the purpose of the analyses, a dichotomous psychosis variable was created using a cutoff point to define the group of individuals with the highest 10% of scores of the SCL-psychosis subscale (hereafter: ‘psychosis expression’), consistent with previous analyses in this sample (Cougnaud et al.,

2007; Henquet et al., 2005) and congruent with the meta-analytic rate for the prevalence of psychotic symptoms in the general population (van Os et al., 2009). Nevertheless, as a 10% cutoff remains arbitrary, sensitivity analyses were conducted using more and less conservative cutoff point values of the highest 5% and the highest 15% of the SCL-psychosis subscale.

A variable was defined indicating the degree of persistence of psychotic experiences over the period T0-T2. This resulted in a summary score variable consisting of 4 levels of psychosis expression: never (0), once (sporadic) (1), twice (recurrent) (2), and thrice (persistent) (3). This variable will hereafter be referred to as ‘psychosis persistence’.

Assessment of Clinical Relevance of Psychotic Experiences at T2 and T3

Clinical relevance related to psychotic experiences was assessed by interview ratings from the DIA-X/M-CIDI in terms of psychotic impairment, representing the first step that needs explaining and predicting in tracking the ontogenesis of psychotic disorder in the general population. In order to define psychotic impairment, secondary dysfunction and help-seeking behavior was only examined in individuals with evidence of DIA-X/M-CIDI-positive psychotic symptoms at T2 (lifetime) and T3 (interval version).

Presence of positive psychotic experiences was broadly defined as any rating of “present” on any of the 20 DIA-X/M-CIDI core psychosis items (G1, G2a, G3-G5, G7-G13, G13b, G14, G17, G18, G20, G20C, G21, and G22a), including 14 delusion items, 5 hallucination items and 1 item on passivity phenomena. Items relate to classic psychotic symptoms involving, eg, persecution, thought interference, auditory hallucinations, and passivity phenomena. Participants were first invited by the psychologist to read a list of all the psychotic experiences and then asked whether they ever experienced such symptoms (list and phrasing available upon request). All these psychosis items were rated in 2 ways: absent (1) and present (5); all the psychosis DIA-X/M-CIDI items used in the present study were coded in a dichotomous manner without intermediate levels.

Help-seeking

Help-seeking behavior secondary to psychotic experiences was assessed using 3 DIA-X/M-CIDI items. Two psychosis section items were used: G16 (delusions) and G23 (hallucinations), which were phrased as follows: “Did you tell a doctor about ... (the psychosis section beliefs/experiences previously acknowledged by the participant along with a visual representation from the response booklet) you have had?” A third item from the concluding section was added (Q1DG); participants were shown a list on which several types of outpatient or inpatient institutions for

mental health problems were mentioned, ranging from general practitioner or school psychologist to psychiatric sheltered housing, and asked whether they had ever sought help at any of these institutions because of psychotic symptoms as elicited in the DIA-X/M-CIDI G section. The 3 items were rated in a dichotomous manner: no (1) and yes (5). Using these 3 help-seeking behavior items, a dichotomous variable ‘help-seeking’ was constructed, indicating a positive answer on any of the 3 questions (value label: 1) vs negative answers on all 3 questions (value label: 0).

Dysfunction

The dysfunction score of the psychosis DIA-X/M-CIDI section assessed the effect of the psychotic experiences on (1) feeling upset, unable to work, go to places, or enjoy oneself, at the time of having these experiences (item G28), (2) being less able to work since these experiences began (item G29), (3) being less able to make friends or enjoy social relationships since these experiences began (item G29a), and (4) how much their life and everyday activities were impaired when these experiences were at their worst (item G36). These 4 items were rated in a dichotomous manner: no (1) and yes (5). A dichotomous variable ‘dysfunction’ was dichotomously constructed, representing a positive answer on any of the 4 questions (value label: 1) vs negative answers on all 4 questions (value label: 0).

The Outcome Measure: Psychotic Impairment

Clinically relevant psychosis was finally defined in terms of ‘psychotic impairment’, a variable created as a combined outcome of help-seeking and dysfunction. This was rated as “0” in subjects with psychotic experiences who scored “0” on both help-seeking and dysfunction, and “1” in subjects scoring “1” on either or both of help-seeking and dysfunction.

Caseness

In order to validate the outcome measure Psychotic Impairment in terms of clinical relevance, the X16 DIA-X/M-CIDI item was used. This item, rating the interviewer’s opinion regarding clinical evidence of psychological ill health, consists of 4 levels: essentially not noticeable (0), not very noticeable (1), clearly ill (2), and very ill (3). The dichotomous variable ‘caseness’ was defined as any score above 1, thus indicating individuals with a noticeable level of psychiatric caseness.

Risk set

All the analyses were conducted in the younger cohort who (1) had been examined in the 4 waves of the study, (2) had completed the psychoticism and paranoia SCL-90-R subscales at T0-T3, and (3) had completed the DIA-X/M-CIDI psychosis G

section at T2 and T3 (n=845). Of the 1395 individuals in the younger cohort at baseline, 845 fulfilled the risk set criteria.

Of the 1022 participants belonging to the younger cohort that completed the 4 waves, 94 individuals did not complete the self-report SCL-90-R at T1, 65 at T2 and 13 at T3. In addition, the G section of the DIA-X/M-CIDI was not available for 5 participants at T2. This resulted in a risk set of 845 participants who were included in the analysis.

Thus, a risk set of 845 participants remained from the total number of 1395 participants that composed the younger cohort at baseline. Of the 550 individuals not included in the risk set (hereafter: 'non-included group'), the reason was loss-to-follow up over the 8-year period in 373 and partial non-response in 177.

Statistical Analyses

All analyses were conducted using the software package STATA, version 9.2 (Stata Corporation, College Station: TX, USA. 2006).

In order to examine representativeness, the risk set (n=845) was compared to the non-included group (n=550) in terms of sociodemographic characteristics such as age, gender, level of education, social status, and urban residence.

The focus of the study was on psychosis persistence in adolescents over a period of approximately 3.5 years (T0-T2), integrating the scores of 3 waves (T0, T1 and T2), and analyzing the influence of the degree of persistence on the onset of psychotic impairment at T3 (Figure 1). To this end, logistic regression analyses were performed to examine the associations between T0-T2 psychosis persistence on the one hand and T3 psychotic impairment on the other. Associations were expressed as odds ratios (ORs) and their 95% confidence intervals (CIs). In order to ensure that the analyses focussed on true new onsets of psychotic impairment at T3, any individual with psychotic impairment assessed lifetime at T2 was excluded.

In order to calculate posttest probabilities (PP) for T0-T2 psychosis persistence in relation to the T3 outcome of psychotic impairment, excluding any individual with lifetime T2 psychotic impairment, the STATA DIAGTEST procedure was used.

For both the logistic regression analyses and the calculation of PPs, a further check was introduced by additionally excluding individuals reporting at T2 that they had received any professional help for any psychological problem (DIA-X/M-CIDI Q1 item).

In addition, sensitivity analyses were conducted using more and less conservative cut-off point values of the highest 5% and the highest 15% of the SCL-psychosis subscale. Logistic regression was used to validate the T3 outcome measure psychosis impairment against the T3 caseness variable.

Results

Subject Characteristics

The average age of the risk set at T0 was 15.08 years (range: 14–17; SD=1.1). Of all participants, 444 were boys (52.5%) and 401 girls (47.5%). Other demographic characteristics are depicted in Table 1.

In comparison with the risk set (n=845), individuals from the nonincluded group (n=550) were of similar age (mean age=15.18 years), gender distribution (boys: 49.1%), or urban residence (69.1% vs 72% for included vs nonincluded, respectively). The nonincluded group had a lower level of education (included lower level: 9.7% vs nonincluded lower level: 28.6%; $\chi^2=100.41$, $p=.000$) and lower social status (included lower status: 3.4% vs nonincluded lower status: 6.6%; $\chi^2=12.36$, $p=.006$).

Occurrence of Psychotic Experiences

The mean score of the continuous SCL-psychosis subscale was 21.5 (SD=5.6) at T0, 19.5 (SD=4.9) at T1, 19.5 (SD=4.7) at T2, and 18.7 (SD=4.7) at T3. With the interview ratings of the DIA-X/M-CIDI, the lifetime prevalence of psychotic symptoms at T2 was 21.8% (n=184), and the interval cumulative incidence of psychotic symptoms at T3 was 12.7% (n=107).

The distribution of the SCL-90-R psychosis persistence variable over T0-T2 was: never: 78.9% (n=666), once (sporadic): 15.6% (n=132), twice (recurrent): 3.9% (n=33), and thrice (persistent): 1.7% (n=14). Of the 83 individuals with psychosis expression at T0, 32 (38.6%) again had psychosis expression at either T1 or T2. Of the 72 individuals with psychosis expression at T1, 29 (40.3%) had psychosis expression at T2. Based on the DIA-X/M-CIDI interview ratings, of the 184 (21.8%) individuals with any DIA-X/M-CIDI psychotic symptom at T2, 51 (27.7%) again had evidence of psychotic symptoms at DIA-X/M-CIDI interview at T3.

Table 1. Characteristics of Subjects at T0

T0 (n = 845)	n	%
Gender		
Male	444	52.5
Female	401	47.5
Level of education		
Low	82	9.7
Medium	223	26.4
High	540	63.9
Social status		
Lower	29	3.4
Middle	516	61.1
Upper	282	33.4
Other	18	2.1
Residence		
Rural	261	30.9
Urban	584	69.1

Note: Level of education: low (mandatory basic school or learning a profession), medium (high school) and high (high school preparing for university and university). The participants were asked which level of education they were attending or, in the case of discontinuation, which was the highest level they had attended (demographic section, item A3 of the Munich-Composite International Diagnostic Interview [DIA-X/M-CIDI]). Social status: lower (lower class, lower middle class), middle (middle middle class), upper (higher middle class, upper class), other (none of the above and missing values). The participants were asked to choose from specified options, which class he or she believed to be in (demographic section, item A16 of the DIA-X/M-CIDI). Residence: urban (the German city of Munich) and rural (the surrounding areas of Munich), obtained through population registries. The population density of the Munich surroundings areas was 553 persons per square mile and that of the city 4061 persons per square mile.

Occurrence of Psychotic Impairment

Of the 184 individuals with lifetime presence of DIA-X/M-CIDI psychotic symptoms at T2, 64 (34.8%) had evidence of psychotic impairment. Of the 107 individuals with interval presence of DIA-X/M-CIDI psychotic symptoms at T3, 45 (42.1%) had evidence of psychotic impairment.

Of the 64 individuals with psychotic impairment at T2, 11 (17.2%) had again evidence of psychotic impairment at T3.

Proportion of T3 Psychotic Impairment with Prior T0-T2 Psychosis Expression

In terms of attributable risk, of the 47 individuals who displayed T3 psychotic impairment, 18 (38.3%) had evidence of psychosis expression at any time point between T0-T2, of which 9 (19.6%) more than once.

Transition to T3 Psychotic Impairment

There was a strong association between T3 psychotic impairment and the T3 clinical caseness variable (OR=9.4, 95%CI: 3.1-28.6).

The absolute rate and relative risk of onset of T3 psychotic impairment as a function of the degree of T0-T2 psychosis persistence are depicted in Table 2. Excluding those with lifetime evidence of psychotic impairment at T2, the rates of T3 transition to psychotic impairment at the 4 levels of psychosis persistence (from 0 to 3) were 3.7% (n=23), 5.3% (n=6), 16.0% (n=4), and 27.3% (n=3), yielding ORs (levels 1-3 relative to 0) of 1.5 (95%CI: 0.6-3.7; p=.414), 5.0 (95%CI: 1.6-15.9; p=.006) and 9.9 (95%CI: 2.5-39.8; p=.001), respectively. Additional exclusion of those with T2 receipt of professional help for mental ill health similarly did not change these results (ORs of 1.1 [95%CI: 0.4-3.2; p=.893], 3.1 [95%CI: 0.7-14.0; p=.151] and 16.5 [95%CI: 3.7-73.6; p=.000], respectively).

Sensitivity analyses, using more and less conservative cutoff values for the SCL-psychosis subscale, showed the same pattern of increase in the rates of T3 transition to psychotic impairment. Thus, for the more conservative 5% cutoff, risk of transition increased from the sporadic (OR=2.8; 95%CI: 1.1-7.1) to the persistence level (OR=12.6; 95%CI: 1.1-143.2). For the less conservative 15% cutoff, risk for transition increased similarly from the sporadic (OR=1.6; 95%CI: 0.7-3.7) to the persistence level (OR=7.5; 95%CI: 2.3-24.8).

The PPs for T0-T2 psychosis persistence in relation to T3 psychotic impairment, excluding individuals with lifetime evidence of T2 psychotic impairment, increased progressively from the sporadic (PP:5.3%; CI: 3.7%-6.9%) to the persistence level (PP:27.3%; CI: 23.8%-30.7%) (Table 2). Predictive values were even higher when the risk set was additionally restricted to individuals with no T2 receipt of professional help for mental health problems (Table 2).

Table 2. Levels of T0-T2 Psychosis Persistence and Transition to T3 Psychotic Impairment

T0-T2 Psychosis Persistence		Transition to T3 Psychotic Impairment ^a				Transition to T3 Psychotic Impairment with additional exclusion ^b						
		Absolute rates		Relative Risk (Logistic regression)		Posttest probability	Absolute rates		Relative Risk (Logistic regression)		Posttest probability	
<i>n</i>	%	<i>n</i>	%	OR (CI)	<i>p</i>	PP (%) (CI)	<i>n</i>	%	OR (CI)	<i>p</i>	PP (%) (CI)	
Levels of Psychosis Persistence												
level 0; never	666	78.9	23	3.7	1 ^c	—	21	3.5	1 ^c	—	0 ^c	
level 1; once (sporadic)	132	15.6	6	5.3	1.5 (0.6–3.7)	0.414	4	3.8	1.1 (0.4–3.2)	0.893	3.8 (2.4–5.2)	
level 2; twice (recurrence)	33	3.9	4	16.0	5.0 (1.6–15.9)	0.006	2	10	3.1 (0.7–14.0)	0.151	10.0 (7.6–12.4)	
level 3; thrice (persistence)	14	1.7	3	27.3	9.9 (2.5–39.8)	0.001	3	37.5	16.5 (3.7–73.6)	0.000	37.5 (33.7–41.4)	
Total subjects	845	100	36	4.3	—	—	30	3.5	—	—	—	

Note. OR=odds ratio, CI=95% confidence interval, *p* = *p* value, PP = posttest probability

^aWith exclusion of those with lifetime psychotic impairment at T2

^bWith additional exclusion of individuals with T2 receipt professional help for mental ill-health (item Q1 of the Munich-Composite International Diagnostic Interview)

^cReference category

Discussion

Findings

This is the first study examining the influence of persistence of subclinical psychotic experiences in a sample of adolescents and young adults in the general population in relation to the transition to clinically relevant psychosis. The results showed, first, that subclinical psychosis was confirmed to be common (psychosis expression rates of 22%) and mostly transitory, recurrence or persistence occurring in 30-40% of cases. Second, the findings demonstrated that persistent positive symptoms at a subclinical level pose a significant risk and can be considered a marker of emerging clinical states. A dose-response relationship was found: the longer the period over which subclinical psychosis remained abnormally nontransitory, the greater the risk of developing associated impairment. Third, although most subclinical psychosis was transitory, these results showed that the impact of the relationship between the clinical and the subclinical was not negligible: Around two-fifths of new onset, clinically relevant psychosis in young adults could be traced to the subclinical psychosis phenotype expressed up to 8 years earlier, and one-fifth had displayed evidence of a recurrent or persistent subclinical phenotype. For some individuals, psychosis is thus the denouement of a long process of subclinical experiences and functional deficits. Consequently, these findings provide evidence for the continuity over time from subclinical persistent psychotic experiences to clinical psychotic states, yielding insight into the dynamics preceding the clinical onset of psychotic disorder from a population perspective.

Persistence of Subclinical Psychosis Expression

The recurrence-persistence rate of subclinical psychosis in this study was higher than reported in previous population-based studies. In a 2-year follow-up of a general population sample aged 18-64 years, Hanssen et al (M. Hanssen et al., 2005) found a 2-year 8% persistence rate of baseline subclinical psychosis, and an 8% transition rate from subclinical to clinical psychosis. In the present study, the recurrence-persistence rate was 30-40% over time, considerably higher. The most likely factor to explain this difference is the much younger age of the current sample. Given the rapid decline of psychosis expression with age (Peters et al., 1999; van Os et al., 2000; Verdoux et al., 1998), continuity over time will become less likely with advancing age. Thus, in a previous follow-up study of adolescents, a 3-year persistence rate was found of 40%, similar to that of the current study (Escher, Romme, Buiks, Delespaul, & Van Os, 2002).

The Persistent Subclinical Psychosis Pathway into Clinical Psychosis

Although the development of subclinical psychotic symptoms is an initial step to the emergence of psychotic disorder in a significant proportion of cases, not more than two-fifths of all psychotic impairment could be attributed to this pathway. This likely represents an underestimate, however, caused in part by the uneven sampling intervals from T0 to T3. Thus, the relatively wide sampling interval between T2 and T3 (4.9 y on average) may have resulted in participants underreporting experiences and instances of help-seeking. Similarly, the SCL-90-R assesses symptoms over the last two weeks, thus creating the possibility of underreporting psychotic experiences over the period T0-T2. In addition, other domains of psychopathology, such as depression and anxiety, may also contribute to prediction and attributable risk and need to be investigated further (van Os & Delespaul, 2005). Furthermore, more work is needed on the role of cognitive alterations in the ontogenesis of psychotic states, given the fact that meta-analytic work indicates that this domain is orthogonal to the positive and affective symptoms of psychosis (Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2009), yet is likely to impact on the domain of functional impairment in the onset of clinical psychotic states.

Even if it represents a likely underestimation, the fact that 40% of new onset, clinically relevant psychosis can be traced to the early subclinical psychosis phenotype in the general population sheds light on the ontogenesis of psychotic states in the general population. However, much more work is needed in order to understand the process resulting in clinical need in individuals at risk, and the current findings need to be replicated before firm conclusions can be drawn.

From Persistent Subclinical Psychosis to Impairment: Possible Mechanisms

The positive psychosis pathway may be understood as the phenomenological correlate of the classical dopamine (DA) hypothesis which proposes that hyperactivity of DA transmission from DA cell bodies located in the ventral tegmental area of the midbrain to their terminal fields in the nucleus accumbens and limbic cortex results in the development of positive psychotic symptoms (Laruelle, 2000; Lieberman, Sheitman, & Kinon, 1997). DAergic hyperactivity may be associated with what has been called a state of endogenous sensitization (Laruelle, 2000). The liability for psychosis may involve deficits in neural regulation resulting in a pathological condition of neurochemical sensitization of the mesolimbic DAergic system analogous to the preclinical model of behavioral sensitization induced by administration of DA-releasing drugs (Lieberman et al., 1997). Behavioral sensitization is a progressive, enduring enhancement of behaviors that develops following repeated stimulant administration. It is mediated in part by DAergic pathways that are also thought to modulate the development of psychosis (Wolf, White, Nassar, Brooderson, & Khansa, 1993).

Endogenous neurochemical sensitization may arise in part as a result of exposure to environmental conditions (Laruelle, Kegeles, & Abi-Dargham, 2003). For example, environmental stress can induce sensitization and has been demonstrated to be cross-reactive with many types of pharmacologically induced sensitization, including DA and opiate agonists (Lieberman et al., 1997). It has been suggested that several environmental risk factors, eg, perinatal injury, childhood trauma, repeated life events and drug abuse, may contribute to DA sensitization during development (Murray, McDonald, & Bramon, 2002). It is attractive to speculate that a genetic tendency to abnormal DA sensitization is associated with the tendency to express low-grade psychotic experiences that in most individuals will only be expressed transitorily over development. However, in the case of developmental exposure to environmental risk factors, individuals may develop a sensitized DA system resulting in abnormally persistent and, eventually, clinically relevant psychotic states (Cougnard et al., 2007).

Methodological Issues

First, the dynamic hypothesis of psychosis onset was examined in the context of a large-scale epidemiological study not specifically designed for this purpose. It was thus constrained by the specific psychometric tools and sampling frame.

Second, the group comparison between the risk set ($n=845$) and the nonincluded group ($n=550$) showed that the latter had a lower level of education and social status. Because these are risk factors for psychotic experiences (Johns & van Os, 2001; van Os et al., 2000), attrition of these individuals may have led to an underestimation of psychosis outcomes in our sample. Bias of reported associations, however, would have occurred only in the unlikely event that high levels of psychosis persistence would be associated with lower rates of transition to clinical psychosis in this group.

Third, in order to measure persistence of psychotic experiences, the SCL-90-R was used. The fact that this instrument only covers the past 2 weeks may have led to an underestimation of the T0-T2 psychosis persistence measure. As it is difficult to see how this would result in a spurious association with interviewer-assessed psychotic symptoms and impairment 5 years later, any error resulting from underestimation would have likely been random. Similarly, to the degree that the SCL-90-R overestimates the rate of psychotic symptoms (because of the misunderstandings arising from self-report), any resulting error would likely also be random. Furthermore, the way the measure of psychosis persistence in the present study was constructed, only considering those individuals with the highest 10% of scores of the continuous SCL-psychosis subscale, prevented misclassification due

to overestimation of such experiences on the basis of incidental misunderstanding of items.

Four, the DIA-X/M-CIDI was used to measure clinical relevance of psychotic experiences in terms of psychotic impairment, evaluating secondary dysfunction and help-seeking behavior. On the one hand, help-seeking may have led to an underestimation of true positives in the case of individuals who did not seek for help in spite of suffering from true clinical psychotic symptoms. On the other hand, dysfunction may have led to an overestimation of true positives in the case that individuals reported secondary dysfunction only based on subjective level of distress. Nonetheless, the validation of the outcome variable against the clinical judgment of illness strongly supports the validity of psychotic impairment as a proxy measure of clinical relevance.

Five, the number of cases with recurrence-persistence of psychosis expression that developed psychotic impairment was relatively small, conform the expected low rate in the general population, resulting in wide CIs.

Six, the main instruments to assess psychotic experiences and symptoms in the current study (SCL-90-R and DIA-X/M-CIDI) are essentially self-report. Although this is likely to have generated false-positive psychotic experiences, likely increasing random error as discussed earlier, there is nevertheless a substantial literature on the (predictive or other forms of) validity of self-reported psychotic symptoms, assessed with DIA-X/M-CIDI, SCL-90-R and other instruments (van Os et al., 2009). For example, one study validated self-reported psychotic symptoms against a clinical interview with the Brief Psychiatric Rating Scale (Overall & Gorham, 1962) in a sample of psychotic patients, concluding that self-reported scores reflect clinical experience of psychosis (van Os et al., 1999). Poulton et al (Poulton et al., 2000) presented strong evidence for predictive validity of CIDI self-reported psychotic symptoms. Similarly, Hanssen et al (M. S. Hanssen, Bijl, Vollebergh, & van Os, 2003) confirmed that the probability of having a psychotic disorder increased in a dose-response fashion with the level of self-reported psychotic experiences in the general population. In 2006, Konings et al (Konings, Bak, Hanssen, van Os, & Krabbendam, 2006) confirmed the validity and reliability for the measurement of psychotic experiences with a self-reported instrument in the general population. A recent, 20-year longitudinal cohort study on psychotic symptoms using the SCL-90-R also showed high predictive validity of the SCL-90-R psychosis items used in the current sample in terms of deficiencies in social achievement and functioning (Rossler et al., 2007).

Finally, the current study had a longitudinal, population-based epidemiological perspective, contrasting with the shorter term, selective, sample-enriching approach

focusing on help-seekers in the ultrahigh-risk literature (van Os & Delespaul, 2005). The two perspectives and their respective populations, instruments and outcomes are too different to make findings readily comparable.

Funding

This work is further part of the EDSP Study and is supported by the German Federal Ministry of Education and Research (BMBF) project no. 01EB9405/6, 01EB9910/6, EB10106200, 01EB0140, and 01EB0440. Part of the field work and analyses were also additionally supported by grants of the Deutsche Forschungsgemeinschaft (DFG) LA1148/1-1, WI2246/7-1, and WI709/8-1; European Community's Sixth Framework Programme (Marie Curie Early Stage Research Training Fellowship under contract number MEST-CT-2005-020589 to M.d.G.D.); Dutch Medical Council (VENI grant nr 916.76.147 to M.W).

Acknowledgements

Declarations of interest: None. *Data Access and responsibility:* Principal investigators of the EDSP Study are Dr Wittchen and Dr Lieb. Both take responsibility for the integrity of the study data. All authors and coauthors had full access to all study data. Data analysis and manuscript preparation were completed by the authors and coauthors of this article, who take responsibility for its accuracy and content. Core staff members of the EDSP group are Dr. Kirsten von Sydow, Dr. Gabriele Lachner, Dr. Axel Perkonigg and Dr. Peter Schuster –Dipl Stat; Michael Höfler, Holger Sonntag, Tanja Brückl, Elzbieta Garczynski, Dr. Barbara Isensee, Barbara Spiegel, Andrea Schreier, Dr. Ursula wunderlich, Dr. Petra Zimmermann, Datja Beesdo, and Antje Bitner –Dipl Psych; Agnes Nocon and Dr. Chris Nelson –Dipl Inf; Hildegard Pfister and Dr. Victoria Reed –Dipl Soz. Scientific advisors are Dr. Jules Angst (Zurich), Dr. Jürgen Margraf (Basel), Dr. Günther Esser (Potsdam), Dr. Kathleen Merikangas (National Institute of Mental Health, Bethesda), Dr. Ron Kessler (Harvard, Boston) and Dr. van Os (Maastricht). *Financial Disclosure:* Dr. Lieb-speaker honoraria: Wyeth; Dr. Wittchen-research support: Eli Lilly and Company, Novartis, Pfizer, and Schering-Plough; consulting: Eli Lilly, GlaxoSmithKline Pharmaceuticals, Hoffmann-La Roche Pharmaceuticals, Novartis, Pfizer and Wyeth; speaker honoraria: Novartis, Schering-Plough, Pfizer and Wyeth. Dr. van Os-past/present unrestricted research support: Eli Lilly, GSK, Organon, BMS and AstraZeneca; independent speaker honoraria: Eli Lilly, BMS, Lundbeck, Organon, Janssen-Cilag and AstraZeneca.

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CHAPTER 4

AFFECTIVE DYSREGULATION AND REALITY DISTORTION: A 10-YEAR PROSPECTIVE STUDY OF THEIR ASSOCIATION AND CLINICAL RELEVANCE

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Abstract

Objective

Evidence from clinical patient populations indicates that affective dysregulation is strongly associated with reality distortion, suggesting that a process of misassignment of emotional salience may underlie this connection.

Method

To examine this in more detail without clinical confounds, affective regulation–reality distortion relationships, and their clinical relevance, were examined in a German prospective cohort community study. A cohort of 2524 adolescents and young adults aged 14–24 years at baseline was examined by experienced psychologists. Presence of psychotic experiences and (hypo)manic and depressive symptoms was assessed at two time points (3.5 and up to 10 years after baseline) using the Munich-Composite International Diagnostic Interview. Associations were tested between level of affective dysregulation on the one hand and incidence of psychotic experiences, persistence of these experiences and psychotic impairment on the other.

Results

Most psychotic experiences occurred in a context of affective dysregulation, and bi-directional dose-response was apparent with greater level of both affective dysregulation and psychotic experiences. Persistence of psychotic experiences was progressively more likely with greater level of (hypo)manic symptoms (OR trend=1.51, $p<0.001$) and depressive symptoms (OR trend=1.15, $p=0.012$). Similarly, psychotic experiences of clinical relevance were progressively more likely to occur with greater level of affective dysregulation (depressive symptoms: OR trend=1.28, $p=0.002$; (hypo)manic symptoms: OR trend=1.37, $p=0.036$).

Conclusions

Correlated genetic liabilities underlying affective and non-affective psychotic syndromes may be expressed as correlated dimensions in the general population. Also, affective dysregulation may contribute causally to the persistence and clinical relevance of reality distortion, possibly by facilitating a mechanism of aberrant salience attribution.

Key words

Epidemiology, Adolescent, Psychosis, Affective Symptoms

Introduction

Evidence from multiple domains indicates that affective dysregulation is strongly associated with reality distortion (Garety, Bebbington, Fowler, D, & Kuipers, 2007; Myin-Germeys & van Os, 2007). Genetic epidemiological studies have demonstrated that the liabilities for bipolar disorder and schizophrenia are correlated (Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2002; Craddock & Owen, 2007; Lichtenstein, Yip, & Bjork, 2009). Psychopathological studies have demonstrated that psychotic experiences are reported within the context of a range of affective clinical disorders (Dunayevich & Keck, 2000; Sareen, Cox, Goodwin, & Asmundson, 2005) and, conversely, high rates of affective symptoms have been demonstrated in patients diagnosed with DSM-IV non-affective psychotic disorders (Peralta & Cuesta, 2009; Zisook et al., 1999) and schizotypy (Debbane, van der Linden, Gex-Fabry, & Eliez, 2009). Specific aspects of delusional content and severity of psychotic experiences are associated with dysfunctional emotional processes (Bentall, Rowse, & Shryane, 2009; Green, Garety, & Freeman, 2006; Smith, Fowler, & Freeman, 2006). Although most of the work in this area is cross-sectional and conducted in clinical samples, making it difficult to disentangle the direction of effects between affective and cognitive processes, and to distinguish between illness cause and illness consequence, the strong and consistent associations between affective states and reality distortion may imply causality.

Experimental work by Holt and colleagues (Holt et al., 2006) indicates that patients with a diagnosis of schizophrenia who had delusions were more likely to assign (negative) affective meanings to neutral stimuli compared to those without delusional ideation. The magnitude of this response bias correlated with the severity of delusions. The findings were interpreted as consistent with an inappropriate activation of a stimulus-independent internal ‘salience detector’, leading to misassignment of emotional salience to neutral, ambiguous stimuli and ultimately to the formation of delusions (Holt et al., 2006). Thus, affective dysregulation may result in maladaptive appraisal patterns of events, triggering a search for an explanation of their meaning that in turn increases the risk for positive psychotic experiences in vulnerable individuals (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001). Dysregulation in dopamine transmission, facilitating stimulus-independent release of dopamine, causing aberrant assignment of salience and motivational significance to external objects (leading to delusions) and internal representations of percepts and memories (leading to hallucinations) may represent the underlying neurobiological vulnerability mediating the process of reality distortion (Kapur, 2003).

Research on associations between variable clinical characteristics such as affective symptoms and psychotic experiences in clinical samples cannot examine

to what degree such associations may arise as a result of the illness itself, and how interacting affective and cognitive processes, from a perspective of risk, may contribute to the onset of need for care and patient status. Finally, to the degree that the affective and cognitive processes in patients with psychotic disorder are universal, that is, are quantitative variations of normal human mentation (van Os & Kapur, 2009), more fundamental knowledge is needed on their association in the general population, as otherwise a correct interpretation of their role in pathological states such as psychotic disorder is not possible.

It has long been recognized that schizophrenia-related pathology is also expressed, at attenuated levels, in individuals with ‘schizotypal’ or ‘schizoid’ personality traits. Systematic review of general population surveys indicates that the experiences associated with schizophrenia and related categories, such as paranoid delusional thinking and auditory hallucinations, are observed, in an attenuated form, in 5-8% of healthy people (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). These attenuated expressions may be conceived as the behavioral expression of the underlying distributed liability for schizophrenia and related disorders, just as higher levels of blood pressure express higher liability for cardiovascular disease in a dose-response fashion. This interpretation is validated by longitudinal research showing a link between psychotic experiences in the general population and later outcomes of psychotic disorder. Since the seminal study by Chapman and colleagues (Chapman, Chapman, Kwapil, & Zinser, 1994), there is replicatory evidence from 2 birth cohorts (Poulton et al., 2000; Welham, Scott, & Williams, 2008) and 3 representative general population cohorts (Dominguez, Wichers, Lieb, Wittchen, & van Os, 2009; Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005; Werbeloff, Drukker, & Dohrenwend, 2009) that low grade psychotic experiences such as delusional thinking and mild hallucinatory experiences may precede the diagnosis of psychotic disorder, including clinical diagnosis of schizophrenia requiring hospital admission by many years. It has been shown that particularly persistence of subclinical psychotic experiences over time is associated with increased risk of later transition to clinically relevant psychosis (Cougnard, Marcelis, & Myin-Germeys, 2007; Dominguez et al., 2009). Additional evidence is provided by a body of work on help-seeking individuals with low-grade psychotic experiences who, when followed over time, display high conversion rates to clinical psychotic disorder (Cannon, Cornblatt, & McGorry, 2007).

Therefore, epidemiological research in the general population can be useful in complementing clinical research on the link between affective dysregulation, emotional salience misattribution and psychosis, particularly when a longitudinal perspective can be added in order to clarify the direction of effects and to study the relationship with onset of impairment. Earlier general population surveys in Greece and the Netherlands have shown a high degree of overlap between psychotic

experiences and affective symptoms below the threshold for clinical disorder (Kaymaz et al., 2007; Krabbendam, Myin-Germeys, Bak, & van Os, 2005; Krabbendam, Myin-Germeys, Hanssen et al., 2005; Krabbendam & van Os, 2005; Stefanis et al., 2002). For the current study, it was hypothesized that (i) level of affective dysregulation, in the form of depression or (hypo)mania symptoms (regardless of the presence of formal mood disorder) in the general population, would be strongly and linearly associated with experience of reality distortion, expressed as psychotic experiences (ii) presence of affective dysregulation would be associated with persistence of reality distortion over time and (iii) affective dysregulation would be associated with psychotic impairment in the context of reality distortion.

Methods

Study Design and Population

The Early Developmental Stages of Psychopathology (EDSP) study is a prospective-longitudinal cohort community study which collected data on the prevalence, incidence, risk factors, comorbidity and course of mental disorders. Following ethics committee approval, a representative population sample was randomly drawn from the 1994 German government population registers. The sample consisted of adolescents and young adults living in the Munich area aged 14-24 years at baseline. Because the primary goal of the study was to examine the incidence and developmental risk factors for psychopathology, stratification of the sample was performed by sampling 14 and 15-year olds, presumed to have the highest incidence density, at twice the rate of 16 to 21-year olds, and by sampling 22 to 24-year olds at half this rate. The 4,809 sampled individuals were approached through letter and phone. Of these, 4263 were located and determined to be eligible for the study. Most interviews took place at the participant's home. The study consisted of a baseline survey (T0, n=3021) and 3 follow-up investigations (T1, T2 and T3), covering a time period of approximately 1.6 years (T0-T1, SD = 0.2), 3.5 years (T0-T2, SD = 0.3) and 8.6 years (T0-T3, range 7.4-10.6 years, SD = 0.7) respectively. Written informed consent was obtained from all participants. The study design and sample has been described in detail in previous reports (Lieb, Isensee, Von Sydow, & Wittchen, 2000; Wittchen, Perkonig, Lachner, & Nelson, 1998).

Instruments

Interviews were conducted using the Computer-Assisted Personal Interview (CAPI) version of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI (Wittchen & Pfister, 1997)), an updated version of the World Health

Organization's CIDI version 1.2. The DIA-X/M-CIDI is a comprehensive, fully standardized diagnostic interview and assesses symptoms, syndromes and diagnoses of various mental disorders in accordance with the definitions and criteria of DSM-IV, along with information about onset, duration, severity and psychosocial impairment. The CIDI is divided into 16 sections: a socio-demographic section, 12 sections consisting of 288 symptom questions regarding groups of mental disorders and three final sections containing concluding questions, interviewer observations and interviewer ratings. High validity (Reed et al., 1998) as well as high interrater and test-retest reliability of the CIDI have been established (Wittchen, 1994; Wittchen et al., 1991). In order to ensure reliability of the assessments, fully trained and experienced clinical psychologists who were allowed to probe with clinical follow-up questions conducted the interviews. At baseline, the lifetime version of the DIA-X/M-CIDI was used; for the follow-up interviews, the DIA-X/M-CIDI interval version was used, covering the respective time periods between interviews. As data on the DIA-X/M-CIDI G-section concerning psychosis and its clinical relevance were only collected at T2 (lifetime version, assessing lifetime cumulative incidence up to T2) and T3 (interval version, assessing onset of new, incident, symptoms or interval rate of any symptom between T2 and T3), the current analyses are limited to T2 and T3. The response rate was 84% at T2 ($n=2548$) and 73% at T3 ($n=2210$), covering an interval period of 4.9 years on average ($SD=0.6$).

Assessment of Reality Distortion

Information from the CIDI psychosis section and the clinical interview rating section with its embedded *Brief Psychiatric Rating Scale* (Overall & Gorham, 1962) were used to derive measures of the psychosis dimensions. In order to calculate measures of frequency of psychopathological experiences, such as lifetime cumulative incidence and interval incidence rates, as well as persistence estimates, discrete variables indicating their presence or absence across interview waves were, per definition, necessary.

Reality distortion, expressed as psychotic experiences, was the focus of the current analyses. All expressions of psychotic experiences, regardless of the presence of a formal psychotic disorder, were included. Psychotic experiences were assessed at T2 and T3 using the DIA-X/M-CIDI core psychosis section on delusions (14 items), hallucinations (5 items) and passivity (1 item). Specifically, items used were G1, G2a, G3-5, G7-G13, G13b, G14, G17, G18, G20, G20c, G21 and G22a. These items concern classic psychotic symptoms including but not limited to persecution, thought interference and passivity phenomena. Participants were first asked to read a list of all the psychotic experiences and then asked whether they ever experienced such symptoms by the psychologist (list and phrasing available upon request). All of these psychosis items can be rated in two

ways: 1 (absent) and 5 (present), without intermediate levels. The presence of positive psychotic experiences was defined as any rating of “5” on any of the 20 DIA-X/M-CIDI core psychosis items (Dominguez et al., 2009). In order to examine dose-response as a function of level of psychotic experiences, an additional variable was constructed reflecting the presence of 0, 1, 2 or 3 or more psychotic experiences (hereafter: Psychosis Load).

Assessment of Psychotic Impairment

In order to assess functional impact of psychotic experiences, secondary dysfunction and help-seeking behavior were examined in individuals with evidence of DIA-X/M-CIDI psychotic experiences at T2 and T3; the following procedures were followed as described in an earlier report (Dominguez et al., 2009). First, two DIA-X/M-CIDI psychosis section items for help-seeking were used: G16 (delusions) and G23 (hallucinations). These items were phrased as follows: “Did you tell a doctor about ... (insert the psychosis section beliefs/experiences previously acknowledged by the participant along with a visual representation from the response booklet) you have had?” These items were rated in a dichotomous manner (0=no, 1=yes). In addition, participants were shown a list on which several types of outpatient or inpatient institutions for mental health problems were mentioned, ranging from general practitioner or school psychologist to psychiatric sheltered housing, and asked whether they had ever sought help at any of these institutions because of psychotic symptoms as elicited in the DIA-X/M-CIDI G-section. This item was rated in a dichotomous manner (0=no, 1=yes). Using these three help-seeking items, a dichotomous variable “Help-seeking” was constructed, indicating whether help-seeking behavior had been present (1) or absent (0).

Second, the level of dysfunction related to psychotic experiences was assessed using the DIA-X/M-CIDI items G28, G29, G29a and G36. The dysfunction score assessed the effect of the psychotic experiences on: (i) feeling upset, unable to work, go places, or enjoy oneself, at the time of having these experiences (item G28); (ii) being less able to work since these experiences began (item G29); (iii) being less able to make friends or enjoy social relationships since these experiences began (item G29a); (iv) how much their life and everyday activities were impaired when these experiences were at their worst (item G36). These four psychosis section items were rated in a dichotomous manner (0=no, 1=yes). A dichotomous variable ‘Dysfunction’ was constructed, representing a positive answer on any of the four questions (value label 1) versus negative answers on all four questions (value label 0).

Based on these two assessments, a combined outcome was created (hereafter ‘Psychotic impairment’). Psychotic impairment was absent and scored as ‘0’ for

subjects scoring '0' on both help seeking behavior and dysfunction. Subjects scoring '1' on either or both help seeking behavior and dysfunction scored '1' on Psychotic Impairment.

Validation of this variable using third variables was presented previously (Dominguez et al., 2009), using two variables: Caseness and Antipsychotic Treatment. Briefly, The X16 DIA-X/M-CIDI item rated the interviewer's opinion regarding clinical evidence of psychological ill-health in 4 levels: essentially not noticeable (0), not very noticeable (1), clearly ill (2), and very ill (3). The dichotomous variable 'Caseness' indicated individuals with a noticeable level of psychiatric caseness (any score above "1"). As part of the CIDI treatment module, participants were shown a list of different types of medication, rating their use because of any psychopathological or psychosomatic problem. The acknowledgement of any antipsychotic medication (Q1EA4) reported at T2 and T3 was used to derive treatment ('Antipsychotic Treatment': 0=no, 1=yes). Validation analyses revealed that Psychotic Impairment was strongly associated with both the Caseness (OR=10.3, 95%CI=7.0-15.2) and the Antipsychotic Treatment (OR=15.3, 95%CI=6.1-38.4) variable.

Assessment of Affective Dysregulation

Affective dysregulation was assessed at T2 and T3 using the 28 symptom items (DSM-IV and ICD-10) of the DIA-X/M-CIDI depression and dysthymia section (items regarding feeling depressed, loss of interest, loss of energy, hopelessness, decreased concentration, loss of appetite, weight loss, sleep disturbances, feelings of worthlessness or guilt, decreased self-esteem and suicidal ideation/attempt) and the 11 symptom items of the DIA-X/M-CIDI mania section (items regarding increase in goal directed-activity, psychomotor agitation, spending sprees, sexual indiscretions, increased talkativeness, flight of ideas, increased self-esteem or grandiosity, decreased need for sleep and distractibility). Symptom items were rated either yes or no. Depression symptoms were only rated if present for at least two weeks; (hypo)mania symptoms if present for at least 4 successive days. In case the participant endorsed the presence of a particular symptom, additional probes ascertained whether the symptom was the direct result of alcohol or drug use or of physical diseases or conditions. If this were the case, the CIDI codes for substance use or somatically induced symptoms were used, and the item was not counted towards the diagnosis of a primary mood disorder. Furthermore, symptoms were only assessed and rated if at least one of the DIA-X/M-CIDI core depressive (depressed mood or loss of interest / pleasure) or core (hypo)mania symptoms (unusual happiness or excitement or unusual irritability) was present. Only participants having core (hypo)mania symptoms that were either noticed by others or because of which participants experienced problems were included.

Binary and Continuous Affective Variables

Both binary and continuous affective variables were constructed as described previously (Krabbendam et al., 2004; Regeer et al., 2006) (Tijssen, van Os, & Wittchen, 2009): ‘Binary (hypo)mania’ and ‘binary depression’: An a priori binary (hypo)mania variable was defined as at least two DIA-X/M-CIDI mania symptoms and a binary depression variable as at least three DIA-X/M-CIDI depression symptoms.

In addition, guided by previous work (Krabbendam et al., 2004; Regeer et al., 2006; Tijssen et al., 2009) a continuous ‘(hypo)mania score’ and a continuous ‘depression score’ variable were constructed. These variables represented two continuous sum scores of symptom ratings: a sum score of (hypo)mania symptoms with a minimum of 0, and a maximum score of 11 endorsements (hereafter: “(Hypo)mania Score”), and a sum score of depression symptoms with a minimum of 0, and a maximum score of 28 endorsements (hereafter: “Depression Score”). Subsequent, we created, for both symptom groups, progressively stricter and overlapping subcategories of these sum scores, indicating the degree of symptom loading. For depression, 6 categories were created of no symptoms (0), at least 1 symptom (1), at least 3 symptoms (2) at least 5 symptoms (3), at least 7 symptoms (4) and at least 9 symptoms (5). For (hypo)mania, the categories were similar except that the highest category was at least 5 symptoms due to the very small number of subjects with 6 or more symptoms.

Statistical Analysis

Analyses were conducted in STATA, version 10 (STATACORP, 2008). Associations were expressed as odds ratios (OR) and 95% confidence intervals (95%CI) derived from logistic regression.

Associations between Affective Dysregulation and Psychotic Experiences

Cumulative incidence measures of affective dysregulation and psychotic experiences up until T2 were tested for association in order to establish their lifetime comorbidity (risk set n=2524). Similarly, interval incidence of psychotic experiences at T3 (i.e. individuals with psychotic experiences at T3 free from psychotic experiences at T2) were modeled as a function of measures of level of affective dysregulation at T3 (risk set n=1564). This latter analysis provided a temporally more precise test of the hypothesis that affective dysregulation accompanies the onset of psychotic experiences. Finally, T2 and T3 associations between individual psychotic experiences on the one hand and the level of depressive and (hypo)mania symptoms on the other were tested in order to gain insight in possible patterns of association between specific psychotic experiences and affective dysregulation.

Psychosis Persistence

In order to assess the association between level of affective dysregulation and persistence of psychotic experiences over the period T2-T3, associations between T3 level of affective dysregulation and T3 psychotic experiences were assessed in individuals with evidence for psychotic experiences at T2 (risk set n=464).

Psychotic Impairment

In order to assess the relationship between level of affective dysregulation and incident Psychotic Impairment, associations between T3 Psychotic Impairment and T3 level of affective dysregulation were assessed in individuals with evidence of psychotic experiences at T3 but free from Psychotic Impairment at T2 (risk set n=191).

Results

At T2, over half (51%) of the sample was male and the mean age was 21.7 years (SD 3.4). At T2, 574 (23%) of all subjects presented with one or more lifetime psychotic experiences, with a stronger representation of delusions (21%) compared to hallucinations (5%). At T3, the rates were lower, representing only the occurrence of psychotic experiences over the interval from T2 to T3 (Table 1). At T2, 978 subjects (32%) had experienced two or more (hypo)mania or three or more depression symptom; at T3, this was the case for 925 subjects (31%). Within the subgroup of subjects with two or more (hypo)mania or three or more depression symptoms at T2 (n=978), 57% did not report similarly defined (hypo)mania or depression symptoms at T3. Conversely, within the subgroup of subjects that did not experience two more (hypo)mania or three or more depression symptoms at T2, 25% did present similarly defined (hypo)mania or depression symptoms at T3. The lifetime cumulative incidence up until T2 and the T2-T3 interval rates, assessed at T3, of hallucinations, delusions, (hypo)mania and depression symptoms are provided in Table 1.

Affective Dysregulation and Reality Distortion Co-Occurrence

Of the 574 subjects with psychotic experiences, 35% also presented with at least 2 (hypo)mania symptoms at T2, compared to 15% of subjects without lifetime psychotic experiences at T2. At T3, these figures were 27% and 11%, respectively. Similarly, 43% of the 574 subjects with psychotic experiences presented with at least 3 depression symptoms at T2, compared to 23% of subjects without psychotic experiences. At T3, these figures were 46% and 31%, respectively. At both T2 and T3, the majority of psychotic experiences occurred in the context of affective dysregulation (at least 2 (hypo)mania symptoms or at least 3 depression symptoms; Table 2).

Table 1. Lifetime Cumulative Incidence (T2) and Interval Rates (T3) of various Symptoms.

	T2 (n, total n; %)	T3 (n, total n; %) ^a	T3 (n, total n; %) ^b
Ever experienced hallucinations (at least 1)	117 (2524; 4.6%)	69 (2210; 3.1%)	51 (1937; 2.6%)
Ever experienced delusions (at least 1)	529 (2524; 21.0%)	248 (2210; 11.2%)	121 (1598; 7.6%)
Ever experienced hallucinations or delusions (at least 1 symptom)	574 (2524; 22.7%)	274 (2210; 12.4%)	128 (1564; 8.2%)
(Hypo)mania symptoms (at least 2 symptoms)	495 (2525; 19.6%)	285 (2210; 12.9%)	121 (1598; 7.6%)
Depressive symptoms (at least 3 symptoms)	695 (2529; 27.5%)	780 (2210; 35.3%)	392 (1391; 28.2%)

Note. For each clinical characteristic, the size of the sample varies due to missing data on individual variables.

^aAnalyses were performed in the complete sample at T3, regardless of presence of psychotic experiences at T2. ^bAnalyses were performed in the T3 sample free of the specific type of symptom at T2, thus representing interval incidence of symptoms (e.g. the interval incidence of (hypo)mania symptoms at T3 in subjects without (hypo)mania symptoms at T2 was 7.6%).

Table 2. Frequency of Affective Dysregulation as a Function of Presence of Psychotic Experiences at T2 and T3

		At least 2 (hypo)mania symptoms present	At least 3 depression symptoms present	At least 2 (hypo)mania symptoms and/or at least 3 depression symptoms present
T2	Psychotic experience absent (n, n total; %)	295 (1950; 15.1%)	446 (1950; 22.8%)	630 (1950; 32.3%)
	Psychotic experience present (n, n total; %)	200 (574; 34.8%)	247 (574; 43.0%)	346 (574; 60.3%)
T3 ^a	Psychotic experience absent (n, n total; %)	212 (1936; 11.0%)	636 (1936; 32.9%)	756 (1936; 39.1%)
	Psychotic experience present (n, n total; %)	73 (274; 26.6%)	144 (274; 52.6%)	169 (274; 61.7%)
T3 ^b	Psychotic experience absent (n, n total; %)	147 (1436; 10.2%)	420 (1436; 29.3%)	506 (1436; 35.2%)
	Psychotic experience present (n, n total; %)	33 (128; 25.8%)	60 (128; 46.9%)	70 (128; 54.7%)

Note. For each clinical characteristic, the size of the sample varies due to missing data on individual variables.

^aAnalyses were performed in the complete sample, regardless of presence of psychotic experiences at T2.

^bAnalyses were performed in the sample free of the specific type of symptom at T2. For example, first column, last row: the proportion of people with at least 2 (hypo)mania symptoms present in those with psychotic experiences at T3 and no hypomania symptoms at T2 was 25.8%.

Bi-directional Dose-response Associations between Affective Symptoms and Reality Distortion

The probability of lifetime psychotic experiences at T2 was progressively higher with greater level of co-occurrent affective dysregulation in a dose-response fashion ((Hypo)mania Score OR linear trend over 4 levels=1.70, 95%CI: 1.55, 1.87; $p<.001$; Depression Score OR linear trend over 6 levels: OR=1.31, 95%CI: 1.24, 1.38; $p<.001$; Table 3). Incident psychotic experiences at T3 (i.e. psychotic experiences at T3 in subjects free from psychotic experiences at T2) were similarly associated with (Hypo)mania Score and Depression Score in a dose-response fashion (Table 3).

Similarly, the above OR linear trends expressing the association between psychotic experiences and affective dysregulation became progressively greater at higher level of Psychosis Load, both for mania and depression, and both at T2 and at T3 (Table 4).

Psychosis Persistence

(Hypo)mania Score and Depression Score were associated with persistence of psychotic experiences over the period T2-T3. Thus, within the sample of subjects with psychotic experiences at T2 and interviewed again at T3 (risk set $n=464$), the probability of persistence of psychotic experiences was progressively greater with higher (Hypo)mania Score (OR linear trend 4 categories=1.51; 95%CI: 1.22, 1.88; $p<0.001$) and higher Depression Score (OR linear trend 6 categories=1.15; 95%CI=1.03, 1.28; $p=0.012$).

Psychotic Impairment

Two-hundred and twenty-eight subjects (9%) presented at T2 with Psychotic Impairment. At T3, the number with Psychotic Impairment was 118 (5%). Of these 118, 70 subjects had not presented previously with Psychotic Impairment at T2, representing incident Psychotic Impairment. Affective dysregulation was associated with incident Psychotic Impairment: within the sample of subjects without Psychotic Impairment at T2 and presence of at least one psychotic experience at T3 (risk set $n=191$), the probability of Psychotic Impairment at T3 was progressively higher with higher (Hypo)mania Score at T3 (OR linear trend 4 categories=1.37, 95%CI: 1.02, 1.83; $p=.036$) and higher Depression Score at T3 (OR linear trend 6 categories=1.28, 95%CI: 1.10, 1.49; $p=.002$).

Table 3. Odds Ratios of Psychotic Experiences with Increasing Load of Affective Dysregulation at T2 (risk set $n=2524$) and T3 (risk set $n=1564$).

	T2: Lifetime psychotic experiences (up to T2)			T3: T2-T3 Interval incident psychotic experiences		
	n total at T2	n (%) with psychotic experiences	OR (95% CI)	n total at T3	n (%) with psychotic experiences	OR (95% CI)
(Hypo)mania score 0	1966	360 (18.3%)	^a	1338	90 (6.7%)	^a
(Hypo)mania score 1	169	42 (24.9%)	1.48 (1.02, 2.13) [†]	113	11 (9.7%)	1.50 (0.77, 2.89)
(Hypo)mania score 2	229	83 (36.2%)	2.54 (1.89, 3.40)*	79	16 (20.3%)	3.52 (1.95, 6.35)*
(Hypo)mania score 3	160	89 (55.6%)	5.59 (4.01, 7.80)*	34	11 (32.4%)	6.63 (3.13, 14.04)*
OR linear trend#	OR=1.70, CI: 1.55, 1.87*			OR=1.86, CI: 1.52, 2.26*		
Depression score 0	1710	303 (17.7%)	^a	858	49 (5.7%)	^a
Depression score 1	121	24 (19.8%)	1.15 (0.72, 1.83)	226	19 (8.4%)	1.52 (0.87, 2.63)
Depression score 2	187	56 (30.0%)	1.99 (1.42, 2.78)*	129	11 (8.5%)	1.54 (0.78, 3.04)
Depression score 3	170	48 (28.2%)	1.83 (1.28, 2.61)*	128	13 (10.2%)	1.87 (0.98, 3.55)
Depression score 4	126	38 (30.2%)	2.01 (1.34, 2.99)*	97	13 (13.4%)	2.56 (1.33, 4.90) [†]
Depression score 5	210	105 (50.5%)	4.64 (3.45, 6.25)*	126	23 (18.3%)	3.69 (2.16, 6.30)*
OR linear trend#	OR=1.31, CI: 1.24, 1.38*			OR=1.28, CI: 1.16, 1.40*		

Note. OR=Odds Ratio; CI=Confidence Interval. (Hypo)mania Score and Depression Score variables were constructed as described in text. Higher scores indicate more affective symptoms. ^aReference category: reference category is group without (hypo)mania symptoms and group without depressive symptoms. * $p \leq .001$; [†] $p \leq .01$. # OR linear trend is in the summary increase in risk with one unit change in affective score variable.

Table 4. Linear Associations between Affective Dysregulation and Psychotic Experiences at Different Levels of Psychosis Severity (Psychosis Load)

		No psychotic experiences (n, %)	1 psychotic experience (n, %)	2 psychotic experiences (n, %)	≥3 psychotic experiences (n, %)
T2 lifetime experiences (up to T2)*	(Hypo)mania score 0 (n=1966)	1606 (81.7%)	236 (12.0%)	62 (3.2%)	62 (3.2%)
	(Hypo)mania score 1 (n=169)	127 (75.2%)	25 (14.8%)	8 (4.7%)	9 (5.3%)
	(Hypo)mania score 2 (n=229)	146 (63.8%)	43 (18.8%)	17 (7.4%)	23 (10.0%)
	(Hypo)mania score 3 (n=160)	71 (44.4%)	28 (17.5%)	21 (13.1%)	40 (25.0%)
	OR linear trend#	1#	1.4 (1.2, 1.6)	1.9 (1.6, 2.2)	2.4 (2.0, 2.7)
	Depression score 0 (n=1710)	1407 (82.3%)	192 (11.2%)	59 (3.5%)	52 (3.0%)
	Depression score 1 (n=121)	97 (80.2%)	13 (10.7%)	6 (5.0%)	5 (4.1%)
	Depression score 2 (n=187)	131 (70.1%)	39 (20.9%)	7 (3.7%)	10 (5.4%)
	Depression score 3 (n=170)	122 (71.8%)	30 (17.7%)	7 (4.1%)	11 (6.5%)
	Depression score 4 (n=126)	88 (69.8%)	16 (12.7%)	8 (6.4%)	14 (11.1%)
	Depression score 5 (n=210)	105 (50.0%)	42 (20.0%)	21 (10.0%)	42 (20.0%)
	OR linear trend#	1#	1.2 (1.1, 1.3)	1.3 (1.2, 1.4)	1.6 (1.4, 1.7)
T2-T3 interval incident experiences**	(Hypo)mania score 0 (n=1338)	1248 (93.3%)	66 (4.9%)	13 (1.0%)	11 (0.8%)
	(Hypo)mania score 1 (n=113)	102 (90.3%)	7 (6.2%)	1 (0.9%)	3 (2.7%)
	(Hypo)mania score 2 (n=79)	63 (79.8%)	13 (16.5%)	2 (2.5%)	1 (1.3%)
	(Hypo)mania score 3 (n=34)	23 (67.7%)	2 (5.9%)	5 (14.7%)	4 (11.8%)
	OR linear trend#	1#	1.6 (1.2, 2.0)	2.5 (1.7, 3.7)	2.4 (1.6, 3.6)
	Depression score 0 (n=858)	809 (94.3%)	38 (4.4%)	8 (0.9%)	3 (0.4%)
	Depression score 1 (n=226)	207 (91.6%)	14 (6.2%)	2 (0.9%)	3 (1.3%)
	Depression score 2 (n=129)	118 (91.5%)	8 (6.2%)	2 (1.6%)	1 (0.8%)
	Depression score 3 (n=128)	115 (89.8%)	9 (7.0%)	3 (2.3%)	1 (0.8%)
	Depression score 4 (n=97)	84 (86.6%)	6 (6.2%)	3 (3.1%)	4 (4.1%)
	Depression score 5 (n=126)	103 (81.8%)	13 (10.3%)	3 (2.4%)	7 (5.6%)
	OR linear trend#	1#	1.2 (1.1, 1.3)	1.3 (1.0, 1.6)	1.7 (1.4, 2.2)

*Assessments refer to cumulative incidence of psychopathology up until T2;

**Assessments refer to psychopathology arising between T2 and T3; those with psychotic experiences at T2 were excluded from the analysis

reference category; other odds ratio's in the same row reflect comparison with reference category odds ratio

Table 5. Specific Psychotic Experiences and Associations with Binary Depressive (at least 3 symptoms) and Binary (Hypo)mania (at least 2 symptoms) Variables at T2 (risk set n=2524) and T3 (risk set n=1564).

Psychotic experience	Prevalence of psychotic experience (n, %)			At least 3 depressive symptoms		At least 2 (hypo)mania symptoms	
	T2	T3 ^a		OR (95% CI)	T2	OR (95% CI)	T3 ^a
Being spied on	186 (7.4)	36 (2.3)		2.28 (1.69, 3.09)*	2.38 (1.73, 3.28)*	3.07 (1.46, 6.48)†	
Being followed	107 (4.2)	19 (1.2)		2.42 (1.64, 3.58)*	2.26 (1.50, 3.41)*	4.63 (1.80, 11.91)*	
Being tested	125 (5.0)	34 (2.2)		2.85 (1.99, 4.10)*	2.04 (1.03, 4.04)†	3.50 (2.42, 5.05)*	
Conspiracy	147 (5.8)	29 (1.9)		3.24 (2.31, 4.54)*	6.15 (2.71, 14.00)*	3.18 (2.25, 4.48)*	
Loved by stranger	72 (2.9)	15 (1.0)		1.33 (0.81, 2.19)	1.99 (0.72, 5.52)	2.87 (1.78, 4.65)*	
Can read thoughts	89 (3.5)	12 (0.8)		2.69 (1.76, 4.12)*	2.27 (0.73, 7.09)	3.22 (2.09, 4.97)*	
Can hear thoughts	55 (2.2)	7 (0.5)		1.93 (1.12, 3.32)†	5.69 (1.10, 29.46)†	4.79 (2.80, 8.22)*	
Thoughts being heard	31 (1.2)	3 (0.2)		3.73 (1.82, 7.65)*	1.13 (0.10, 12.49)	3.93 (1.93, 8.01)*	
Controlled by force	21 (0.8)	2 (0.1)		1.99 (0.84, 4.75)	^b	3.78 (1.60, 8.96)†	
Being given thoughts	12 (0.5)	0 (0.0)		2.66 (0.85, 8.26)	^b	4.14 (1.33, 12.88)†	
Thoughts being taken	6 (0.2)	2 (0.1)		0.53 (0.06, 4.53)	^b	4.12 (0.83, 20.46)	
Messages	13 (0.5)	7 (0.5)		8.92 (2.45, 32.51)*	5.69 (1.10, 29.46)†	4.84 (1.62, 14.46)†	
Book or song solely for person	46 (1.8)	5 (0.3)		3.53 (1.96, 6.37)*	1.51 (0.25, 9.05)	3.55 (1.97, 6.40)*	
Being influenced by strange force	25 (1.0)	5 (0.3)		1.77 (0.79, 3.96)	0.56 (0.06, 5.06)	3.27 (1.48, 7.25)†	
Seeing things	27 (1.1)	6 (0.4)		2.88 (1.35, 6.17)†	2.27 (0.46, 11.27)	3.88 (1.81, 8.31)*	
Hearing things	40 (1.6)	14 (0.9)		3.30 (1.76, 6.20)*	4.12 (1.37, 12.37)†	4.69 (2.50, 8.79)*	
Smelling things	26 (1.0)	7 (0.5)		5.09 (2.26, 11.48)*	3.03 (0.68, 13.68)	4.18 (1.93, 9.08)*	
Tasting things	26 (1.0)	6 (0.4)		4.30 (1.94, 9.53)*	1.13 (0.21, 6.19)	3.05 (1.39, 6.69)†	
Feeling things	36 (1.4)	7 (0.5)		4.26 (2.16, 8.37)*	1.70 (0.38, 7.62)	2.66 (1.35, 5.23)†	
Forced to move	24 (1.0)	3 (0.2)		3.75 (1.66, 8.49)*	4.53 (0.41, 50.01)	4.95 (2.20, 11.11)*	

Note. OR=Odds ratio; CI=Confidence Interval. *p≤.001; † p≤.01; ‡ p≤.05. Sample consisted of subjects free of psychotic experiences at T2. ^b Model did not converge.

Associations between Affective Dysregulation and Specific Psychotic Experiences

An overview of specific psychotic experiences and associations with binary depression (at least three symptoms) and (hypo)mania (at least two symptoms) variables is provided in Table 5. For both depression and (hypo)mania symptoms, no specific trend or pattern was apparent among the different psychotic experiences.

Discussion

Clinical studies in help-seeking samples suggest that early intervention in the prodromal phase of psychotic disorder may be feasible (Cannon, Cadenhead, Cornblatt, & 2008). However, knowledge on the developmental mechanisms underlying the epidemiology of prodromal states in the general population remains very limited. The current study connects reality distortion and affective dysregulation in a general population setting from a perspective of risk and a perspective of understanding links with normal mentation. The results suggest that psychotic experiences in the general population are non-specifically associated with affective dysregulation, in a bi-directional dose-response fashion. Second, persistence of psychotic experiences and the onset of impairment associated with reality distortion occur more often if there is a context of affective dysregulation.

Co-expression as a Reflection of Overlapping Genetic Liabilities

Although the delusions and hallucinations of psychosis can be readily recognized, classifying psychotic states remains a major challenge. Psychosis is not exclusive to schizophrenia and occurs across a range of diagnostic categories of psychotic disorder, and even amongst the category of non-psychotic mood disorders (Hanssen et al., 2003). The criteria used to distinguish between the different categories of psychotic disorder are based on duration, dysfunction, associated substance use, “bizarreness” of delusions and presence of depression or (hypo)mania. However, the resulting diagnostic categories of psychotic disorder show overlap in genetic liability amongst themselves. For example, Kendler and colleagues (Kendler et al., 1993) demonstrated a significant familial relationship between non-schizophrenic psychotic disorders with both schizophrenia and schizotypal personality disorder. Family and twin studies similarly demonstrate a degree of overlap in genetic liability between non-affective psychotic disorder and bipolar disorder (Cardno et al., 2002; Craddock & Owen, 2007; Lichtenstein et al., 2009).

Co-expression of (subclinical) affective dysregulation and psychotic experiences in general cohort studies may thus in part reflect overlapping distributed genetic vulnerabilities. The majority of general cohort studies on transition rates from subclinical symptoms to clinical syndromes did not examine

co-expression of reality distortion and affective dysregulation. Multiple studies suggest that subclinical psychotic experiences increase the risk for non-affective psychotic disorder (Chapman et al., 1994; Dominguez et al., 2009; Hanssen et al., 2005; Poulton et al., 2000; Welham et al., 2008; Werbeloff et al., 2009) and similarly subthreshold depression and/or (hypo)mania symptoms have been shown to increase the risk for bipolar disorder (Regeer et al., 2006; Tijssen et al., 2009). Overall, affective dysregulation and reality distortion have been shown to represent the behavioral expression of risk for more severe psychotic states including schizophrenia and bipolar disorder in the general population. In light of the accumulating evidence on overlap in genetic liability (Cardno et al., 2002; Craddock & Owen, 2007; Lichtenstein et al., 2009), suggesting a broad underlying vulnerability that expresses across the different categories, our findings of associations between affective dysregulation and psychotic experiences in the general population may therefore simply reflect passive clustering of the behavioral expression of overlapping genetic risks.

Co-expression as a Reflection of Causal Influence

The fact that co-expression of affective dysregulation predicted persistence of reality distortion and impairment associated with psychotic experiences suggest that, in addition to correlated genetic liabilities, a direct impact of affective dysregulation on the onset of psychotic experiences may be hypothesized. Existent psychological models of symptom formation suggest that the emotional context, and associated beliefs or appraisals, may induce bias in logical reasoning processes and therefore provoke reality distortion in healthy individuals (Garety et al., 2001; Myin-Germeys & van Os, 2007). In the psychological model described by Garety and colleagues (Garety et al., 2007), the experience of a stressful event is thought to potentially give rise to altered pre-existing beliefs and ongoing appraisals of experiences, due to a certain emotional change or a cognitive processing bias. These distorted processes may lead to aberrant experiences that may seem personally significant to the individual and are likely to trigger a search for an explanation as to their meaning and cause that is consistent with affect-associated beliefs. Biased appraisal processes may contribute to a judgment that the experience is in fact externally caused. It is the interpretation that causes the associated distress and disability, rather than the experience itself. Thus, maladaptive appraisal patterns, induced by emotional processes, are suggested to increase the risk for positive symptom formation in vulnerable individuals (Garety et al., 2007). Our findings provide support for a cognitive model of symptom formation, by demonstrating involvement of affective processes in the onset and persistence of reality distortion outside the context of disorder.

Linking Genetic and Cognitive Mechanisms

Evidence on the role of cognitive processes suggests that cognitive biases and appraisals can help explain onset of psychosis (Garety et al., 2007). Attempts have been made to integrate cognitive and neurobiological theories into a single model of psychotic states (Garety et al., 2007; Kapur, 2003; van Os, 2009). Thus, evidence indicates that genetic risk for psychotic disorder is associated with underlying alterations in the dopamine system, including increased dopamine synaptic availability (Hirvonen, van Erp, & Huttunen, 2005), increased striatal dopamine synthesis (Huttunen, Heinimaa, & Svriskis, 2008; Meyer-Lindenberg, Miletich, & Kohn, 2002) and increased dopamine reactivity to stress (Brunelin et al., 2008; Myin-Germeys, Marcelis, Krabbendam, Delespaul, & van Os, 2005). Under normal circumstances, it is the context-driven activity of the dopamine system that mediates the experience of novelty and the acquisition of appropriate motivational salience, detecting new rewards in the environment that facilitate learning and goal-directed behavior. Certain cerebral vulnerabilities, occasioned by interplay between genetic and environmental risks, could trigger context-independent or context-inappropriate release of dopamine. A dysregulated dopamine system may cause aberrant assignment of salience and motivational significance to external objects (leading to delusions) and internal representations of percepts and memories (leading to hallucinations) (Kapur, Mizrahi, & Li, 2005). Thus, theory derived from existent psychological models of psychotic symptom formation predicts that affective dysregulation may impact directly on risk for reality distortion. An integrated model would additionally suggest that the risk to develop a clinical disorder is particularly high in those who additionally have a genetic liability for dopaminergic dysregulation, facilitating aberrant salience attribution.

Limitations

Several limitations should be taken into account when interpreting these results. First, the study was epidemiological, and no direct measurements of affective and cognitive processes such as aberrant salience attribution were available, limiting the explanatory power of the findings on these mechanisms. Second, although longitudinal, measurements were too far apart for dynamic models of the onset of impairment as a function of affective dysregulation. Third, assessment of psychotic experiences, while better than lay-interviewer assessed self-reports, will likely contain false positive answers even when interviewers are clinical psychologists. However, it is unlikely that false positive assessments would produce spurious associations with affective dysregulation – the opposite, more conservative alternative is more likely. Furthermore, the substantial literature on self-reported psychotic experiences, including those assessed with the DIA-X/M-CIDI, indicates substantial predictive and other forms of validity of these phenomena (van Os et al., 2009). Fourth, lifetime rates in excess of 22% may seem high, given an estimate of

5%-8% in a recent systematic review (van Os et al., 2009). However, in another systematic review we are preparing, it is apparent that rates of psychotic experiences are critically dependent on the number of items assessing different psychotic experiences. Previous work using the CIDI also detected rates close to 20% (van Os, Hanssen, Bijl, & Ravelli, 2000). Finally, it could be argued that the measure of psychotic impairment used was broad, resulting in a lifetime rate of 9%, which may be considered very high for psychosis. The high rate is in part inherent to the population-based research paradigm of EDSP, which will always detect many more cases compared to the much lower administrative rates reflecting treatment at the level of services. Furthermore, even the rate of narrowly defined clinical psychotic disorder, when assessed completely, may be as high as 3.5% (Perala et al., 2007). In addition, to the degree that our definition of impairment was broad, it can be argued that in this context, sensitivity is more important than specificity, given the fact that the main clinical application of research on extended phenotypes ultimately is situated in the area of early detection.

Funding

This work is part of the Early Developmental Stages of Psychopathology (EDSP) Study. The EDSP-Study is funded by the German Federal Ministry of Education and Research [BMBF; project no. 01EB9405/6, 01EB 9901/6, EB01016200, 01EB0140, and 01EB0440]. Part of the field work and analyses were also additionally supported by grants of the Deutsche Forschungsgemeinschaft [DFG; project no. LA1148/1-1, WI2246/1-1, WI 709/7-1, and WI 709/8-1].

Acknowledgements

Data Access and Responsibility: Principal investigators of the EDSP-Study are Dr. Hans-Ulrich Wittchen and Dr. Roselind Lieb. Both take responsibility for the integrity of the study data. All authors and co-authors had full access to all study data. Data analysis and manuscript preparation were completed by the authors and co-authors of this article, who take responsibility for its accuracy and content.

Core staff members of the EDSP group are: Dr Katja Beesdo, Dr. Petra Zimmermann, Dr. Axel Perkonig, PhD Dipl.-Stat. Michael Höfler, , Dipl.-Psych. Tanja Brückl, Dipl.-Psych. Agnes Nocon, Dipl.-Inf. Hildegard Pfister, Dipl.-Soz. Barbara Spiegel, Dipl.-Psych. Andrea Schreier. Scientific advisors are Dr. Jules Angst (Zurich), Dr. Kathleen Merikangas (NIMH, Bethesda), Dr. Ron Kessler (Harvard, Boston) and Dr. Jim van Os (Maastricht). The EDSP project and its family genetic supplement has been approved by the Ethics Committee of the Faculty of the Technische Universität Dresden (No: EK-13811). All participants provided informed consent.

Financial Disclosure: I. van Rossum: also employee of Eli Lilly; M.D.G. Dominguez: Nothing to report; Dr. Lieb: Speaker Honoraria: Wyeth; Dr. Wittchen: Research Support: Novartis, Pfizer; Schering-Plough. Consulting: Novartis, Pfizer, Wyeth, Organon, Lundbek. Speaker Honoraria: Novartis, Schering-Plough, Pfizer, Wyeth, Servier.; Dr. van Os is/has been an unrestricted research grant holder with, or has received financial compensation as an independent symposium speaker from Eli Lilly, BMS, Lundbeck, Organon, Janssen-Cilag, GSK, AstraZeneca, Pfizer and Servier – companies that have an interest in the treatment of psychosis.

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CHAPTER 5

ONSET OF CLINICAL PSYCHOSIS: NEGATIVE/DISORGANIZED SYMPTOMS INCREASING RISK FOR POSITIVE SYMPTOMS INCREASING RISK FOR IMPAIRMENT? A 10-YEAR STUDY

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Submitted

Abstract***Objective***

Cognitive and negative symptoms associated with schizophrenia may represent alterations in brain development associated with distributed genetic risk, influencing a final common pathway of neurotransmitter dysregulation resulting in the onset of positive psychotic symptoms, particularly when combined with environmental exposures such as cannabis, developmental trauma and urbanicity. The epidemiological predictions of this model were tested.

Method

A prospective cohort study was conducted in a sample of originally n=3021 adolescents and young adults, aged 14-24 years at outset, over a period of 8.4 years, in Munich, Germany (Early Developmental Stages of Psychopathology Study). Measures of psychopathology and clinical relevance were assessed by clinical psychologists using the Composite International Diagnostic Interview.

Results

Both negative and positive psychotic symptoms were frequent (5-year cumulative prevalence rates of around 12%) and occurred in combination more often than predicted by chance. Negative symptoms revealed a pattern of socio-demographic associations indicative of developmental impairment, whereas the positive symptoms were associated with environmental risk factors such as trauma, cannabis use and urbanicity. Negative symptoms predicted positive symptoms over time, and co-occurrence of positive and negative symptoms was predictive of clinical relevance in terms of secondary functional impairment and help-seeking behaviour.

Conclusions

Results suggest that the liabilities underlying negative features of psychotic illness are distributed at a population level and drive the ontogenesis of positive psychotic experiences after exposure to environmental risks, increasing the likelihood of impairment and need for care.

Key words

Epidemiology, Community, Positive Symptoms, Negative Symptoms, Psychotic disorders, Psychopathology, Environment, Risk Factors.

Introduction

Delusions and hallucinations are not exclusive to schizophrenia and psychotic disorders and occur across a range of diagnostic categories. Differential diagnosis is based on duration, symptom patterns, dysfunction, substance use, “bizarreness” of delusions and presence of depression or mania. However, the resulting diagnostic categories show overlap in genetic liability amongst themselves (Craddock & Owen, 2007; Kendler et al., 1993). Psychotic disorders consist of different symptom dimensions that, while clustering together in the same syndrome, nevertheless also display relative contrasts. Thus, the positive and the negative symptom domains show a pattern of co-clustering in the diagnostic category of schizophrenia, but there is also evidence for a relative contrast: the negative dimension is associated with neurocognitive impairment whilst the positive is not (M. D. G. Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2009), and positive and negative symptoms show a differential pattern of socio-demographic and environmental risk associations (Leung & Chue, 2000; Schultz et al., 1997), alterations in cerebral activity (Schroder et al., 1996) and alterations in neurotransmission (Laruelle, Kegeles, & Abi-Dargham, 2003). Both dimensions also follow differential longitudinal courses (Eaton, Thara, Federman, Melton, & Liang, 1995) and display differential associations with antipsychotic response (Erhart, Marder, & Carpenter, 2006), social functioning (Macdonald, Hayes, & Baglioni, 2000) and prognosis (McGlashan & Fenton, 1992).

Research in clinical samples cannot examine to what degree associations between variable clinical characteristics and other variables may arise as a result of the illness and/or the associated treatments. This is particularly relevant with regard to negative symptom confounds such as dopamine-blocking medications, extrapyramidal symptoms, depression, social exclusion due to stigma and positive psychotic symptoms causing secondary negative symptoms (Kapur, 2004; Malla et al., 2002). Similarly, clinical research cannot determine the degree to which the processes underlying negative and positive symptoms in psychotic patients may be universal, representing quantitative variations of normal human mentation (van Os & Kapur, 2009) or determine if and how interacting processes underlying both symptoms, from a perspective of risk, may contribute to the onset of need for care.

Systematic review of general population surveys indicates that the experiences associated with psychotic categories, such as paranoid delusional thinking and auditory hallucinations, are observed, in an attenuated form, in 5-8% of respondents that have never been diagnosed as having any mental disorder with psychotic features (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). These attenuated expressions may be conceived as the behavioural expression of underlying distributed liability for psychosis (Lataster, Myin-Germeys, Derom,

Thiery, & van Os, 2009). This interpretation is validated by longitudinal research showing a link between psychotic experiences in the general population and increased probability of having a psychotic disorder later in life. There is evidence from two birth cohorts (Poulton et al., 2000; Welham et al., 2009), three representative population cohorts (M. D. Dominguez, Wichers, Lieb, Wittchen, & van Os, 2009; Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005; Werbeloff, Drukker, & Dohrenwend, 2009) and the seminal study by Chapman (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994) that low grade psychotic experiences may precede the diagnosis of psychotic disorder, including hospital admission, by many years.

The above population-based work has focused on experiences resembling positive psychotic symptoms and it is not known if and how attenuated negative symptoms might play a role. It has been suggested that experiences resembling negative symptoms are also expressed in attenuated form in otherwise “healthy” individuals, and that the combination of attenuated positive and negative symptoms are “toxic” in terms of increasing the risk for need for care (Maric et al., 2004). Therefore, epidemiological research on such psychopathological phenomena may be productive, particularly when a longitudinal perspective allows for the clarification of the direction of effects and the relationship with illness onset.

In the current paper, a longitudinal, 10-year study in young people is presented. Hypotheses were derived from the suggestion that cognitive/negative symptoms associated with schizophrenia may represent alterations in brain development associated with distributed genetic risk, influencing a hypothesized final common pathway of neurotransmitter dysregulation resulting in the onset of positive psychotic symptoms, particularly when combined with environmental exposures (van Os & Kapur, 2009). We therefore hypothesized that: (i) subclinical expressions of positive and negative symptoms are distributed in the general population and occur more often together than predicted by chance, (ii) positive symptoms are associated with environmental risks and negative features with indices of developmental impairment, (iii) negative symptoms predict psychotic experiences over time but not the other way round and, finally, (iv) “co-morbid” expression of positive and negative experiences are associated with impairment and risk for patient status.

Method

Sample and Study Design

The Early Developmental Stages of Psychopathology (EDSP) study collected data on the prevalence, incidence, risk factors and course of mental disorders in a

representative random population sample of 14-24-years-old adolescents and young adults in Munich, Germany.

This longitudinal prospective design consisted of a baseline and 3 follow-up surveys, covering a time period of on average 1.6 years (T0-T1), 3.5 years (T0-T2) and 8.6 years (T0-T3; range=7.3-10.5). Because the primary goal of the study was to examine the incidence of and the developmental risk factors for psychopathology, the younger group (14- to 15-years) was sampled at twice the rate of persons aged 16-21 years, and the oldest group (22-24 years) was sampled at half this rate. Subjects aged 14-17 years at baseline were examined at all time-points whereas the entire baseline sample was assessed three times (T0, T2 and T3). Information on the sampling, representativeness, instruments, procedures and statistical methods of the EDSP study was previously described (Lieb, Isensee, von Sydow, & Wittchen, 2000).

The present study is based on the 3,021 individuals aged 14-24 years at baseline and their T2 ($n=2,548$; response rate=84%) and T3 follow-ups ($n=2,210$; 73%). Written informed consent was obtained from all participants.

Instruments

Participants were interviewed with the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen & Pfister, 1997), an updated version of the World Health Organization's CIDI (WHO, 1990). The CIDI is a comprehensive, fully standardized computer-assisted diagnostic interview for the assessment of symptoms, syndromes, and diagnoses of various mental disorders in accordance with the DSM-IV criteria. Acceptable to high validity (Reed, Gander, & Pfister, 1998), interrater (Wittchen et al., 1991) and test-retest reliability (Wittchen, 1994) has been established. Trained and experienced clinical psychologists conducted the interviews at baseline (lifetime version) and follow-up assessments (interval version: covering the assessment period from the last interview until the next).

Assessment of Symptom Clusters

Information from the CIDI psychosis section and the clinical interview rating section with its embedded Brief Psychiatric Rating scale (BPRS; (Overall & Gorham, 1962)) were used to derive measures of psychopathological clusters. In order to calculate measures of frequency (prevalence, incidence and persistence estimates), discrete variables indicating presence or absence of clusters across interview waves were, per definition, necessary.

The Negative-Disorganized Cluster

The ‘Negative-Disorganized Cluster’ (NDC) was designed in accordance with psychopathological findings in the early course of psychosis, showing that the “Bleulerian blend” of negative symptoms, catatonic/motor and disorganization symptoms loaded on a single factor while positive symptoms loaded on another (McGorry, Bell, Dudgeon, & Jackson, 1998). At T0 and T3, two items concerning classic negative and disorganized symptoms from the DIA-X/M-CIDI interview ratings X-section were used: (i) indifference (X11), and (ii) thought incoherence and/or illogicality (X12). These 2 items were rated as: absent (1), very little (2), a little (3), moderately (4), moderately strong (5), a lot (6), very much (7). Each item was dichotomized: absent (0) *versus* present (1) indicating any score above “1”. For the purpose of the analyses, the T0- and T3-NDC were defined as any rating of “present” on any of the 2 items.

At T2, not only the 2 X-section items but also 5 items from the DIA-X/M-CIDI interview observational P-section were available: flat affect (P3), slow speech (P5), slow movement (P6), poverty of speech (P7) and avolition (P8). These 5 items were dichotomously rated: absent (0) *versus* present (1). The T2-NDC was defined as any rating of ‘present’ on any of the 7 items.

The Positive Cluster

Interview ratings from the DIA-X/M-CIDI psychosis G-section (G1, G2a, G3-G5, G7-G13, G13b, G14, G17, G18, G20, G20C, G21 and G22a) on delusions (14 items), hallucinations (5 items) and passivity (1 item) were collected at T2 (lifetime) and T3 (interval version). These 20 items concern classic psychotic symptoms including the cluster of Schneiderian First Rank Symptoms: persecution, conspiracy, thought interference, auditory hallucinations and passivity phenomena. Participants were first invited to read a list of all the psychotic experiences and asked whether they had ever experienced such symptoms. Each psychosis item was rated in 2 ways: absent (1) *versus* present (5). The ‘Positive Cluster (PC) was defined as any rating of “present” on any of the 20 psychosis items (M. D. Dominguez et al., 2009).

Depressive Symptoms

At T2 and T3, the 28 symptom items of the DIA-X/M-CIDI depression E-section were used. If present for at least 2 weeks, items were rated either yes (1) or no (5). A sum score of ‘Depressive Symptoms’ (DS) was formed, with a minimum of 0, and a maximum score of 28 endorsements (Krabbendam et al., 2004).

Assessment of Persistence of Symptoms Clusters

The T2 (lifetime) and T3 (interval) ratings for PC were used to create a summary ‘PC-Persistence’ variable of 3 levels of persistence: never (0); once (1); and twice (2). In order to have a comparable longitudinal measure of ‘NDC-Persistence’, the T0 (lifetime) and T2 measures were combined into a single T0-T2 (lifetime) NDC variable. Together with the information at T3 (interval), this resulted in a summary score variable representing 3 levels of persistence: never (0); once (1); and twice (2).

Assessment of Sociodemographic Characteristics and Environmental Risk Factors

Age, gender, social status, marital status, level of education, urbanicity, cannabis exposure and self-reported trauma were considered (see Tables 1 and 2).

Assessment of Antipsychotic Treatment

As part of the CIDI treatment module, participants were shown a list of different types of medication, rating their use because of any psychopathological or psychosomatic problem. The acknowledgement of any antipsychotic medication (Q1EA4) reported at T2 and T3 was used to derive treatment (‘Antipsychotic Treatment’: no [0] *versus* yes [1]).

Assessment of Clinical Relevance of Psychotic Experiences

Clinical relevance of positive psychotic symptoms was assessed with DIA-X/M-CIDI interview ratings in order to create a variable ‘Psychotic Impairment’ (M. D. Dominguez et al., 2009).

Three help-seeking items assessed whether participants had ever sought help because of psychotic symptoms: seeking doctors’ help because of delusions (G16) or hallucinations (G23), seeking help from other mental health professionals, ranging from general practitioner or school psychologist to psychiatric sheltered housing (Q1DG). The 3 help-seeking items were rated: no (0) and yes (1). A dichotomous ‘Help-seeking’ variable was created indicating a positive answer to any of the 3 questions (1) *versus* negative answers on all (0).

The DIA-X/M-CIDI interview assesses the effect of psychotic experiences on: feeling upset, unable to work, go places or enjoy oneself, at the time of having these experiences (G28), being less able to work (G29) or less able to make friends or enjoy social relationships (G29a) since these experiences began; and how much their life and everyday activities were impaired when these experiences were at their worst (G36). These items were rated: no (0) and yes (1). A dichotomous

‘Dysfunction’ variable was created representing a positive answer on any of the 4 questions (1) *versus* negative answers on all (0).

Finally, a variable ‘Psychotic Impairment’ was created, rated “0” in subjects with psychotic experiences who scored “0” on both Help-seeking and Dysfunction, and “1” in subjects scoring “1” on either or both.

Caseness variable

The X16 DIA-X/M-CIDI item rated the interviewer’s opinion regarding clinical evidence of psychological ill-health in 4 levels: essentially not noticeable (0), not very noticeable (1), clearly ill (2), and very ill (3). The dichotomous variable ‘Caseness’ indicated individuals with a noticeable level of psychiatric caseness (any score above “1”).

Statistical Analyses

All analyses were conducted using the software package STATA 10.1 (StataCorp, 2008).

First, in order to investigate the reliability and the rate of the variables representing the positive and the negative-disorganized psychopathological domains: (i) The Cronbach’s alpha coefficient was used as a measure of the internal consistency for each cluster: the NDC including the 7 items (McGorry et al., 1998) and the PC including the 20 items (M. D. Dominguez et al., 2009) at T2. Alpha values of 0.7 are regarded as satisfactory; (ii) Lifetime cumulative incidence and interval prevalence estimates of both clusters were calculated. Estimates of the NDC were additionally calculated excluding participants exposed to Antipsychotic Treatment; (iii) The distribution of both cluster indicators was examined at T2 and T3 distinguishing individuals with only negative-disorganized symptoms, only positive symptoms or a combination of the two.

Second, associations between psychopathology and demographic and risk factors were examined. It was hypothesized that the NDC would be associated with younger age (Schultz et al., 1997), male sex (Leung & Chue, 2000), single marital status and low educational level (van Os, Hanssen, Bijl, & Ravelli, 2000), whereas female sex (Leung & Chue, 2000), cannabis exposure (Henquet et al., 2005), urbanicity (Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2006a), self-reported trauma (Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2006b) and low level of education (van Os et al., 2000) would show significant associations with the PC. Logistic regression analyses were conducted with the data in the “long” format, i.e. each individual contributing two “time”-point observations (T2 and T3). Clustering within subjects was controlled for by including the variable “time” in the model.

Associations were expressed as odds ratios (OR) and their 95% confidence intervals (95%CI).

Third, in order to examine the natural association between the positive and negative-disorganized clusters (McGorry et al., 1998), cross-sectional associations between the two were examined, controlling for DS. Logistic regression analyses were carried out with the data in the “long” format. Given that cross-sectional associations between symptoms may arise as a function of shared interview variance or represent chronicity effects, associations between clusters were also carried out in longitudinal predictive models across measurement occasions. Logistic regression was used to calculate: (i) the association between the T2-NDC and the T3-PC controlling for DS, and excluding individuals with presence of the T2-PC, and (ii) the association between the T2-PC and the T3-NDC controlling for DS and excluding individuals with presence of lifetime T0-T2 NC.

Fourth, the null hypothesis of independence of the natural courses of the two psychopathological domains (Eaton et al., 1995) was examined analyzing the influence of the degree of persistence (from the interview assessing lifetime presence to T3) of one psychosis cluster (i.e. PC or NDC) on T3 onset of the other cluster and *vice versa*. To this end, logistic regression analyses were performed to examine the associations between: (i) the degree of NDC-Persistence on the one hand and onset of T3-PC on the other in individuals *without* lifetime T2-PC, (ii) the degree of NDC-Persistence on the one hand and T3-PC on the other in individuals *with* lifetime T2-PC; and *vice versa*, controlling for T3-DS.

Fifth, the clinical relevance of the combination of positive and negative experiences was calculated by examining whether the association between the PC and its associated Psychotic Impairment rating was moderated by the NDC. The interaction between the PC and the NDC was calculated on the additive scale (Henquet et al., 2005; Spauwen et al., 2006a, 2006b) using the STATA BINREG command, controlling for depression, with the data in the “long” format. An additive risk model rather than a multiplicative risk model is more likely to yield information on the degree of synergism between causes which can be interpreted biologically in a meaningful way –that is, the extent to which both causes depend on each other or co-participate in disease causation (Darroch, 1997). In order to validate Psychosis Impairment, logistic regression analyses were conducted against the Caseness and Antipsychotic Treatment variables.

Results

Subject Characteristics

The average age of the participants at baseline was 18.3 years (range=14–24). Demographic characteristics are depicted in Table 1.

Table 1. Characteristics of Subjects at Baseline

At baseline (T0) n=3,021		Variables description	n	%
Gender				
Male			1,488	49.26
Female			1,533	50.74
Level of education		The participants were asked which level of education they were attending or, in the case of discontinuation, which was the highest level they had attended (A3 DIA-X/M-CIDI item).		
Low		- mandatory basic school or learning a profession	475	15.72
Medium		- high school	915	30.29
High		- high school preparing for university, and university	1,631	53.99
Social status		The participants were asked to choose from specified options, which class he or she believed to be in (A16 DIA-X/M-CIDI item).		
Lower		- lower class, lower middle class	207	6.85
Middle		- middle middle class	1,804	59.72
Upper		- higher middle class, upper class	950	31.45
Other		- none of the above and missing values	60	1.99
Urbanicity		Obtained through German government population registries. The population density of the Munich surroundings areas was 553 persons per square mile and that of the city 4061 persons per square mile		
Rural		- the surrounding areas of Munich	859	28.43
Urban		- the German city of Munich	2,162	71.57

Natural Occurrence

Items in each psychopathological cluster were strongly correlated yielding satisfactory internal consistency (NDC items: Cronbach's $\alpha=0.7$, 6 items; PC items Cronbach's $\alpha=0.7$, 20 items).

The baseline cumulative lifetime incidence of NDC was 11.4% (n=345) while the interval prevalence was 12.8% (n=325) at T2 and 12.2% (n=270) at T3. Excluding individuals exposed to antipsychotic treatment did not impact on these rates (12.7% (n=322) at T2 and 12.2% (n=269) at T3). The PC cumulative lifetime incidence was 22.7% (n=574) at T2 while the interval prevalence was 12.4% (n=274) at T3.

In terms of population distribution (Table 2), 15.7% of the 2548 participants reported only negative-disorganized symptoms at T2 (lifetime cumulative incidence), 17% reported only positive symptoms whereas 5.5% reported both, more than twice what would be expected by chance alone (2.6%). At T3 (interval), prevalence rates were, respectively, 9.9%, 10.1% and 2.3% of a total of 2210 participants, again more than twice the expected rate (1%).

Associations with Sociodemographic and Environmental Risk Factors

The NDC was significantly associated with younger age, male sex, single marital status and low educational level, whereas the PC was significantly associated with low educational level, cannabis exposure, urbanicity and self-reported trauma. The combination of both clusters was significantly associated with all variables (Table 3).

Associations between Psychopathological Clusters

Cross-sectionally, the NDC was significantly associated with the PC, controlling for DS (OR=1.36, 95%CI=1.10-1.69). The prospective association between the T2-NDC and the T3-PC, excluding individuals with presence of lifetime T2-PC and controlling for DS, was significant (OR=4.65, 95%CI=1.09-19.96). In contrast, the prospective association between the T2-PC and the T3-NDC, excluding individuals with presence of lifetime T0-T2 NC and controlling for DS, was neither large nor significant (OR=0.82, 95%CI=0.55-1.24).

Independence of Natural Course

Controlling for depressive symptoms, NDC-Persistence not only predicted PC-Persistence but also T3 incident psychotic experiences in a dose-response fashion. In contrast, PC-Persistence predicted neither NDC-Persistence nor T3 incident negative-disorganized symptoms (Table 4).

Psychopathological Clusters and Clinical Relevance

Psychotic Impairment was strongly associated with the Caseness (OR=10.3, 95%CI=7.0-15.2) and the Antipsychotic Treatment (OR=15.3, 95%CI=6.1-38.4) variables.

Proportion of T2 and T3 Psychotic Impairment with expression of psychosis clusters are depicted in Table 2. Differences in risk for Psychotic impairment for each psychopathological cluster were statistically significant in the combined T2 and T3 data analysis, as evidenced by the estimated additive interaction between the two clusters in the model of impairment (RD=16.2%, 95%CI=7.3%-25.2%). Analysing T2 and T3 separately revealed replication at both time points (Table 2).

Table 2. Psychopathological Clusters and Risk for Psychotic Impairment

Psychosis Symptoms Clusters						Psychotic Impairment				
Symptom clusters	Population Distribution				Prevalence estimates			Risk Difference		
	T2 (lifetime cumulative incidence)		T3 (interval prevalence)		T2		T3	T2		Both T2 and T3
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	RD (95%CI)	
Negative-Disorganized only	400	15.7	220	9.9	—	—	—	—	0%	0%
Positive only	434	17.0	224	10.1	155	35.7	88	39.3	37% (32%–41%)	37% (34%–41%)
Co-occurrence of both clusters	140	5.5	50	2.3	71	50.7	27	54.0	53 % (43%–64%)	53% (45%–62%)
Total subjects	2548	100	2210	100	226	8.9	115	4.5	—	—

Note. RD: Risk Difference; 95%CI: 95% Confidence Interval

Table 3. Psychopathological Clusters and Patterns of Association with Sociodemographic and Environmental Risk Factors

At T2 (n=2,548) and T3 (n=2,210)	Variables Definition	Negative- Disorganized Cluster OR (95%CI)	Positive Cluster OR (95%CI)	Co-occurrence of Both Symptom Clusters OR (95%CI)
Age	Continuous variable	0.91 (0.89 – 0.93)*	0.99 (0.97 – 1.01)	0.88 (0.84 – 0.93)*
Gender	Male <i>versus</i> Female	0.70 (0.62 – 0.79)*	0.90 (0.77 – 1.05)	0.73 (0.52 – 1.03)
Single marital status	Defined as the single categories (married, living apart, divorced, widowed and never married) <i>versus</i> the married category (A9 DIA-X/M-CIDI item)	2.13 (1.51 – 3.01)*	1.28 (0.97 – 1.70)	15.16 (2.11 – 108.91)*
Lower level of education	Defined as the lower (low) <i>versus</i> the highest levels of education (medium and high) (A3 DIA-X/M-CIDI item)	1.90 (1.62 – 2.23)*	1.36 (1.09 – 1.68)*	1.75 (1.14 – 2.67)*
Cannabis Exposure	A dichotomous variable defined as cannabis use of 5 times or more (Henquet et al., 2005) since the previous interview (T2 and T3). L3B1 DIA-X/M-CIDI item of the Substance-related disorders section which assessed cannabis use: never (0), once (1), twice (2), thrice (3), four times (4) and five times or more (5).	1.12 (0.90 – 1.38)	2.10 (1.61 – 2.75)*	2.05 (1.18 – 3.59)*
Urbanicity	Defined as the surrounding areas of Munich (rural) <i>versus</i> the German city of Munich (urban) (Spauwen et al., 2006a) (German government population registries)	1.12 (0.97 – 1.29)	1.19 (1.01 – 1.41)*	1.51 (1.01 – 2.27)*
Trauma	'Self-reported trauma' at T2 and T3 was labeled with any affirmative response of exposure to any of the 9 traumata from the Trauma module (N1A DIA-X/M-CIDI item) (Spauwen et al., 2006b). Respondents could indicate a positive response on a visually presented list of 9 groups of specified traumatic events such as physical threat, serious accident or sexual abuse.	1.03 (0.87 – 1.24)	1.46 (1.21 – 1.76)*	2.19 (1.36 – 3.39)*

Note. OR= odds ratio, 95%CI= 95% Confidence Interval, *=statistically significant association

Table 4. Longitudinal Association of Natural Courses

Persistence of Symptom Clusters	Levels of Persistence	Incident NDC		Persistent NDC	
		OR	CI	OR	CI
Persistence of Positive Cluster (PC)	0	-	-	-	-
	1	1.3	0.6 - 1.3	1.3	0.7 - 2.3
	2	1.3	0.9 - 1.6	1.4	0.6 - 3.3
		Incident PC		Persistent PC	
		OR	CI	OR	CI
Persistence of Negative-Disorganized (NDC) Cluster	0	-	-	-	-
	1	1.6*	1.1 - 2.4	1.7*	1.1 - 2.8
	2	4.5*	2.3 - 8.7	3.4*	1.3 - 9.0

Note. OR= odds ratio; CI= 95% Confidence Interval; *=statistically significant association

Discussion

Findings

Experiences indicative of the positive (van Os et al., 2009) and negative symptoms seen in psychotic disorders occurred in the general population (5-year interval rates of around 12%), independent of antipsychotic treatment. Positive and negative dimension scores clustered together more often than predicted by chance, independent of depression, yet they displayed a differential pattern of socio-demographic and environmental risk factors associations: the NDC was associated with a profile indicative of developmental impairment and the PC with environmental risks. Their pattern over time revealed that persistent expression of the NDC predicted onset of psychotic experiences; in contrast, persistent expression of psychotic experiences did not predict onset of negative-disorganized features. Finally, “comorbid” expression of the two clusters increased the risk for impairment and, by implication, need for care.

Quantitative Variations of Normal Human Mentation

Self-reported negative-disorganized and positive psychotic features were distributed in the general population suggesting they represent quantitative variation of processes underlying normal human mentation. While dopamine-blocking medications dampen motivational drives causing secondary negative symptoms (Kapur, 2004) in both clinical (Carpenter, Heinrichs, & Alphas, 1985) and healthy samples (Artaloytia et al., 2006), this study highlighted the natural occurrence of attenuated negative symptoms in otherwise healthy and unmedicated individuals. The hypothesis of an exclusively drug-induced nature of non-motor negative symptoms (Artaloytia et al., 2006) therefore is unlikely.

Negative Features Predict Positive Features and Onset of Clinical Psychosis

It has been suggested that cognitive/negative symptoms associated with schizophrenia may represent alterations in brain development associated with distributed genetic risk, influencing a final common pathway of neurotransmitter dysregulation resulting in the onset of positive psychotic symptoms, particularly when combined with environmental exposures (van Os & Kapur, 2009). Several elements in the current epidemiological analysis support this model.

First, the PC and NDC clustered together more often than could be expected by chance alone. Thus, psychotic disorders such as schizophrenia are not the result of the chance cross-section of the separate liabilities of developmental impairment on the one hand and reality distortion on the other; they are linked together in a way that suggests fundamental overlap or interaction of underlying mechanisms.

Second, the pattern of associations for the NDC with young age, male sex, single marital status and lower educational level resembles the pattern seen in clinical samples (Leung & Chue, 2000; Schultz et al., 1997). The psychotic NDC, in contrast to the PC, is associated with neurocognitive impairment (M. D. G. Dominguez et al., 2009) resulting in poorer social functioning (Macdonald et al., 2000), poorer response to antipsychotic treatment (Erhart et al., 2006) and a worse prognosis (McGlashan & Fenton, 1992).

Third, the socio-demographic associations of the PC are in agreement with previous reports linking positive psychotic experiences to environmental risk factors such as cannabis exposure, urbanicity, self-reported trauma and lower educational level (Henquet et al., 2005; Spauwen et al., 2006a, 2006b; van Os et al., 2000). The link between these environmental risk factors and psychotic experiences may be explained in terms of stress-dopamine (DA) interactions and sensitization (Collip, Myin-Germeys, & Van Os, 2008). There is evidence that mesocortical DAergic innervation of the prefrontal cortex may regulate the activity of mesolimbic subcortical DA innervations and that the impact of environmental risk factors may result in taking the prefrontal cortical (PFC) “off-line”, resulting in altered responsiveness of subcortical DAergic innervations (Deutch, Clark, & Roth, 1990). Thus, when DA transmission is increased by exposure to stress or agonist drugs, there may be a shift in the balance of the system away from PFC control and toward limbic predominance, facilitating a DA hyperactivity in the ventral tegmental area of the midbrain, resulting in the development of positive symptoms (Laruelle et al., 2003).

Fourth, importantly, the longitudinal analysis suggested that in this community sample negative features preceded positive features rather than the other way round.

This, together with the associations between positive features and environmental risks, suggests that the NDC reflects an underlying vulnerability that, when combined with environmental exposures, results in positive symptoms increasing the risk of need for care (Figure 1). This latter suggestion is supported by the fact that the combination of positive and negative features predicted impairment and onset of clinical psychosis.

Figure 1. Negative/disorganized Features Predict Positive Features and Onset of Clinical Psychosis

Note. The longitudinal analysis suggested that the negative-disorganized cluster associated with a socio-demographic indicative of developmental impairment reflects an underlying vulnerability that, when combined with environmental exposures such as cannabis use, trauma and urbanicity, results in positive psychotic symptoms increasing the risk of impairment and clinical relevance.

Methodological Issues

First, assessment of psychotic experiences was based on self-report information by the respondents in diagnostic interviews, complemented by clinical ratings of core features of positive and negative symptoms derived from the clinical rating section and selected BPRS items. False-positive psychotic experiences are likely to have occurred, increasing random error; nevertheless, there is a substantial literature on the (predictive and other forms of) validity of self-reported psychotic experiences (van Os et al., 2009).

Second, despite the hazard of under/overestimation of true positive, clinically relevant psychotic experiences (M. D. Dominguez et al., 2009), the validation of the outcome variable against Caseness and Antipsychotic Treatment supports the validity of Psychotic Impairment as a proxy measure of clinical relevance.

Third, the definition of clinically relevant psychosis was contingent on the presence of positive psychotic experiences. This, however, is in line with the diagnostic criteria for schizophrenia, which require positive psychotic experiences for making the diagnosis.

Fourth, the measures of negative symptoms were varying between measurement occasions. This is likely to have generated more random error resulting in a more conservative estimate of associations (i.e., the overlap between PC and NDC may be stronger than reported and the predictive value for positive psychotic experiences may be higher).

Finally, our measure of negative symptoms included features of disorganization in accordance with first-episode studies (McGorry et al., 1998) while studies using more chronic samples reported a separate disorganized dimension (Liddle, Carpenter, & Crow, 1994). Given that the current sample was well before the earliest possible phase of psychotic illness onset, combining negative and disorganized features in one domain appeared the most parsimonious solution. Also, a recent meta-analysis of studies examining associations between psychotic psychopathology and neurocognition reported associations between neurocognition and both the negative and disorganized dimensions, but not the psychotic and affective dimensions (M. D. G. Dominguez et al., 2009).

Acknowledgments

Funding/Support: This work is further part of the Early Developmental Stages of Psychopathology (EDSP) Study and is supported by the German Federal Ministry of Education and Research (BMBF) project no. 01EB9405/6, 01EB9910/6, EB10106200, 01EB0140, and 01EB0440. Part of the field work and analyses were also additionally supported by grants of the Deutsche Forschungsgemeinschaft (DFG) LA1148/1-1, WI2246/7-1, and WI709/8-1.

Data Access and Responsibility: Principal investigators of the EDSP-Study are Dr. Hans-Ulrich Wittchen and Dr. Roselind Lieb. Both take responsibility for the integrity of the study data. All authors and co-authors had full access to all study data. Data analysis and manuscript preparation were completed by the authors and co-authors of this article, who take responsibility for its accuracy and content.

Acknowledgements: Core staff members of the EDSP group are: Dr Katja Beesdo, Dr. Petra Zimmermann, Dr. Axel Perkonig, PhD Dipl.-Stat. Michael Höfler, , Dipl.-Psych. Tanja Brückl, Dipl.-Psych. Agnes Nocon, Dipl.-Inf. Hildegard Pfister, Dipl.-Soz. Barbara Spiegel, Dipl.-Psych. Andrea Schreier. Scientific advisors are Dr. Jules Angst (Zurich), Dr. Kathleen Merikangas (NIMH, Bethesda), Dr. Ron Kessler (Harvard, Boston) and Dr. Jim van Os (Maastricht).

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CHAPTER 5

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CHAPTER 6

DISCUSSION

DISCUSSION: CONTENTS

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Delusions and hallucinations are not exclusive to schizophrenia and psychotic symptoms occur across a wide range of diagnostic categories with their differential diagnosis being based on duration, symptoms patterns, level of dysfunction, substance use, “bizarreness” of delusions and presence of depression or mania. However, diagnostic categories show overlap in their genetic liability (Kendler & Diehl, 1993), suggesting a shared genetic liability across non affective psychosis and bipolar disorder (Craddock & Owen, 2007). A consilience model of clinical psychosis (van Os & Kapur, 2009) postulates that observed phenomenological heterogeneity of psychosis is associated with different genetic liabilities: (i) positive psychotic symptoms, shared by all psychotic diagnostic categories, occupy a central position in the model, and plausibly result from gene-environment interactions; (ii) social-interpersonal style and negative symptoms, associated with neurocognitive impairment, may be the phenomenological expression of altered brain development; and (iii) affective genetic risk may lead to the expression of positive psychotic symptoms or reality distortion through the mechanism of aberrance salience attribution.

Psychotic experiences have been shown to be expressed at levels well below its clinical manifestation. A systematic review of general population surveys suggests that phenomena indicative of schizophrenia and related disorders –e.g. persecutory delusions and auditory hallucinations- are observed in an attenuated form, in around 5-8% of healthy people (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). These attenuated expressions may be the behavioural expression of an underlying continuous psychosis liability (Lataster, Myin-Germeys, Derom, Thiery, & van Os, 2009). This is further supported by longitudinal studies demonstrating a link between psychotic experiences in the general population and increased probability of having a psychotic disorder later in life (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005; Poulton et al., 2000; Welham et al., 2009; Werbeloff, Drukker, & Dohrenwend, 2009). To date, no published study has clearly demonstrated abnormal persistence of (normally transitory) developmental subclinical psychosis like symptoms to be the precursor state of clinical presentation. Furthermore, the population-surveys have focused on positive psychotic-like experiences only, ignoring if and how another attenuated symptom domains may play a role driving subclinical psychosis expression to clinical states. Therefore, population-based research on such psychopathological phenomena may be productive, particularly when a longitudinal perspective allows for the epidemiological prediction of the model of clinical psychosis.

The studies described in this thesis aim to investigate the evolution of psychosis from a starting position of mental health to the onset of clinical psychosis within a large representative sample of adolescents in the general population (the Early

Developmental Stages of Psychopathology (EDSP) study; (Lieb, Isensee, von Sydow, & Wittchen, 2000; Wittchen, Perkonig, Lachner, & Nelson, 1998)) who were followed up for maximum of 10 years, by examining (i) the quantitative variation of psychometric expressions of the psychosis phenotype (chapters 3, 4 and 5), (ii) the hypothesis of continuity over time from abnormal persistence of commonly transitory psychotic-like experiences to clinically relevant psychosis (chapter 3), and (iii) if and how interacting processes underlying psychopathological dimensions (the associations of which were obtained by a meta-analysis of associations between psychosis dimensions and the intermediary phenotype of neurocognition (chapter 2)), from a perspective of risk, may contribute to the onset of clinical psychosis (chapter 4 and 5).

Quantitative Variation of Normal Human Mentation

Self-reported psychopathological experiences resembling the positive psychotic, negative-disorganized, depressive and manic symptoms are also expressed in attenuated form in otherwise “healthy” individuals (Chapman et al., 1994; Hanssen et al., 2005; Krabbendam et al., 2004; Krabbendam, Myin-Germeys, Hanssen et al., 2005; Maric et al., 2004; Poulton et al., 2000; Reed, Gander, & Pfister, 1998; van Os, Hanssen, Bijl, & Ravelli, 2000) (chapters 3, 4 y 5). Attenuated expressions of psychosis symptom domains therefore seem to be distributed in the general population to the degree that they represent quantitative variations of normal human mentation.

In the EDSP study, subclinical psychosis was confirmed to be relatively common (Psychosis Expression rates of 22%) and mostly transitory, recurrence or persistence occurring in 30-40% of cases (chapter 3). The recurrence-persistence rate of subclinical psychosis in our study was higher than reported in previous population-based studies. In a two-year follow-up of a general population sample aged 18-64 years, Hanssen and colleagues found a two-year 8% persistence rate of baseline subclinical psychosis, and an 8% transition rate from subclinical to clinical psychosis (Hanssen et al., 2005). In our study, the recurrence-persistence rate was 30-40% over time, considerably higher. The most likely factor to explain this difference is the much younger age of the EDSP sample. Given the rapid decline of psychosis expression with age (Peters, Joseph, & Garety, 1999; van Os et al., 1999; Verdoux et al., 1998), continuity over time will become less likely with advancing age. Thus, in a previous follow-up study of adolescents, a 3-year persistence rate was found of 40%, similar to that of the current study (Escher, Romme, Buiks, Delespaul, & van Os, 2002).

Affective symptoms in our study have also been shown to be expressed at levels well below its clinical manifestation (chapter 4) existing along a spectrum including

subclinical expressions, evidenced by relatively high rates of expression of bipolar spectrum symptoms and subthreshold depressive states (Akiskal & Vazquez, 2006; Angst & Cassano, 2005).

Experiences indicative of negative symptoms seen in psychotic disorders also occurred in the EDSP population sample (5-year cumulative prevalence rates of around 12%), independent of antipsychotic treatment (chapter 5). While dopamine-blocking medications dampen motivational drives causing secondary negative symptoms (Kapur, 2004) in both clinical (Carpenter, Heinrichs, & Alphas, 1985) and healthy samples (Artaloytia et al., 2006), the present work highlighted the natural occurrence of attenuated negative symptoms in otherwise healthy and unmedicated individuals. The hypothesis of an exclusively drug-induced nature of non-motor negative symptoms (Artaloytia et al., 2006) therefore is unlikely.

The Psychosis Proneness-Persistence-Impairment Model

Longitudinal cohort studies have consistently shown an association between subclinical psychotic experiences and increased likelihood of developing a psychotic disorder later in life (Chapman et al., 1994; Poulton et al., 2000; Welham et al., 2009)(Hanssen et al., 2005; Werbeloff et al., 2009). Population-based studies demonstrate that subclinical delusional-like thinking and mild hallucinatory experiences in the general population are usually transitory (Chapman et al., 1994; Hanssen et al., 2005; Poulton et al., 2000), but when combined with exposure to additional environmental risks during critical developmental periods, e.g cannabis use, childhood trauma and urban environment (Cougnard et al., 2007) the usually transitory phenomena become abnormally persistent and are more likely to progress to a clinical psychotic state.

Chapter 3 (M.D.G. Dominguez, Wichers, Lieb, Wittchen, & van Os, 2009) presents the first study to epidemiologically describe the evolution of transitory psychosis-like symptoms to the development of abnormal persistence increasing the probability of clinical deterioration. In the study described in this thesis, subclinical psychosis was confirmed to be common (Psychosis Expression rates of 22%) and mostly *transitory*. *Persistent* positive symptoms at a subclinical level posed a significant risk for clinically relevant psychosis over time and thus can be considered a marker of emerging clinical states. An exposure gradient was found with longer duration of (more persistent) subclinical psychosis carrying a greater risk of *impairment*. Although most subclinical psychosis was transitory, this study demonstrates the impact of the relationship between the clinical and the subclinical is not negligible: around 40% of new onset, clinically relevant psychosis in young adults was associated with subclinical psychosis ten years earlier, and furthermore one fifth displayed recurrent or persistent subclinical psychosis. Therefore for some

individuals, psychosis is the result of a long process manifest by subclinical experiences and functional deficits. Two consequences arise from these findings: first, positive psychotic experiences can be regarded as the behavioural expression of underlying distributed vulnerability for psychosis and, second, a significant proportion of psychotic disorder may be conceptualised as the rare poor outcome of a more common developmental phenotype characterised by persistence of psychometrically detectable subclinical psychotic experiences. Consequently, these findings provide evidence for the continuity over time from subclinical persistent psychotic experiences to clinical psychotic states, yielding insight into the dynamics preceding the clinical onset of psychotic disorder from a population perspective; this has been summarised descriptively as a Psychosis Proneness-Persistence-Impairment model of psychotic disorder (M.D.G. Dominguez et al., 2009; van Os et al., 2009).

From Persistent Subclinical Psychosis to Impairment: Behavioural, Environmental and Neurobiological Interactions

The positive psychosis pathway may be understood as the phenomenological correlate of the classical dopamine hypothesis which proposes that hyperactivity of dopamine (DA) transmission from DA cell bodies located in the ventral tegmental area of the midbrain to their terminal fields in the nucleus accumbens and limbic cortex results in the development of positive psychotic symptoms (Laruelle, 2000; Lieberman, Sheitman, & Kinon, 1997). Dopaminergic hyperactivity may be associated with what has been called a state of endogenous sensitization (Laruelle, 2000). The liability for psychosis may involve deficits in neural regulation resulting in a pathological condition of neurochemical sensitization of the mesolimbic dopaminergic system analogous to the preclinical model of behavioral sensitization induced by administration of dopamine releasing drugs (Lieberman et al., 1997). Behavioral sensitization is a progressive, enduring enhancement of behavior that develops following repeated stimulant administration. It is mediated in part by dopaminergic pathways that are also thought to modulate the development of psychosis (Wolf, White, Nassar, Brooderson, & Khansa, 1993).

Endogenous neurochemical sensitization may arise in part as a result of exposure to environmental conditions (Laruelle, Kegeles, & Abi-Dargham, 2003). For example, environmental stress can induce sensitization and has been demonstrated to be cross-reactive with many types of pharmacologically induced sensitization, including dopamine and opiate agonists (Lieberman et al., 1997). It has been suggested that several environmental risk factors, e.g., perinatal injury, childhood trauma, repeated life events and drug abuse, may contribute to dopamine sensitization (Collip, Myin-Germeys, & van Os, 2008). It is attractive to speculate that a genetic tendency to abnormal dopamine sensitization is associated with the

tendency to express low grade psychotic experiences that in most individuals will only be expressed transitorily over development. However, in the case of developmental exposure to environmental risk factors, individuals may develop a sensitized dopamine system resulting in abnormally persistent (Cougnard et al., 2007) and, eventually, clinically relevant psychotic states (M.D.G. Dominguez et al., 2009).

Understanding How Interacting Processes Underlying Psychopathological Dimensions Contribute to the Onset of Clinical Psychosis

Epidemiological research on psychosis at the level of the general population has mainly focused on positive psychotic-like experiences. Although the pool of symptom dimensions from the psychosis phenotype has also been observed at a subclinical level (Krabbendam et al., 2004; Krabbendam, Myin-Germeys, Hanssen et al., 2005; Maric et al., 2004; Stefanis et al., 2002), how development of the various underlying symptom domains contribute to the risk of clinical psychosis has not been investigated.

The Cluster of Disorganized and Negative Symptoms versus Positive and Affective Ones in Psychotic Disorders

Previous published work has not been able to define the pattern of intercorrelations of psychosis dimensions either at a population-level or in clinical samples (chapter 1). Hundreds of studies have examined the association between psychotic psychopathology and neurocognitive intermediary phenotypes but their findings have been inconsistent. Therefore, chapter 2 (M. D. G. Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2009) describes a meta-analysis of psychosis dimensions (including affective and non-affective measures of psychopathology) and the intermediary phenotype of neurocognition (considering all neurocognitive measures) in subjects with a lifetime history of non-affective psychosis. Furthermore the patterns of inter dimensional correlation were examined.

The systematic review (58 studies, 5009 individuals) concluded that psychopathological heterogeneity was weakly but differentially related to distinct patterns of neurocognitive function: negative and disorganized dimensions were modestly but meaningfully associated with neurocognitive impairment in the majority of neurocognitive domains whereas positive and depressive dimensions were not. Associations were in the expected direction but small to moderate in magnitude (correlations ranging from -0.29 to -0.12). In addition, significantly higher correlations were found for the negative dimension in relation to verbal fluency (p-value: 0.005), and for the disorganized dimension in relation to reasoning and problem solving (p-value: 0.004), and attention/vigilance (p-value:

0.03). These results further suggest that distinguishing multiple domains of cognitive functioning in schizophrenia is useful, even though the deficit is to a large extent generalized and may even be accounted for statistically by a single-factor model (as suggested by the CATIE trial, (Keefe et al., 2006)). Furthermore, the patterns of association for the four psychosis dimensions were stable across neurocognitive domains and independent of age, gender and chronicity of illness. Thus, cognitive impairment in psychosis (Aleman, Hijman, de Haan, & Kahn, 1999; Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Heinrichs & Zakzanis, 1998; Johnson Selfridge & Zalewski, 2001; Lee & Park, 2005; Pelletier, Achim, Montoya, Lal, & Lepage, 2005) does not appear to be entirely orthogonal to psychopathology, as heterogeneity in non-affective psychosis is weakly but meaningfully associated with measures of neurocognition. Differential patterns of cognitive performance among the different psychopathological indicated some meaningful contrasts, suggesting differential latent cerebral mechanisms underlying the cluster of disorganized and negative symptoms on the one hand, and positive and affective on the other.

Different Underlying Pathophysiological Processes Associated with Different Intermediary Phenotypes May Account for a Substantial Part of Psychopathological Heterogeneity

Findings at different levels of neuroscientific and neurocognitive research have suggested some evidence of meaningful contrasts in the underlying patterns of cerebral dysfunction in relation to the psychopathological heterogeneity of psychosis. Functional brain imaging studies have demonstrated different patterns of altered cerebral activity in schizophrenia. The negative (Andreasen, Paradiso, & O'Leary, 1998; Sanfilipo et al., 2000; Schroder et al., 1996) and disorganization (Cridler, 1997; Liddle et al., 1992) symptoms were associated with alterations in frontal lobe functioning, whereas auditory hallucinations produced normal activation of the left prefrontal cortex, but exhibited less activation of the left middle temporal gyrus and supplementary motor area (Lennox, Park, Medley, Morris, & Jones, 2000; McGuire et al., 1995; Shergill, Brammer, Williams, Murray, & McGuire, 2000; Shergill, Bullmore, Simmons, Murray, & McGuire, 2000). At the level of neurotransmission, different patterns involving several interconnected limbic, cortical and subcortical structures have been implicated in the different symptom dimensions in psychosis. An overactivity in neurotransmission from DA cell bodies (DA-D2 receptors), located in the ventral tegmental area of the midbrain, may result in the development of positive symptoms. A hypodopaminergic state in the prefrontal cortical terminal fields of the mesocortical DA neurons (DA-D1 receptors) has been hypothesized to underlie cognitive impairment and negative symptoms of schizophrenia, and may in turn contribute to

the disinhibition of subcortical DA function (Duncan, Sheitman, & Lieberman, 1999; Kellendonk et al., 2006).

The putative intermediary phenotype of an altered sensitivity to stress, associated with genetic risk of psychosis, was associated with increased levels of affective and positive psychotic symptoms following exposure to small stressors in the flow of daily life (Myin-Germeys & van Os, 2007), whilst it correlated negatively with cognitive impairment in patients with schizophrenia (Myin Germeys, Krabbendam, Jolles, Delespaul, & van Os, 2002). Furthermore, positive psychotic symptomatology has been associated with impaired social cognition, such as alterations in self-monitoring (Bentall, 1990; Johns et al., 2001), a probabilistic reasoning bias referred to as jumping-to-conclusions (Garety & Freeman, 1999; Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001; van Dael et al., 2006), and mentalizing deficits (Versmissen et al., 2007). Where examined, research suggests that the association between altered social cognition and symptoms is weakest for the negative and disorganization dimensions (van Dael et al., 2006).

In sum, neuroimaging, neuropharmacological and neurocognitive findings concur showing weak but systematic patterns of associations with symptom dimensions. This finding may explain at least some of the psychopathological heterogeneity in non-affective psychosis and may be refined in future studies to the extent that they become nosologically useful.

Integrating Affective Dysregulation and Reality Distortion from a Perspective of Risk

Psychopathological studies have shown psychotic experiences to co-occur in the range of affective disorders (Dunayevich & Keck, 2000; Sareen, Cox, Goodwin, & G, 2005) and, conversely, high rates of affective symptoms have been demonstrated in patients diagnosed with DSM-IV non-affective psychotic disorders (Peralta & Cuesta, 2009) and schizotypy (Debbane, van der Linden, Gex-Fabry, & Eliez, 2009). Family studies demonstrate a degree of overlap in genetic liability between non-affective psychotic disorder and bipolar disorder (Cardno, Rijsdijk, Sham, Murray, & McGuffin, 2002; Craddock & Owen, 2007; Lichtenstein et al., 2009). Turning to epidemiological settings, subthreshold depressive and/or hypomanic symptoms have been shown to represent the behavioural expression of risk for more severe psychotic states such as bipolar disorder (Regeer et al., 2006; Tijssen et al., 2009). Furthermore, earlier general population surveys in Greece and the Netherlands have shown a high degree of overlap between psychotic experiences and affective symptoms below the threshold for clinical disorder (Kaymaz et al., 2007; Krabbendam, Myin-Germeys, Bak, & van Os, 2005; Krabbendam et al., 2004; Krabbendam, Myin-Germeys, Hanssen et al., 2005; Stefanis et al., 2002).

Nonetheless, the majority of general cohort studies on transition rates from subclinical symptoms to clinical syndromes did not examine co-expression of reality distortion and affective dysregulation. Chapter 4 connects reality distortion and affective dysregulation from a perspective of risk to the onset of clinical psychosis at a population-based level. The results suggest that psychotic experiences in the general population are non-specifically associated with affective dysregulation, in a dose-response fashion. In addition, persistence of psychotic experiences and the onset of impairment occur more often if there is a context of affective dysregulation – that is, the higher the affect dysregulation in terms of subclinical depressive or hypomanic symptoms, the higher the incidence and persistence of psychotic experiences, and the higher the incidence of clinical psychosis. In light of the accumulating evidence on overlap in genetic liability, suggesting a broad underlying vulnerability that expresses across the different psychosis categories, our findings of associations between affective dysregulation and psychotic experiences in the general population may thus in part reflect passive clustering of the behavioral expression of overlapping distributed genetic vulnerabilities.

The fact that co-expression of affective dysregulation predicted persistence of reality distortion and secondary impairment (chapter 4) suggests that, in addition to correlated genetic liabilities, a direct impact of affective regulation on clinical relevance of psychotic experiences may be hypothesized. Existent psychological models of symptom formation suggest that the emotional context, and associated beliefs or appraisals, may induce bias in logical reasoning processes and therefore provoke reality distortion in healthy individuals (Garety et al., 2001; Myin-Germeys & van Os, 2007). In the psychological model described by Garety and colleagues (2007), the experience of a stressful event is thought to potentially give rise to altered pre-existing beliefs and ongoing appraisals of experiences, due to a certain emotional change or a cognitive processing bias. These distorted processes may lead to aberrant experiences that may seem personally significant to the individual and are likely to trigger a search for an explanation as to their meaning and cause that is consistent with affect-associated beliefs. Biased appraisal processes may contribute to a judgment that the experience is in fact externally caused. It is the interpretation that causes the associated distress and disability, rather than the experience itself. Thus, maladaptive appraisal patterns, induced by emotional processes, are suggested to increase the risk for positive symptom formation in vulnerable individuals (Garety, Bebbington, Fowler, Freeman, & Kuipers, 2007). Our findings provide support for a cognitive model of symptom formation, by demonstrating involvement of affective processes in the onset and persistence of reality distortion outside the context of disorder.

Attempts have been made to integrate cognitive and neurobiological theories on psychosis (Garety et al., 2007; Kapur, 2003; van Os & Kapur, 2009). There is evidence that psychotic symptoms are associated with underlying alterations in the dopamine system, including increased dopamine synaptic availability (Hirvonen et al., 2005), increased striatal dopamine synthesis (Huttunen et al., 2008; Meyer-Lindenberg et al., 2002) and increased dopamine reactivity to stress (Brunelin et al., 2008; Myin-Germeys & van Os, 2007). Under normal circumstances, it is the context-driven activity of the dopamine system that mediates the experience of novelty and the acquisition of appropriate motivational salience, detecting new rewards in the environment that facilitate learning and goal-directed behavior. Certain cerebral vulnerabilities, occasioned by interplay between genetic and environmental risks, could trigger context-independent or context-inappropriate release of dopamine. Such a dysregulated dopamine system may cause aberrant assignment of salience and motivational significance to external objects (leading to delusions) and internal representations of percepts and memories (leading to hallucinations (Kapur, Mizrahi, & Li, 2005). Thus, theory derived from existent psychological models of psychotic symptom formation predicts that affective dysregulation may impact directly on risk for reality distortion; additionally, the risk for clinically relevant psychosis may be particularly high in those who have a genetically liability for dopaminergic dysregulation facilitating aberrant salience attribution.

***Negative and Disorganized Features Increasing Risk for Positive Symptoms
Increasing Risk for Impairment***

Several elements in the analysis of chapter 5 support the epidemiological prediction of the hypothesis that cognitive alterations and negative features associated with schizophrenia may represent alterations in brain development associated with distributed genetic risk, influencing a final common pathway of neurotransmitter dysregulation resulting in the onset of positive psychotic symptoms, particularly when combined with environmental exposures, such as cannabis, developmental trauma and urbanicity (van Os & Kapur, 2009).

First, a pattern of socio-demographic associations for the negative-disorganized cluster with young age, male sex, single marital status and lower educational level was found, reflecting a profile indicative of developmental impairment which resembles the pattern seen in clinical samples (Leung & Chue, 2000; Schultz et al., 1997). This developmental profile is in accordance with the association found in chapter 2 between neurocognitive impairment and the psychotic negative - disorganized dimensions which are known to result in poorer social functioning (Macdonald, Hayes, & Baglioni, 2000), poorer response to antipsychotic treatment

(Erhart, Marder, & Carpenter, 2006) and a worse prognosis (McGlashan & Fenton, 1992).

Second, the socio-demographic associations of the positive dimension are in agreement with previous reports linking positive psychotic experiences to environmental risk factors such as cannabis exposure, urbanicity, self-reported trauma and lower educational level (Henquet et al., 2005; Spauwen, Krabbendam, Lieb, Wittchen, & van Os, 2006a, 2006b; van Os et al., 2000). The link between these environmental risk factors and psychotic experiences has been described in terms of stress-dopamine (DA) interactions and sensitization (Collip et al., 2008). Linking cortical and subcortical dopaminergic processes, there is evidence that mesocortical DAergic innervation of the prefrontal cortex may regulate the activity of mesolimbic subcortical DA innervations and that the impact of environmental risk factors may result in taking the prefrontal cortical (PFC) “off-line”, resulting in altered responsiveness of subcortical DAergic innervations (Deutch, Clark, & Roth, 1990). Thus, when DA transmission is increased by exposure to stress or agonist drugs, there may be a shift in the balance of the system away from PFC control and toward limbic predominance, facilitating a DA hyperactivity in the ventral tegmental area of the midbrain, resulting in the development of positive symptoms (Laruelle et al., 2003).

Third, in the EDSP study, experiences indicative of the negative/disorganized and positive symptoms in the general population clustered together more often than predicted by chance, independent of depression. Thus, psychotic disorders such as schizophrenia are not the result of the chance cross-section of the separate liabilities of developmental impairment on the one hand and reality distortion on the other; they are linked together in a way that suggests fundamental overlap or interaction of underlying mechanisms.

Fourthly, the longitudinal analysis suggested that in this community sample negative-disorganized features preceded positive features rather than the other way round. Persistent expression of the negative-disorganized features predicted onset of psychotic experiences; in contrast, persistent expression of psychotic experiences did not predict onset of the negative-disorganized ones. This, together with the associations between positive features and environmental risks, suggests that the negative-disorganized symptoms cluster reflects an underlying vulnerability that, when combined with environmental exposures, results in positive symptoms increasing the risk of need for care. This latter suggestion is supported by the fact that the “comorbid” expression of positive and negative features increased the risk for impairment and, by implication, onset of clinical psychosis.

A Dynamic Model of the Onset of Clinical Psychosis from an Epidemiological Perspective

The aforementioned population-based studies details the dynamics of the onset of clinically relevant psychosis (Figure 1) in a large sample of 3021 adolescents and young adults from the general population (EDSP study). Self-reported psychopathological experiences resembling the positive, negative-disorganized, depressive and hypomanic symptom clusters are shown to be expressed in attenuated form in otherwise “healthy” individuals (chapters 3, 4 and 5). Their population distribution suggests that they represent quantitative variations of normal human mentation. Based on the present studies, psychometric manifestations of the psychosis phenotype represent the behavioural expression of differential underlying liabilities to psychosis that, in interaction with environmental factors, contribute to the onset of clinical psychosis.

With regard to the positive psychotic dimension, evidence for continuity over time from subclinical persistent psychotic experiences to clinical psychotic states was tested using the longitudinal prospective design of the EDSP study (chapter 3; (M.D.G. Dominguez et al., 2009)). The dynamics preceding the clinical onset of psychotic disorder from a population perspective may be summarised descriptively as a Psychosis Proneness-Persistence-Impairment model of psychotic disorder, mechanisms of which were explained by behavioural, environmental and neurobiological interactions. A significant proportion of psychotic disorder may be conceptualised as the rare poor outcome of a common developmental phenotype. Positive psychotic experiences can thus be regarded as the behavioural expression of underlying distributed liability for psychosis.

With the processes underlying the various dimensions of psychotic psychopathology may be derived from the associations between psychosis dimensions and the intermediary phenotype of neurocognition in non-affective psychosis obtained from our meta-analytic work (chapter 2; (M. D. G. Dominguez et al., 2009)). Differential associations for the cluster of disorganized and negative symptoms on the one hand, and that of positive and affective on the other were in accordance with the formulation of the consilience model of psychosis (Van Os & Kapur, 2009): the phenomenological expression of the altered brain development in the form of interpersonal style and negative features was associated with the intermediary phenotype of neurocognitive impairment, which may represent the pole of ‘Development Expression’ within the psychosis syndrome. In contrast, the opposite pole of ‘Affective Dysregulation’ and psychotic experiences was not associated with that of neurocognition.

The epidemiological prediction of this model was tested in the EDSP study by examining:

(i) Associations between affective dysregulation and reality distortion in the general population resulted in higher risk for clinical psychosis in part reflecting overlapping distributed genetic vulnerabilities. The interaction between the two psychopathological domains was interpreted through the role of neurobiological activity and cognitive processes facilitated by the mechanism of aberrant salience attribution (chapter 4).

(ii) The association of negative and disorganized features corroborated that these psychopathological expressions, in co-existence with neurocognitive impairment, may represent alterations in brain development associated with distributed developmental genetic risk. When combined with environmental exposures, such as cannabis, developmental trauma and urbanicity, a final common pathway of neurotransmitter dysregulation may result in the onset of positive psychotic symptoms, increasing the risk for onset of clinical psychosis (chapter 5).

The present epidemiological work may contribute to tracing a dynamic model for the development of psychosis expression from mental health to pathological states; quantitative variations of normal human mentation in the context of interactions between individuals and their environments act in such a way that their interacting underlying processes do pose a risk for the onset of clinical psychosis.

Figure 1. A Dynamic Model of the Onset of Clinical Psychosis from an Epidemiological Perspective

Nosological Implications

The findings of the present thesis raise questions about our conceptualization and nosological classification of psychotic disorders, with obvious repercussions to clinical practice in the diagnostic process, clinical management and intervention.

Given that there is quantitative variation in symptom dimension scores across current diagnostic categories rather than qualitative differences, it is unlikely that the current psychotic categories represent discrete nosological entities (Dikeos et al., 2006). Additionally, evidence has been given for shared genetic causes underlying diagnoses of psychotic disorders (Kendler & Diehl, 1993), including bipolar disorder (Craddock & Owen, 2007). Therefore, a flexible scoring of dimensions across all psychotic and major affective disorders may be potentially more informative than a system where categorical diagnoses are kept artificially dimension-specific. Models using both categorical and dimensional representations have shown better discriminative validity than either model independently, suggesting that the most powerful approach to classification is the complementary use of both categorical diagnoses and dimensional scores (Allardyce, McCreadie, Morrison, & van Os, 2007). In this context, a major likely change in DSM-V and ICD-11 is expected to be the addition of dimensional indicators that can be applied across diagnostic categories of affective and non-affective psychotic disorder (van Os & Kapur, 2009).

Our findings add evidence for continuity with normal mentation enlightening differential pathways of interaction across symptoms domains to the onset of clinical psychosis. Firstly, this shows that the underlying latent structure of psychopathology is continuous. Secondly, these differential pathways can be traced longitudinally: (i) the one characterized by affective dysregulation, closely linked to stress-related environmental factors, and (ii) that of developmental expression, portrayed by negative and disorganized features associated with cognitive alterations, which strongly resembles the epidemiological prediction of the purest clinical concept of non-affective psychosis.

Clinical Implications

Recent work suggests that it is possible to intervene early in the course of prodromal psychotic states in selected samples at the level of mental health services (Cannon et al., 2008; McGorry, 2002). Systematic reviews suggest that longer duration of untreated psychosis before treatment is initiated predicts poorer outcome (Farooq, Large, Nielssen, & Waheed, 2009; Marshall et al., 2005; Perkins, Gu, Boteva, & Lieberman, 2005). At the level of the population, however, there is very little knowledge about how such prodromal states develop and which factors

are important in the course of the very earliest expressions of psychosis. Given the possibilities of early intervention, more knowledge is urgently required on the population distribution of psychometric risk states for psychosis, and how these may develop into prodromes and clinical psychotic states (McGorry, Yung, Bechdolf, & Amminger, 2008).

The results from our work can have important impact on early intervention. Our findings suggest that many clinical psychotic states can be traced to earlier attenuate phenotypic expressions years before the onset of the illness. The findings therefore support the notion of early intervention in psychosis although not all onsets of clinical psychotic states may benefit from these. In addition, the findings suggest that isolated subclinical positive psychotic experiences themselves cannot be considered as “prodromal” symptoms in spite of their severity; however, psychometric expression of psychosis risk may be particularly informative if assessed (i) repeatedly, (ii) in interaction with psychopathological dimensions rather than isolated psychotic symptoms and (iii) in the context of environmental risks (Cougnard et al., 2007). Multiple assessments will also help reduce the risk of false positive findings (McGorry et al., 1995; Van Os & Delespaul, 2005).

Directions for Future Research

The present thesis offers a longitudinal epidemiological approach of the dynamic process to the onset of clinical psychosis, based on psychopathological, functional, socio-demographic and environmental data. Its conceptual implications question our understanding of psychosis; the repercussions of which need to be tested within the recent advances of genetics, imaging, cognitive sciences and psychopharmacology.

In the present work, the associations between psychosis dimensions and the intermediary phenotype of neurocognition in clinical psychosis were investigated (chapter 2). Establishing differential patterns of the intermediary phenotypes in the field of cognitive sciences, combining neurocognition (M. D. G. Dominguez et al., 2009) and the emerging field of social cognition (Garety et al., 2007), among the different psychopathological dimensions of clinical psychosis, and investigating their differential functional outcomes (Ventura, Helleman, Thames, Koellner, & Nuechterlein, 2009), may yield further insight in the underlying mechanisms of psychosis heterogeneity.

Turning to the population-based research, psychosis epidemiology can provide information to guide future research. However, while epidemiology is useful for generating candidate risk factors and tracing the longitudinal course of phenomenological features, it can not always deliver studies that enlighten

pathophysiology and prove causality (McGrath & Richards, 2009). Genetic epidemiological studies suggest that gene-environment interaction in schizophrenia and related diagnostic categories is common (van Os, Rutten, & Poulton, 2008) and recent studies are suggestive for interaction between environmental exposures and specific molecular genetic variation (Caspi et al., 2005; Henquet et al., 2006). Likewise, imaging studies combining structural brain volume measures with functional activity enlighten the mechanisms how neurochemical abnormalities may converge to cause psychosis (Howes & Kapur, 2009). Therefore, the challenge in the years to come is to bring together the various disciplines that are necessary to examine models of psychosis pathophysiology and disease causation.

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SUMMARY

This thesis, *A Dynamic Model of the Onset of Clinical Psychosis from an Epidemiological Perspective*, examines the psychosis phenotype as it exists in nature and the dynamic process of psychosis evolution from mental wellbeing to the onset of clinical psychosis, from an epidemiological perspective.

Chapter 1 describes epidemiological methods examining person-environment interactions and how they influence the development of major psychiatric disorders. It focuses on the occurrence of the psychosis phenotype in nature and the potentially predictive value of conceptualizing the evolution of psychosis as a dynamic process. Psychosis is firstly considered within the clinical setting, where psychosis was initially described, investigated and conceptualized. Clinical heterogeneity is not fully explained by the categorical diagnoses found in the current classification systems. One way to more fully define the phenomenological variation is to search for patterns of overlap across symptom dimensions. A narrative review of inter-dimensional correlations is presented, as well as associations between psychosis dimensions and the intermediary phenotype of neurocognition. In this context, a consilience model of clinical psychosis, which integrates cognitive and neurobiological theories of psychosis and, in particular, establishes links among phenomenological heterogeneity, intermediary phenotypes and pathophysiological processes, is presented.

Secondly, the population-based studies of psychotic-like experiences and the continuity between clinical and subclinical psychosis phenotypes are presented together with their conceptual implications for the consilience model of psychosis. The crucial issues of psychometric assessment with self-report instruments and that of clinical relevance are discussed in order to introduce the aims of the present thesis: (i) to assess how universal psychotic symptoms are and to introduce the possibility that they represent quantitative variations of normal human mentation, and (ii) to test the epidemiological prediction of a dynamic model to the onset of clinical psychosis. For that purpose, the prospective, observational Early Developmental Stages of Psychopathology (EDSP) study consisting of a large, general population sample of 3021 adolescents and young adults from Munich, Germany, followed over a period of up to ten years is presented.

Chapter 2 investigates the association between psychotic psychopathology and the intermediary phenotype of neurocognition in non-affective psychosis since demonstrating differential patterns of cognitive performance among the different psychopathological dimensions could yield insight into the underlying mechanisms which result in the ubiquitous heterogeneity inherent in the psychosis phenotype. A systematic review of published studies examining the correlations between symptom dimensions and neuropsychological performance was performed- the abstracts of 3129 articles were examined for possible inclusion in the analysis. Our meta-analysis (58 studies, 5009 individuals) showed negative and disorganized dimensions to be significantly but modestly associated with cognitive deficits, whereas affective and positive dimensions were not. The patterns of association for the four psychosis dimensions were stable across neurocognitive domains and independent of age, gender and chronicity of illness. We therefore concluded that psychotic symptoms and neurocognition are not entirely orthogonal, suggesting that differential cerebral mechanisms may underlie the disorganized and negative symptoms dimensions *versus* positive and affective ones.

Chapter 3 describes data from the large EDSP sample of adolescents and young adults in the general population. To our knowledge, this is the first study examining the influence of persistence of subclinical psychotic experiences in relation to the transition to clinically relevant psychosis. The hypothesis was investigated that developmental expression of psychometric risk, in the form of subclinical psychotic experiences in the general population, is usually transitory but in some instances may become abnormally persistent and progress to a clinical psychotic state. The findings are i), subclinical psychosis was confirmed to be common and mostly transitory, ii) persistent subclinical positive psychotic-like symptoms are a marker of emerging clinical relevant psychopathology. A dose-response gradient was demonstrated: the longer the duration of subclinical psychosis, the greater the risk of developing clinical impairment, iii) although most subclinical psychosis was transitory, relationship between the clinical and the subclinical manifestations was not negligible: a significant proportion of psychotic disorders were best conceptualised as the poor outcome of a relatively common developmental phenotype characterised by persistence of psychometrically detectable subclinical psychotic experiences. For some individuals, psychosis is thus the result of a long developmental process of subclinical experiences and functional deficits. This may be summarised descriptively as a psychosis proneness-persistence-impairment model of psychotic disorder. Possible mechanisms explaining the transition from persistence of subclinical psychosis to impairment are likely based on behavioural, environmental and neurobiological interactions.

Chapter 4 describes data from the EDSP study connecting reality distortion and affective dysregulation from a risk perspective, at a population-based level. It

examines the relationship between attenuated positive and affective symptoms and the onset of clinical psychosis. The results suggest that psychotic experiences in the general population are associated with affective dysregulation, and provide evidence of a dose response gradient. Furthermore, persistence of psychotic-like experiences and the onset of impairment are higher when affective dysregulation is present. In light of the accumulating evidence suggesting an overlap in genetic liability, across the different psychosis categories, our findings suggest genetic liabilities underlying affective and non-affective psychotic syndromes may be expressed as correlated dimensions in the general population. The longitudinal prediction of reality distortion in affective dysregulation is discussed in the context of existent psychological models of symptom formation and neurobiological activity, suggesting a process of misassignment of emotional salience underlying this connection.

Chapter 5 describes data from the EDSP study examining the natural occurrence of negative symptoms in the general population and if and how attenuated positive and negative measures of psychopathology, from a risk perspective, may contribute to the onset of clinical psychosis. A priori hypotheses suggest that cognitive/negative symptoms associated with schizophrenia may represent alterations in brain development associated with distributed genetic risk. When combined with stress-related environmental exposures, a final common pathway of neurotransmitter dysregulation may result in the onset of positive psychotic symptoms. This study highlighted the natural occurrence of attenuated negative symptoms in otherwise healthy individuals, independent of antipsychotic treatment. Negative symptoms revealed a pattern of socio-demographic associations indicative of developmental impairment, whereas the positive symptoms were associated with environmental risk factors such as trauma, cannabis use and urbanicity. Both psychosis dimensions were frequent and occurred in combination more often than predicted by chance. Negative symptoms predicted positive symptoms over time, and co-occurrence of positive and negative symptoms was predictive of clinical relevance in terms of secondary functional impairment and help-seeking behaviour. Results suggested that the liabilities underlying negative features of psychotic illness are distributed at a population level and drive the ontogenesis of positive psychotic experiences after exposure to environmental risks, increasing the likelihood of impairment and need for care.

In **Chapter 6**, the results of this thesis including the systematic review of clinical studies and the population-based studies are discussed and integrated into *A Dynamic Model of the Onset of Clinical Psychosis from an Epidemiological Perspective*. Nosological and clinical implications of the findings of this thesis are provided as well as directions for future research.

SAMENVATTING

Deze thesis, *Een dynamisch model van het begin van klinische psychose vanuit een epidemiologisch perspectief*, onderzoekt het psychosefenotype zoals het bestaat in de natuur en het dynamische proces van psychose-evolutie van mentaal welzijn naar het begin van klinische psychose, vanuit een epidemiologisch perspectief.

Hoofdstuk 1 beschrijft epidemiologische methodes die interacties onderzoeken tussen persoon en omgeving en de invloed daarvan op het ontwikkelen van belangrijke psychiatrische stoornissen. Het hoofdstuk focust op het voorkomen van het psychosefenotype in de natuur en de potentiële voorspellende waarde voor het conceptualiseren van de evolutie van een psychose als een dynamisch proces.

Psychose wordt in de eerste plaats gezien binnen het klinische kader, waarin men psychose voor het eerst beschreef, onderzocht en conceptualiseerde. Klinische heterogeniteit wordt niet volledig verklaard door de categorische diagnoses in de huidige classificatiesystemen. Een manier om de fenomenologische variatie volledig te definiëren is om te zoeken naar overlappingspatronen in de symptoomdimensies. Een narratief overzicht van inter-dimensionale correlaties wordt voorgesteld, alsook verbanden tussen psychosedimensies en het intermediaire fenotype van neurocognitie. In deze context wordt een verzoeningsmodel van klinische psychose voorgesteld dat cognitieve en neurobiologische theorieën over psychose integreert en, in het bijzonder, verbanden legt tussen fenomenologische heterogeniteit, intermediaire fenotypen en pathofysiologische processen.

In de tweede plaats worden de op populatie gebaseerde studies van op psychose gelijkende ervaringen en de continuïteit tussen klinische en subklinische psychosefenotypen voorgesteld samen met hun conceptuele implicaties voor het verzoeningsmodel van psychose. De cruciale kwesties van psychometrische beoordeling met tools voor zelfrapportage en van klinische relevantie worden besproken ter inleiding van de doelstellingen van deze thesis: (i) beoordelen hoe universeel psychotische symptomen zijn en het suggereren dat ze kwantitatieve variaties vertonen van de normale menselijke geestestoestand, en (ii) het testen van de epidemiologische voorspelling van een dynamisch model tot het begin van klinische psychose. Hiervoor wordt de toekomstgerichte, observationele studie

Early Developmental Stages of Psychopathology (EDSP) voorgesteld die een grote, algemene steekproef van 3021 adolescenten en jonge volwassenen van München, Duitsland, bevat, die gedurende 10 jaar werden gevolgd.

Hoofdstuk 2 onderzoekt het verband tussen psychotische psychopathologie en de het intermediaire fenotype van de neurocognitie in niet-affectieve psychose, aangezien het aantonen van differentiële patronen van cognitieve prestatie onder de verschillende psychopathologische dimensies inzicht zou kunnen bieden in de onderliggende mechanismen die resulteren in de alomtegenwoordige heterogeniteit inherent aan het psychosefenotype. Een systematische studie van de gepubliceerde studies die de correlaties tussen symptoomdimensies en de neuronpsychologische prestatie onderzoeken, werd uitgevoerd – de samenvattingen van 3129 artikels werden onderzocht om mogelijk in de analyse te worden opgenomen. Onze meta-analyse (58 studies, 5009 individuen) toonde aan dat negatieve en verstoorde dimensies duidelijk maar in bescheiden mate geassocieerd zijn met cognitieve gebreken, terwijl dit bij affectieve en positieve dimensies niet het geval was. De associatiepatronen van de vier psychosedimensies waren stabiel over de neurocognitieve domeinen heen en stonden los van leeftijd, geslacht en chroniciteit van de ziekte. Daarom besloten we dat psychotische symptomen en neurocognitie niet volledig orthogonaal zijn, wat suggereert dat de differentiële hersenmechanismen de oorzaak kunnen zijn van verstoorde en negatieve *versus* positieve en affectieve symptoomdimensies.

Hoofdstuk 3 beschrijft gegevens van de grote EDSP-steekproef van adolescenten en jonge volwassenen in de algemene populatie. Voor zover wij weten is dit de eerste studie die de invloed van de persistentie van subklinische psychotische ervaringen onderzoekt in relatie tot de transitie naar klinisch relevante psychose. De hypothese werd onderzocht dat ontwikkelende expressie van psychometrisch risico, in de vorm van subklinische psychotische ervaringen in de algemene populatie gewoonlijk van voorbij gaande aard is maar in sommige gevallen abnormaal kan aanhouden en kan evolueren tot een klinische, psychotische status. De bevindingen zijn i), subklinische psychose werd bevestigd als zijnde algemeen voorkomend en meestal tijdelijk, ii) aanhoudende subklinische positieve op psychose lijkende symptomen zijn een aanduiding van een groeiende klinisch relevante psychopathologie. Er werd een dosisreactiegradiënt aangetoond: hoe langer de subklinische psychose duurt, hoe groter het risico op ontwikkeling van een klinische stoornis, iii) hoewel in de meeste gevallen de subklinische psychose tijdelijk was, kon men het verband tussen de klinische en subklinische manifestaties niet verwaarlozen: een duidelijke proportie van de psychotische stoornissen werden het best geformuleerd als het magere resultaat van een relatief gewoon ontwikkelingsfenotype gekenmerkt door het aanhouden van psychometrisch opspoorbare subklinische psychotische ervaringen. Voor sommige individuen is de

psychose bijgevolg het resultaat van een lang ontwikkelingsproces van subklinische ervaringen en functionele gebreken. Dit kunnen we samenvattend beschrijven als een model van psychotische stoornis op basis van psychosevatbaarheid en aanhoudende beschadiging. Mogelijke mechanismen die de overgang van aanhoudende subklinische psychose naar beschadiging verklaren zijn wellicht gebaseerd op gedrags-, omgevings- en neurobiologische interacties.

Hoofdstuk 4 beschrijft gegevens van de EDSP-studie die realiteitsvertekening en affectieve dysregulatie verbindt vanuit een risicoperspectief, op een op populatie gebaseerd niveau. Het onderzoekt het verband tussen afgezwakte positieve en affectieve symptomen en het begin van een klinische psychose. De resultaten suggereren dat psychotische ervaringen in de algemene populatie verband houden met affectieve dysregulatie en leveren een bewijs van het bestaan van een dosisreactiegradiënt. Bovendien zijn het aanhouden van op psychose gelijkende ervaringen en het begin van de beschadiging sterker wanneer een affectieve dysregulatie aanwezig is. In het licht van het groeiende bewijs dat een overlapping suggereert in genetische vatbaarheid over de verschillende psychosecategorieën heen, suggereren onze bevindingen dat genetische vatbaarheden die onderliggend zijn aan affectieve en niet-affectieve psychotische syndromen kunnen worden uitgedrukt als gecorreleerde dimensies in de algemene populatie. De langetermijnvoorspelling van realiteitsvertekening in affectieve dysregulatie wordt besproken in de context van bestaande psychologische modellen van symptoomvorming en neurobiologische activiteit, wat suggereert dat een proces van foutieve toekenning van emotionele salientie aan de bron ligt van dit verband.

Hoofdstuk 5 beschrijft gegevens van de EDSP-studie die het natuurlijke voorkomen van negatieve symptomen in de algemene populatie onderzoekt en of en hoe verzwakte positieve en negatieve maten van psychopathologie, vanuit een risicoperspectief, kunnen bijdragen tot het ontstaan van klinische psychose. A priori hypothesen suggereren dat cognitieve / negatieve symptomen die zijn geassocieerd met schizofrenie veranderingen in de hersenontwikkeling kunnen vertonen die verband houden met gedistribueerd genetisch risico. Wanneer het wordt gecombineerd met stressgerelateerde blootstellingen aan de omgeving kan een “final common pathway” (een uiteindelijk in dezelfde richting wijzend pad) van de neurotransmitterdysregulatie leiden tot het ontstaan van positieve psychotische symptomen. Deze studie benadrukte het natuurlijke voorkomen van verzwakte negatieve symptomen bij verder gezonde individuen, los van antipsychotische behandeling. Negatieve symptomen onthulden een patroon van sociodemografische verbanden die indicatief zijn voor ontwikkelingsbeschadiging, terwijl de positieve symptomen in verband werden gebracht met omgevingsrisicofactoren zoals trauma, cannabisgebruik en verstedelijking. Beide psychosedimensies kwamen frequent voor en kwamen vaker in combinatie voor dan bij willekeur kon worden voorspeld.

Negatieve symptomen voorspelden mettertijd positieve symptomen, en het tegelijk voorkomen van positieve en negatieve symptomen was een aanwijzing voor klinische relevantie voor wat betreft secundaire functionele beschadiging en hulpzoekend gedrag. Resultaten suggereerden dat de vatbaarheden die onderliggend zijn aan negatieve kenmerken van psychotische ziekte worden verspreid op het niveau van de populatie en de ontogenese van positieve psychotische ervaringen voeden na blootstelling aan omgevingsrisico's, wat de waarschijnlijkheid op beschadiging en de zorgbehoefte vergroot.

In **Hoofdstuk 6** worden de resultaten van deze thesis, met inbegrip van de systematische studie van klinische op de populatie gebaseerde studies, besproken en geïntegreerd in *Een dynamisch model van het begin van klinische psychose vanuit epidemiologisch perspectief*. Hier worden ook de nosologische en klinische implicaties van de bevindingen van deze thesis vermeld, alsook richtingen voor toekomstig onderzoek.

ACKNOWLEDGEMENTS

To everyone who contributed towards the realization of this thesis, I thank you for sharing this exhilarating and enriching experience.

Many thanks to my promotor, Jim van Os, for guiding me along this research path with such geniality. Thank you for sharing your creativity, analytical understanding and broad knowledge-base of human mentation and psychosis. To my co-promotors, Marieke Wichers, for your care during my time in Maastricht, and your support during my first STATA statistical analyses -thanks. Dear Lydia Krabbendam, the quality of your research is an inspiration. For your support and encouragement during my PhD, I am truly grateful.

To all the collaborators I have met during my time here in Maastricht a big thank you. Wolfgang Viechtbauer, for your overwhelming meta-analytical knowledge. Claudia Simons, for your contribution in the neurocognitive data extraction task. Meram Can Saka, what an opportunity to have met in this country, far away from home which has resulted in this research collaboration. Inge van Rossum, for disentangling the affective dysregulation in the psychotic world. Deniz Arik, for sharing my introduction to social interaction studies, through our joint clinical perspective. Miriam Dietvorst and David, for all the Dutch translation and sharing your office space during my very first year. Nicole Geschwind, for the two years in which we have kindly shared every single day of research. Anne Fett, for the agreeable times working together. Mari Aguilera, my Spanish namesake, for our friendship kindled during our “dummiest” first research steps in this Dutch-land. Judith Allardyce, for your thoughtful psychiatric discussions, your friendship and, last but not least, thanks for having gone through all the writing of the current thesis!

To the research group of the Early Developmental Stages of Psychopathology Study at the Max Planck Institute of Psychiatry, Munich, Germany; Prof. dr. Uli-Hans Wittchen and Prof. dr. Roselind Lieb, Thank you for this special opportunity to collaborate and analyse this unique dataset. Thank-you for your useful comments and unhesitatingly support during the publication process.

ACKNOWLEDGEMENTS

Finally, I would like to thank to all the colleagues of the Department of Psychiatry and Neuropsychology at Maastricht University.

My journey started in Spain, I need to thank Ana González Pinto for introducing me to psychiatric research, in Vitoria, Spain, whose fruitful research collaborations allowed me to work with Jim van Os in Maastricht. I would like to thank all my clinical psychiatrist colleagues and mentors at the Santiago Apostol Hospital, in Vitoria. Especially: Maite Ramírez, for introducing me in the interesting world of the psychopathological evaluation; Ana Blanca Yoller, for your encouraging and keen psychiatric rehabilitation to the people suffering from severe mental disorder; Sofía Álvarez de Eulate, for initiating me in the psychotherapeutic approach; Juan Medrano, for being as a psychiatric opened book and thank you for your truthful mentorship; and undoubtedly Ainara Jiménez, for who the appealing world of psychiatry provided the base for our psychiatric and ‘real life’ friendship.

To my nearest and dearest, whose support, love and friendship have been immeasurable. Ana and Pilar, my heartfelt thanks, for sharing our lives in this intense lived experience. Berta for our deep and never-ending friendship and your uncountable flights! Mia and Jamil, thanks for your proximity, and sharing your culture so warmly here in Maastricht. Claudia Vaz, Maastricht will always be the starting point of our friendship. My family, papa, mama, Javier, Nati, Pablo y Javier, Segundo y Raquel, thanks for giving me not only life, but also for giving me a enriching perspective on life. It is with deep gratitude that I thank all those people who see, trust and decide to walk through the treasures of life, with the truth in their hearts, and the depth and freedom of their love. Desde lo más profundo de mi ser, mi corazón agradecido.

CURRICULUM VITAE

María de Gracia Domínguez was born on November, 1974 in Pamplona, Spain. She attended medical school at the University of Navarra, Spain. She completed her specialist clinical training in psychiatry at the Santiago Apostol Hospital in Vitoria, Spain (2002-2006). Her interest in academic psychiatry developed when she was a clinical trainee and began her academic career in the Department of Neuroscience, Santiago Apóstol Hospital, University of the Basque Country, UPV-EHU, Spain. She completed the doctorate courses in neuroscience (2003-2004), obtaining the certificate of Advance Studies in Neuroscience (2005). In 2006 she received a Marie Curie Early Stage Research Training Fellowship, and moved to the Research Institute for Brain and Behaviour, Department of Psychiatry and Neuropsychology, Maastricht University, The Netherlands, headed by Prof. Dr. Jim van Os, where she has developed her interest and expertise in psychiatric epidemiology. She attended epidemiology courses at Harvard School of Public Health, Harvard University, Boston MA, USA, while studying towards a PhD and continues to work in the Department of Psychiatry & Neuropsychology, School of Mental Health and Neuroscience, Maastricht University.

PUBLICATIONS

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Van Rossum, Inge; **Dominguez, Maria de Gracia**; Lieb, Roselind; Wittchen, Hans-Uli; Van Os, Jim. Affective Dysregulation and Reality Distortion: A Longitudinal Investigation of their Association and Clinical Relevance. *Schizophrenia Bulletin*, doi:10.1093/schbul/sbp101

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Research grants

- Marie Curie Early Stage Research Training Fellowship of the European Community's Sixth Framework Program under contract number "MEST-CT-2005-020589" (July 2006 – June 2008).