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Paranymfen

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Contents

Chapter 1

Introduction

PHENOMENOLOGY OF BIPOLAR DISORDER

Bipolar disorder is one of the most disabling mental disorders (Murray and Lopez, 1996; Wittchen et al., 2003). It is associated with reduced emotional and social functioning (Pini et al., 2005), increased suicidal behaviour (Ten Have et al., 2002), increased utilization of mental health services (Judd and Akiskal, 2003), and more days of bed rest and absenteeism compared to other mental disorders (Ten Have et al., 2002).
In textbooks, the most important division of bipolar disorder is between bipolar I disorder and bipolar II disorder. According to the DSM-IV-TR, bipolar I disorder is characterized by at least one manic or mixed episode, while bipolar II disorder is characterized by the combination of at least one hypomanic episode and at least one major depressive episode. The core symptom of manic or hypomanic episodes (hereafter '(hypo)manic episodes') is an elated, expansive or irritable mood, and the core symptoms of depressive episodes are a depressed mood and a loss of interest or pleasure in activities. Except for symptoms of a hypomanic episode, symptoms need to cause clinically significant distress or impairment in social, occupational or other important areas of functioning. Furthermore, symptoms should not be the result of the acute effects of substance use or a medical condition (American Psychiatric Association 2000). Prevalence rates of bipolar I disorder and bipolar II disorder vary between approximately 1% and 2% (Kessler et al., 1994; Regier et al., 1988; Weissman et al., 1996). These rates, however, are based principally on clinical samples while a considerable number of people suffering from bipolar disorder are not in care (Ghaemi et al., 2002). Thus, these rates are likely an underestimation and the use of general population samples is necessary to determine the true prevalence rate (Wittchen et al., 2003).

BIPOLAR DISORDER AS A CONTINUOUS DISORDER

Using the DSM-IV-TR criteria, a clear-cut division can be made between 'healthy' individuals and those with a bipolar disorder. In reality, unfortunately, a clear cut-off point does not exist and this has led to the development of the terms 'subthreshold bipolar disorders', 'subclinical bipolar disorders' and 'bipolar spectrum disorders' (terms that are used interchangeably throughout this thesis). Although these disorders do not fulfil all DSM-IV-TR criteria, they are comparable to a DSM-IV bipolar disorder (Lewinsohn et al., 2004). Many

people in the general population suffer from subthreshold bipolar disorder (Merikangas et al., 2007): prevalence rates of 5-8% are reported (Angst 1998; Lewinsohn et al., 1995; Szádóczky et al., 1998). Prevalence rates vary depending on the criteria (e.g. number of DSM-IV-TR criteria necessary) and on the severity measures used for diagnosis (e.g. need of mental health care included as a criterion). Several authors have therefore hypothesized that the bipolar phenotype may be better conceptualized as a distribution along a continuum on which all (hypo)manic manifestations of varied length, frequency and severity can be presented (Angst and Marneros, 2001), and that dimensional measures can perhaps replace the dichotomous diagnostic criteria. The use of dimensional measures offers several advantages. First, by improving the search for the determinants of onset and change, it facilitates monitoring the onset and progression of psychiatric phenotypes (Van Os and Verdoux, 2003). Second, it allows for a fuller examination of the impact of symptoms on well-being and functioning, severity and distress (Regeer 2006). For example, Judd and Akiskal (2003) concluded that the level of expression of psychopathology is associated with the level of disability experienced (Judd and Akiskal, 2003). Third, it allows for the separate study of manic and depressive dimensions (Regeer et al., 2006). This could be important in view of indications that the manic and depressive dimensions in bipolar disorder might be more loosely associated than once assumed (Regeer et al., 2006). Fourth, it may facilitate recognition of at-risk states and thus make early intervention possible (Birmaher and Axelson, 2006; Egeland et al., 2000; Hanssen et al., 2005). To summarize, the use of several dichotomous definitions of bipolar disorder has led to variation in the reported prevalence rates of bipolar disorder. The bipolar phenotype may in fact be better conceptualized as a distribution along a continuum. Using a dimensional approach instead of a categorical definition can have distinct advantages.

BIPOLAR DISORDER AS A DEVELOPMENTAL DISORDER

Age of onset

For decades, bipolar disorder has been regarded typically as a disorder of adulthood that is scarce in children (Wozniak et al., 1995). However, a growing body of research suggests that the onset of bipolar disorder can be traced back to adolescence or even childhood (e.g. Akiskal et al., 1985; Geller and Luby, 1997; Lewinsohn et al., 1995). A substantial number of adults with bipolar disorder report retrospectively an initial display of (hypo)manic symptoms dur-

ing childhood or adolescence (Joyce 1984). Furthermore, several investigators have reported the presence of (hypo)manic symptoms in adolescents (Birmaher et al., 2006; Carlson and Kashani, 1988; Egeland et al., 1987; Lewinsohn et al., 1995). On the other hand, researchers have emphasized that mood swings are commonly encountered during adolescence (Rutter et al., 1976), and symptoms during this phase of life might simply be part of a normal development.

In order to distinguish between both hypotheses, information regarding the course of these subthreshold phenotypes in relation to the later onset of disorder is essential. Currently, contradictive findings are presented in the literature. For instance, Lewinsohn and colleagues (2000) did not find an elevated rate of bipolar disorder in young adulthood or a recurrence of subsyndromal bipolar disorder when he examined adolescents who had been diagnosed with subsyndromal bipolar disorder (Lewinsohn et al., 2000). However, Birmaher and colleagues (2006) assessed the longitudinal course of bipolar spectrum disorders in children and adolescents and concluded the existence of a dimensional continuum of bipolar symptom severity, from subsyndromal to mood syndromes (Birmaher et al., 2006).

Recent work in psychosis has shown that subthreshold phenotypes that tend to persist at the subclinical level over longer periods of time (i.e. years) carry the greatest risk for transition in a dose-response fashion (Dominguez et al., submitted; Rössler et al., 2007). A similar relationship might be found for bipolar disorder, and if the persistence of symptoms is an additional necessity in order for transition to bipolar disorder to occur, this might explain the differences in transition rates between studies.

In conclusion, a growing amount of literature indicates that (hypo)manic symptoms can occur during adolescence. However, it is not yet clear whether these symptoms can predict transition to bipolar disorder or whether they are simply part of a normal adolescent development. The length of time (hypo)manic symptoms persist might be crucial in determining the clinical relevance of symptoms.

Association with ADHD

There appears to be an association between bipolar disorder and childhood disorders, in particular attention/deficit-hyperactivity disorder (ADHD). In addition to the many similarities between ADHD and bipolar disorder, there is a high level of comorbidity (Geller et al., 1995; Wozniak et al., 1995). However, the way in which ADHD is connected to bipolar disorder is still unclear.

In the literature, several explanations are given that suggest a developmental pathway in which ADHD might increase the risk for later expression of bipolar disorder (Dienes et al., 2002; Faraone et al., 1997a; Faraone et al., 1997b; Hirshfeld-Becker et al., 2006; Masi et al., 2003; Strober et al., 1988). Nevertheless, extensive research that focuses specifically on the association between ADHD and bipolar disorder is required in order to differentiate between these explanations. Although the intention of this thesis is not to provide clarity regarding the way in which ADHD is connected to bipolar disorder, where relevant it does present the degree to which ADHD is associated with bipolar disorder.
To conclude, the high level of association between ADHD and bipolar disorder implies a developmental pathway. The degree of association between ADHD and bipolar disorder is described in this thesis.

BIPOLAR DISORDER AS A MULTIFACTORIAL DISORDER

Bipolar disorder is a highly hereditary disorder with a well-recognized genetic contribution, as demonstrated by data from family, twin and adoption studies (Alda 1997). However, genetic and biological processes cannot fully explain the differences in the expression, timing and polarity of bipolar symptoms, and the impact of environmental factors needs to be considered (Alloy et al., 2005). In fact, several investigators claim that an interaction of genes and environmental factors is most likely to occur (Caspi and Moffitt, 2006; Hunter 2005; Kendler 2005a; Rutter et al., 2006). Thus, they state that the modulation of gene expression by environmental factors is likely in complex disorders, given the multiple pathways leading to disease and the probabilistic rather than deterministic effect of almost all risk factors, whether genetic or environmental (Kendler 2005a; Kendler 2005b; Rutter et al., 2006). Evidence for gene-environment interactions has been found for several somatic disorders (Rutter et al., 2006), as well as for psychiatric disorders like schizophrenia (Van Os and Verdoux, 2003), and the importance of gene-environment interactions in a complex disorder like bipolar disorder seems a given. Indeed, both Johnson and colleagues (2000) and Post and colleagues (2001) have concluded that environmental factors interact with genetic factors in bipolar disorder (Johnson et al., 2000; Post et al., 2001). Established environmental risk factors for bipolar disorder that might be involved are, for example, the experience of stressful life events (Alloy et al., 2005; Garno et al., 2005; Leverich et al., 2002) and substance use

(Henquet et al., 2006; Strakowski and DelBello, 2000). Furthermore, personality style has been indicated as a possible risk factor for bipolar disorder (Angst et al., 2003), and might thus be of influence.
In conclusion, the aetiology of bipolar disorder is probably multifactorial, with both genetic and environmental factors playing a role. Interaction of these risk factors might influence the course of bipolar disorder.

INVESTIGATING BIPOLAR DISORDER

Many conclusions regarding bipolar disorder are based on clinical samples and/or retrospective analyses. Unfortunately, as explained before, these designs could have caused distorted results. Therefore, the Early Developmental Stages of Psychopathology (EDSP) study was used for this thesis. The EDSP study has a unique design and several advantages that diminish the chance that distortion will occur (Wittchen et al., 2003). Specifically, the EDSP study is a prospective longitudinal cohort study that focuses on a young, general population sample. By using a population sample, it was ensured that data were representative of the entire population and were not influenced by, for example, help-seeking or treatment issues, and by using a young sample, future bipolar patients were included (i.e. before psychopathology occurred). In combination with the prospective longitudinal design, this created the possibility to carry out an unbiased investigation of the course of psychopathology and an unbiased identification of risk factors and protective factors.

AIMS AND OUTLINE OF THE THESIS

The overall aim of this thesis is to provide clarity regarding the development and longitudinal course of bipolar disorder by using prospective longitudinal data from a large representative cohort of adolescents.
For this purpose, several epidemiologic aspects of bipolar disorder were examined.

In **Chapter 2,** the bipolar population morbidity force of dimensional (hypo)manic phenotypes was investigated, independent of receipt of mental health care, in a prospective longitudinal cohort study of adolescents. Prevalence and incidence rates were analysed in relation to age, sex and urbanicity.

Finally, the association between the dimensional (hypo)manic phenotypes and childhood disorders as ADHD was investigated.

In **Chapter 3**, it was investigated whether the number of (hypo)manic or depressive symptoms present is associated with the risk of transition to bipolar disorder. Furthermore, it was investigated whether a differential course of (hypo)manic or depressive symptoms (i.e. difference in level of persistence) is associated with differential risk for transition to full-blown bipolar disorder.

The main goal of **Chapter 4** was to investigate which risk factors of bipolar disorder are associated with (1) onset and (2) persistence of bipolar symptoms in adolescents. Furthermore, it was investigated whether the risk factors for onset and persistence of symptoms differ depending on the kind of symptoms investigated (i.e. (hypo)manic symptoms vs a combination of (hypo)manic and depressive symptoms).

In **Chapter 5**, a brief summary of the findings is presented, along with an interactive developmental model in which these findings can be integrated. Further discussion of possible theoretical backgrounds is given. Finally, the implications of the findings and directions for future research are presented.

LITERATURE

Akiskal HS, Downs J, Jordan P, Watson S, Daugherty D, Pruitt DB. (1985) Affective disorders in referred children and younger siblings of manic-depressives. Mode of onset and prospective course. *Arch Gen Psychiatry*, 42(10):996-1003.

Alda M. (1997) Bipolar disorder: from families to genes. *Can J Psychiatry*, 42(4):378-387.

Alloy LB, Abramson LY, Urosevic S, Walshaw PD, Nusslock R, Neeren AM. (2005) The psychosocial context of bipolar disorder: environmental, cognitive, and developmental risk factors. *Clin Psychol Rev*, 25(8):1043-1075.

American Psychiatric Association. (2000) *Diagnostical and Statistical Manuals of Mental Disorders-Text Revised (DSM-IV-TR)*. (4th ed). Washington, DC: American Psychiatric Association.

Angst J. (1998) The emerging epidemiology of hypomania and bipolar II disorder. *J Affect Disord*, 50(2-3):143-151.

Angst J, Marneros A. (2001) Bipolarity from ancient to modern times: conception, birth and rebirth. *J Affect Disord*, 67(1-3):3-19.

Angst J, Gamma A, Endrass J. (2003) Risk factors for the bipolar and depression spectra. *Acta Psychiatr Scand Suppl*, (418):15-19.

Birmaher B, Axelson D. (2006) Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Dev Psychopathol*, 18(4):1023-1035.

Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Keller M. (2006) Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry*, 63(2):175-183.

Carlson GA, Kashani JH. (1988) Manic symptoms in a non-referred adolescent population. *J Affect Disord*, 15(3):219-226.

Caspi A, Moffitt TE. (2006) Gene-environment interactions in psychiatry: joining forces with neuroscience. *Nat Rev Neurosci*, 7(7):583-590.

Dienes KA, Chang KD, Blasey CM, Adleman NE, Steiner H. (2002) Characterization of children of bipolar parents by parent report CBCL. *J Psychiatr Res*, 36(5):337-345.

Dominguez M, Wichers M, Lieb R, Wittchen HU, Van Os J. (submitted) Evidence that onset of clinical phenotypes is the outcome of progressively more persistent subclinical psychotic experiences: an 8 year cohort study. *Am J Psychiatry*.

Egeland JA, Blumenthal RL, Nee J, Sharpe L, Endicott J. (1987) Reliability and relationship of various ages of onset criteria for major affective disorder. *J Affect Disord*, 12(2):159-165.

Egeland JA, Hostetter AM, Pauls DL, Sussex JN. (2000) Prodromal symptoms before onset of manic-depressive disorder suggested by first hospital admission histories. *J Am Acad Child Adolesc Psychiatry*, 39(10):1245-1252.

Faraone SV, Biederman J, Wozniak J, Mundy E, Mennin D, O'Donnell D. (1997a) Is comorbidity with ADHD a marker for juvenile-onset mania? *J Am Acad Child Adolesc Psychiatry*, 36(8):1046-1055.

Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T. (1997b) Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? *J Am Acad Child Adolesc Psychiatry*, 36(10):1378-1387; discussion 1387-1390.

Garno JL, Goldberg JF, Ramirez PM, Ritzler BA. (2005) Impact of childhood abuse on the clinical course of bipolar disorder. *Br J Psychiatry*, 186:121-125.

Geller B, Sun K, Zimerman B, Luby J, Frazier J, Williams M. (1995) Complex and rapid-cycling in bipolar children and adolescents: a preliminary study. *J Affect Disord*, 34(4):259-268.

Geller B, Luby J. (1997) Child and adolescent bipolar disorder: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry*, 36(9):1168-1176.

Ghaemi SN, Ko JY, Goodwin FK. (2002) "Cade's disease" and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. *Can J Psychiatry*, 47(2):125-134.

Hanssen M, Bak M, Bijl R, Vollebergh W, Van Os J. (2005) The incidence and outcome of subclinical psychotic experiences in the general population. *Br J Clin Psychol*, 44(Pt 2):181-191.

Henquet C, Krabbendam L, De Graaf R, Ten Have M, Van Os J. (2006) Cannabis use and expression of mania in the general population. *J Affect Disord*, 95(1-3):103-110.

Hirshfeld-Becker DR, Biederman J, Henin A, Faraone SV, Dowd ST, De Petrillo LA, Markowitz SM, Rosenbaum JF. (2006) Psychopathology in the young offspring of parents with bipolar disorder: a controlled pilot study. *Psychiatry Res*, 145(2-3):155-167.

Hunter DJ. (2005) Gene-environment interactions in human diseases. *Nat Rev Genet*, 6(4):287-298.

Johnson L, Andersson-Lundman G, Åberg-Wistedt A, Mathé AA. (2000) Age of onset in affective disorder: its correlation with hereditary and psychosocial factors. J Affect Disord, 59(2):139-148.

Joyce PR. (1984) Age of onset in bipolar affective disorder and misdiagnosis as schizophrenia. *Psychol Med*, 14(1):145-149.

Judd LL, Akiskal HS. (2003) The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *J Affect Disord*, 73(1-2):123-131.

Kendler KS. (2005a) Toward a philosophical structure for psychiatry. *Am J Psychiatry*, 162(3):433-440.

Kendler KS. (2005b) "A gene for. ..": the nature of gene action in psychiatric disorders. *Am J Psychiatry*, 162(7):1243-1252.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry*, 51(1):8-19.

Leverich GS, McElroy SL, Suppes T, Keck PE, Jr., Denicoff KD, Nolen WA, Altshuler LL, Rush AJ, Kupka R, Frye MA, Autio KA, Post RM. (2002) Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biol Psychiatry*, 51(4):288-297.

Lewinsohn PM, Klein DN, Seeley JR. (1995) Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry*, 34(4):454-463.

Lewinsohn PM, Klein DN, Seeley JR. (2000) Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disord*, 2(3 Pt 2):281-293.

Lewinsohn PM, Shankman S, Gau JM, Klein DN. (2004) The prevalence and co-morbidity of subthreshold psychiatric conditions. *Psychol Med*, 34:613-622.

Masi G, Toni C, Perugi G, Travierso MC, Millepiedi S, Mucci M, Akiskal HS. (2003) Externalizing disorders in consecutively referred children and adolescents with bipolar disorder. *Compr Psychiatry*, 44(3):184-189.

Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC. (2007) Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*, 64(5):543-552.

Murray CJL, Lopez AD. (1996) The global burden of disease : a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. In: Health HSoP, ed. *Global burden of disease and injury series*. Cambridge: World Health Organization. Harvard School of Public Health.

Pini S, de Queiroz V, Pagnin D, Pezawas L, Angst J, Cassano GB, Wittchen HU. (2005) Prevalence and burden of bipolar disorders in European countries. *Eur Neuropsychopharmacol*, 15(4):425-434.

Post RM, Leverich GS, Xing G, Weiss RB. (2001) Developmental vulnerabilities to the onset and course of bipolar disorder. *Dev Psychopathol*, 13(3):581-598.

Regeer EJ, Krabbendam L, De Graaf R, Ten Have M, Nolen WA, Van Os J. (2006) A prospective study of the transition rates of subthreshold (hypo)mania and depression in the general population. *Psychol Med*, 36(5):619-627.

Regier DA, Boyd JH, Burke JD, Jr., Rae DS, Myers JK, Kramer M, Robins LN, George LK, Karno M, Locke BZ. (1988) One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. *Arch Gen Psychiatry*, 45(11):977-986.

Rössler W, Riecher-Rössler A, Angst J, Murray R, Gamma A, Eich D, Van Os J, Gross VA. (2007) Psychotic experiences in the general population: a twenty-year prospective community study. *Schizophr Res*, 92(1-3):1-14.

Rutter M, Graham P, Chadwick OF, Yule W. (1976) Adolescent turmoil: fact or fiction? *J Child Psychol Psychiatry*, 17(1):35-56.

Rutter M, Moffitt TE, Caspi A. (2006) Gene-environment interplay and psychopathology: multiple varieties but real effects. *J Child Psychol Psychiatry*, 47(3-4):226-261.

Strakowski SM, DelBello MP. (2000) The co-occurrence of bipolar and substance use disorders. *Clin Psychol Rev*, 20(2):191-206.

Strober M, Morrell W, Burroughs J, Lampert C, Danforth H, Freeman R. (1988) A family study of bipolar I disorder in adolescence. Early onset of symptoms linked to increased familial loading and lithium resistance. *J Affect Disord*, 15(3):255-268.

Szádóczky E, Papp Z, Vitrai J, Ríhmer Z, Füredi J. (1998) The prevalence of major depressive and bipolar disorders in Hungary. Results from a national epidemiologic survey. *J Affect Disord*, 50(2-3):153-162.

Ten Have M, Vollebergh W, Bijl R, Nolen WA. (2002) Bipolar disorder in the general population in The Netherlands (prevalence, consequences and care utilisation): results from The Netherlands Mental Health Survey and Incidence Study (NEMESIS). *J Affect Disord*, 68(2-3):203-213.

Van Os J, Verdoux H. (2003) Diagnosis and classification of schizophrenia: categories versus dimensions, distributions versus disease. In: Murray RM, Jones P, Susser E, Van Os J, Cannon M, eds. *The epidemiology of Schizophrenia*. first ed. Cambridge, United Kingdom: Cambridge University Press;364-410.

Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, Joyce PR, Karam EG, Lee CK, Lellouch J, Lepine JP, Newman SC, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen H, Yeh EK. (1996) Cross-national epidemiology of major depression and bipolar disorder. *Jama*, 276(4):293-299.

Wittchen HU, Mühlig S, Pezawas L. (2003) Natural course and burden of bipolar disorders. *Int J Neuropsychopharmacol*, 6(2):145-154.

Wozniak J, Biederman J, Kiely K, Ablon JS, Faraone SV, Mundy E, Mennin D. (1995) Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *J Am Acad Child Adolesc Psychiatry*, 34(7):867-876.

Chapter 2

Evidence that Bipolar Disorder is the Poor Outcome Fraction of a Common Developmental Phenotype: An 8-year cohort study in young people

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ABSTRACT

Background. Reported population rates of bipolar syndromes are highly variable. The bipolar population morbidity force, separating continuous phenotypic expressions of (hypo)mania, distress and need for care was estimated.
Methods. In 1395 adolescents aged 14-17 years, symptoms of (hypo)mania, distress and use of mental health care were measured at baseline and approximately 1.5 year, 4 years, and 10 years later using the Munich-Composite International Diagnostic Interview.
Results. At its broadest definition (any (hypo)manic symptom), the cumulative lifetime incidence at T3 (CLI) was 37.9%. At the syndromal, DSM-IV-definition, CLIs and standardized yearly incidence rates were respectively 3.3% and $309/10^5$ person-years for DSM-IV manic episode, 4.5% and $410/10^5$ person-years for DSM-IV hypomanic episode, and 7.6% and $714/10^5$ person-years for DSM-IV manic and hypomanic episode combined ('(hypo)manic episode'). Most individuals with DSM-IV-defined hypomanic and manic episodes were never in care (87% vs. 62%) and most did not display comorbid depressive episodes (69% vs. 60%). Mental health care use was linearly associated with number of symptoms and level of distress. Incidence of the (hypo)manic phenotype occurred mostly before age 22, with a noticeable decline afterwards (Hazard Ratio 0.031; 95% Confidence Interval 0.0050-0.19 for DSM-IV (hypo)manic episodes). Incidence rates, particularly at the level of clinical morbidity, were strongly associated with previous childhood disorder, notably ADHD, and male sex.
Conclusions. Bipolar disorder may be best conceived as the extreme of a continuously expressed population phenotype, the ontogenesis of which can be traced largely to the adolescent developmental period as well as disorders with childhood onset.

INTRODUCTION

The World Health Organisation (WHO) identified bipolar disorder as the sixth leading cause of disability-adjusted life years in the world among people aged 15-44 years (Murray and Lopez, 1996). True prevalence and incidence rates of (hypo)manic disorder, however, remain unclear. Lifetime prevalence estimates vary from around 1-2% (Kessler et al., 1994; Regier et al., 1988; Weissman et al., 1996) to 5-8% (Angst 1998; Carlson and Kashani, 1988; Judd and Akiskal, 2003; Lewinsohn et al., 1995; Szádóczky et al., 1998). Incidence rates vary between 4-33/10^5/year (Bebbington and Ramana, 1995).

Reported variability in bipolar population morbidity force may be caused by several factors. First, nearly all incidence studies on bipolar disorder are based on participants in clinical care, which likely results in a substantial underestimation of rates (Wittchen et al., 2003), since many possible cases either have not sought help or are not diagnosed correctly and thus are not in care for bipolar disorder (Ghaemi et al., 2002).

Second, previous work suggests that the age of the population under study may be crucial, particularly for estimating onset, episode risk and lifetime risk, as there are indications that much of the population lifetime risk for bipolar disorder is consumed in adolescence (Lewinsohn et al., 2003). Thus, a young study population as used in the Early Developmental Stages of Psychopathology Study (EDSP) is most appropriate (Wittchen et al., 2003). The issue of age is also important in view of considerable psychopathological, longitudinal and familial/genetic overlap between bipolar disorder and childhood disorders, in particular attention-deficit/hyperactivity disorder (ADHD), but also oppositional-defiant disorder (ODD) and conduct disorder (CD) (Henin et al., 2007; Nierenberg et al., 2005). Studying the onset of (hypo)manic symptoms in the general population of adolescents allows for quantification of the amount of bipolar population morbidity force that can be traced to disorders with onset in childhood.

Third, diagnostic criteria used have a major impact on population rates (Akiskal et al., 2000; Angst et al., 2003b). Many people in the general population suffer from subthreshold bipolar disorder (Merikangas et al., 2007). Therefore, widening criteria for bipolar disorder will naturally increase the number of cases.

An informative way of describing the bipolar population morbidity force is to replace dichotomous diagnostic criteria with dimensional measures. Angst and Marneros suggest a natural continuum might exist on which all (hypo)manic

manifestations of varied length, frequency and severity can be represented (Angst and Marneros, 2001). This dimensional approach has been shown to be more sensitive and more informative in the search for determinants of onset and change than the categorical representation, making it easier to monitor onset and progression of psychiatric phenotypes more closely (Van Os and Verdoux, 2003). Furthermore, a continuous distribution of the number of symptoms allows for fuller examination of the impact of symptoms on wellbeing and functioning, severity and distress (Regeer et al., 2006). Thus, the greater the level of expression of psychopathology, the higher the probability for service use, need for welfare/disability benefits, and suicidal behaviour compared to controls (Judd and Akiskal, 2003). The use of dimensional measures may also facilitate recognition of at-risk states and early intervention (Birmaher and Axelson, 2006; Egeland et al., 2000; Hanssen et al., 2005). For bipolar disorder, a dimensional approach has the additional advantage of allowing for the separate study of manic and depressive dimensions, the co-occurrence of which in the same mood episode is common in clinical practice and therefore represents an important parameter for study in epidemiological and taxonomic investigations. Thus, the possible use of dimensional measures in bipolar disorder is currently being examined in DSM-V (First 2006).
Finally, the advantage of a continuous definition can be found in the increase of statistical power without loss of clinical utility.
Therefore, the aim was to investigate dimensional (hypo)manic phenotypes, independent of receipt of mental health care, in a large representative cohort of adolescents followed over a period of up to 10 years.

METHOD

Sample

This study is part of the Early Developmental Stages of Psychopathology study (EDSP), a prospective-longitudinal cohort study. Detailed information about design, sample, instruments, procedures, and statistical methods of the EDSP is presented elsewhere (Lieb et al., 2000; Wittchen et al., 1998b). Data were collected in a representative population sample of adolescents and young adults living in the Munich area (Germany), aged 14-24 years at baseline. The study sample was randomly drawn from the 1994 government population registers. Fourteen to 15-year-olds were sampled at twice the rate of 16- to 21-year-olds, and 22- to 24-year-olds were sampled at half this rate.

Study design

The present study is based on a subset of EDSP respondents, aged 14-17 years at baseline (T0, *n*=1395, response rate 75%), thus ensuring a population at risk of developing incident bipolar disorder. Participants completed a baseline survey (T0, *n*=1395) and 3 follow-up investigations (T1, T2, T3), covering a time period of approximately 1.6 years (T0-T1, SD 0.2), 3.4 years (T0-T2, SD 0.3) and 8.3 years (T0-T3, range 7.4-10.6 years, SD 0.7) respectively. Response rates (conditional on T0 completion) were respectively 88% at T1 (*n*=1228), 83% at T2 (*n*=1169) and 73% at T3 (*n*=1022).

Instruments

Interviews were conducted using the computerized version of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen and Pfister, 1997), an updated version of the WHO's CIDI version 1.2 (WHO 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 definitions and criteria of the DSM-IV. High interrater and test-retest reliability of the CIDI have been established (Wittchen et al., 1991; Wittchen 1994), as well as validity (Reed et al., 1998). Test-retest reliability (kappa) of the DIA-X/M-CIDI was 0.68 (p<0.001) for DSM-IV major depressive disorder and 0.64 (p<0.001) for DSM-IV bipolar disorder (Wittchen et al., 1998a). To assure reliability of the assessments, fully trained and experienced psychologists who were allowed to probe with follow-up questions conducted the interviews. At baseline, the lifetime version of the DIA-X/M-CIDI was used, for subsequent investigations the DIA-X/M-CIDI interval version.

Dichotomous DSM-IV algorithms of (hypo)manic phenotypes

A categorical subdivision was made using M-CIDI/DSM-IV diagnostic algorithms (Pfister and Wittchen, 1995). Participants were divided into 4 groups; participants (1) suffering from neither hypomanic nor manic episodes, (2) suffering from DSM-IV manic episodes, (3) suffering from DSM-IV hypomanic episodes and (4) suffering from either manic or hypomanic episodes (hereafter: (hypo)manic episodes). The last 3 groups were subsequently subdivided into participants (a) with lifetime comorbid depressive episode, and (b) without lifetime comorbid depressive episode.

Mania phenotypes based on dimensional (hypo)manic symptom score

(Hypo)manic symptoms were assessed using 11 items of the DIA-X/CIDI mania section, and concerned 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. These items were rated yes (1) or no (0) and were only rated if (a) at least one of the core symptoms "unusual happiness or excitement" or "unusual irritability" was present; (b) core symptoms were either noticed by others or caused participants problems; (c) symptoms were present for at least 4 successive days; (d) symptoms were not a result of alcohol/drugs use. Guided by previous work (Regeer et al., 2006), a sum score of symptom ratings was formed (range 0-11 symptoms). Five progressively stricter and overlapping subcategories of this sum score were created (I: no symptoms; II: ≥1 symptom; III: ≥4 symptoms; IV: ≥7 symptoms; V: ≥10 symptoms). These subcategories represented the underlying continuous score of (hypo)manic symptoms.

Distress dimension

In participants with ≥4 (hypo)manic symptoms, a division was made based on the level of distress associated with these symptoms, as reported as part of the DIA-X/M-CIDI mania section. Distress was assessed by asking participants if, at the moment the symptoms were at their worst, they interfered with life, work or leisure activities, and was coded (1) no interference (2) some interference (3) considerable interference (4) much interference.

Stratification by mental health care

In participants fulfilling criteria for at least one of the above phenotypes, stratification was applied based on whether or not mental health care had been received at the respective assessment. First, participants were asked if they were ever treated in a hospital or spoke to a professional because of (hypo)manic symptoms. Secondly, participants were shown a list on which several types of outpatient, inpatient or day patient institutions for mental health problems were mentioned, after which they were asked if they had ever sought help at any of these institutions because of *mental health* problems. All participants who responded positively to either one of these questions at the respective assessment were considered to belong to the group in receipt of mental health care.

Childhood disorders

Between T0 and T1, face-to-face interviews were carried out with respondents' parents to collect information regarding ODD, CD and ADHD (hereafter collectively referred to as 'childhood disorders'). These childhood disorders were assessed with questions covering the criteria defined by the DSM-IV. Information was mostly based on maternal responses (97.4%). Response rate of parents was 86% (n=1053).

Statistical Analysis

Cumulative lifetime incidence and person-year incidence rates

Weighting occurred to account for differences in sampling probabilities as well as systematic non-response at baseline according to age, gender and geographical location (Lieb et al., 2000). Cumulative lifetime incidence up to T3 (CLI) of both the (hypo)manic phenotypes and the separate (hypo)manic symptoms was calculated at T3.

Survival analysis was conducted to determine incidence rates (IRs) between T0 and T3 using the ST commands in STATA, version 9.2 (Statacorp 2005). CLI and IR estimates were calculated stratified by receipt of mental health care. The IR is defined as the number of new cases of disease during a given time period divided by the sum of time that each person remains under observation and is free from disease (the total person-time of observation). After defining appropriate risk sets, incidence rates were calculated for each phenotype. The risk set is defined as the set of individuals at risk of *developing* a certain phenotype during the study. Therefore, participants with past or current evidence of this phenotype at baseline were excluded from analysis, in which the strictest possible exclusion criteria were used (e.g. all participants experiencing ≥1 symptom excluded for analyses of incidence of (hypo)manic symptoms). The total person-time of observation of the individual risk sets thus defined are presented in table 2.1.

Childhood Morbidity Sensitivity Analyses (CMSA)

In order to assess how much of the incidence of bipolar phenotypes could be traced to childhood morbidity, comorbidity with childhood disorders (ODD, CD and ADHD) was assessed and sensitivity analyses ('CMSA') performed for both CLI and IRs. First, lifetime comorbidity between T0 lifetime (hypo)manic episodes and childhood disorders was assessed using logistic regression. Second,

Cox regression was used to calculate associations between childhood disorders and incidence of new (hypo)manic episodes between T0 and T3. Third, CLI and IRs for bipolar phenotypes were recalculated with exclusion of individuals with these childhood disorders. Similar sensitivity analyses were done for the other (hypo)manic phenotypes, i.e. participants suffering from at least one (hypo)manic symptom and for participants experiencing at least some distress.

Demographic risk factors

IRs were calculated stratified by age group as a time-varying variable (15-16 years, 17-18 years, 19-21 years, 22-24 years and 25-28 years; age = age during any moment of the study), sex and urbanicity (living in rural or city area at baseline; city area defined as the city of Munich (Spauwen et al., 2006). Statistical differences in IRs within age, sex, or urbanicity categories were tested using cox regression analysis yielding hazard ratios (HRs), using the 15 years age group, male sex, and rural area as reference categories. In order to assess whether any association with demographic factors was independent of the others and unconfounded by comorbid current or childhood psychopathology, HRs of all phenotypes were adjusted for age, sex, urbanicity, presence of depression and presence of childhood disorders using the STATA STRATA option for adjustment by stratification in Cox regression. HRs of the distress phenotypes were additionally adjusted for number of (hypo)manic symptoms. As part of the CMSA, HRs were calculated similarly after exclusion of participants suffering from childhood disorders.

RESULTS

Analyses are based on a total of 1395 adolescents (51% male). Mean age at baseline was 15.1 years (SD 1.1). Four-hundred fifteen adolescents (30%) were living in a rural area. Of the 1395 adolescents, 1022 completed T3. Drop-out rates were almost equal for sex (28.8% females vs. 24.8% males), urbanicity (25.3% rural vs. 27.3% Munich city), and age (22.4% 13-year-olds vs. 23.8% 14-year-olds vs. 29.6% 15-year-olds vs. 25.7% 16-years-olds vs. 29.5% 17-year-olds).

Rates of DSM-IV (hypo)manic episodes

CLI rate

The CLI varied between 1.3-7.6% for the different DSM-IV episodic phenotypes (Table 2.1).

Restriction to episodes plus mental health care reduced the CLI to 0.3-1.8%. Mean duration of (hypo)manic episodes was 24.5 days (SD 89.3; range 4-≥996 days); mean number of lifetime episodes was 15.8 episodes (SD 23.7; range 1-≥97 episodes).

Approximately a third (35.5%) of participants had comorbid depressive episodes. Seventy-six participants (7.2%) were diagnosed with any childhood disorder, mostly with ADHD (4.1%, n=43). Of these participants, 2 had a lifetime (hypo)manic episode at T0 (2.6%), whereas 5 (6.6%) developed incident (hypo)manic episodes between T0 and T3. Thus, these participants had a 2.6% risk of suffering from lifetime (hypo)manic episodes at T0, compared to a 2.4% risk in participants without childhood disorder (see online supportive material, Table 1-B at www.mania.homestead.com for detailed results). This association was not significant (OR 1.25; 95% CI 0.33-4.79, p=0.747). After CMSA, the CLI decreased slightly only for participants experiencing manic episodes (by a factor 1.2 if analysed irrespective of mental health care and by a factor 1.5-2 for participants with mental health care) (see Table 1-C at www.mania.-homestead.com).

Person-year IR

IRs for DSM-IV episodic phenotypes ranged from $104/10^5$ to $714/10^5$ person-years and, after restriction to episodes plus mental health care, from $3/10^5$ to $133/10^5$ person-years (Table 2.1). The association between the different incident (hypo)manic phenotypes and childhood morbidity was large and significant (HR 5.29; 95% CI 2.01-13.91, p=0.001 for (hypo)manic episode) (Table 2.2). Thus, CMSA reduced incidence rates for DSM-IV episodic phenotypes by approximately a factor 1.3, ranging from $76/10^5$ to $434/10^5$ person-years. Restriction to episodes plus mental health care yielded similar reductions, with IRs ranging from $3/10^5$ to $81/10^5$ person-years (see Table 1-C at www.mania.-homestead.com).

Table 2.1. Cumulative Lifetime Incidence up to T3 and Incidence Rates (T0-T3) of (Hypo)manic Phenotypes, Stratified By Care

(Hypo)manic Phenotype	Restriction	Cumulative Lifetime Incidence up to T3[§]			Incidence (T0-T3)[‖]			Incidence (T0-T3)[¶]		
		Total[‡]	DEP+	DEP-	Total[‡]	DEP+	DEP-	Total[‡]	DEP+	DEP-
DSM-IV Manic Episode	None	**3.3** (*n* = 45)	1.3 (n = 18)	2.0 (n = 27)	**308.9**	103.8	201.9	**28.7/9277**	9.8/9403	18.9/9358
	MHC+	**1.2** (*n* = 17)	0.6 (n = 9)	0.6 (n = 8)	**113.9**	50.6	62.9	**10.7/9419**	4.8/9448	5.9/9454
DSM-IV Hypomanic Episode	None	**4.5** (*n* = 62)	1.4 (n = 20)	3.1 (n = 43)	**409.5**	165.9	237.6	**37.6/9184**	15.6/9410	22/9258
	MHC+	**0.6** (*n* = 8)	0.3 (n = 4)	0.3 (n =4)	**27.5**	24.5	2.9	**2.6/9437**	2.3/9467	0.3/9453
DSM-IV (Hypo)manic Episode*	None	**7.6** (*n* = 106)	2.7 (n = 37)	4.9 (n = 69)	**713.5**	262.3	433.7	**64.1/8982**	24.5/9334	39.6/9131
	MHC+	**1.8** (*n* = 25)	0.8 (n = 12)	0.9 (n = 13)	**132.6**	65.8	66.0	**12.4/9376**	6.2/9436	6.2/9424
1 or more Symptoms	None	37.9 (*n* = 528)			**1720.0**			**153.2/8909**		
	MHC+	6.3 (*n* = 87)			**363.7**			**32.9/9054**		
4 or more Symptoms	None	26.5 (*n* = 370)			**1112.2**			**101/9080**		
	MHC+	4.8 (*n* = 67)			**225.6**			**21/9145**		
7 or more Symptoms	None	8.5 (*n* = 119)			**377.9**			**35.4/9379**		
	MHC+	2.4 (*n* = 34)			**94.7**			**8.8/9328**		
10 or more Symptoms	None	1.0 (*n* = 13)			**77.9**			**7.4/9465**		
	MHC+	0.5 (*n* = 7)			**27.7**			**2.6/9455**		
Some Distress[†]	None	10.8 (*n* = 151)			**1072.7**			**97.3/9075**		
	MHC+	1.8 (*n* = 25)			**167.0**			**15.6/9358**		
Much Distress[†]	None	4.1 (*n* =58)			**267.0**			**25.0/9371**		
	MHC+	1.0 (*n* =14)			**96.2**			**9.1/9436**		
Considerable Distress[†]	None	0.8 (*n* = 12)			**51.4**			**4.9/9468**		
	MHC+	0.2 (*n* = 3)			**18.4**			**1.7/9464**		

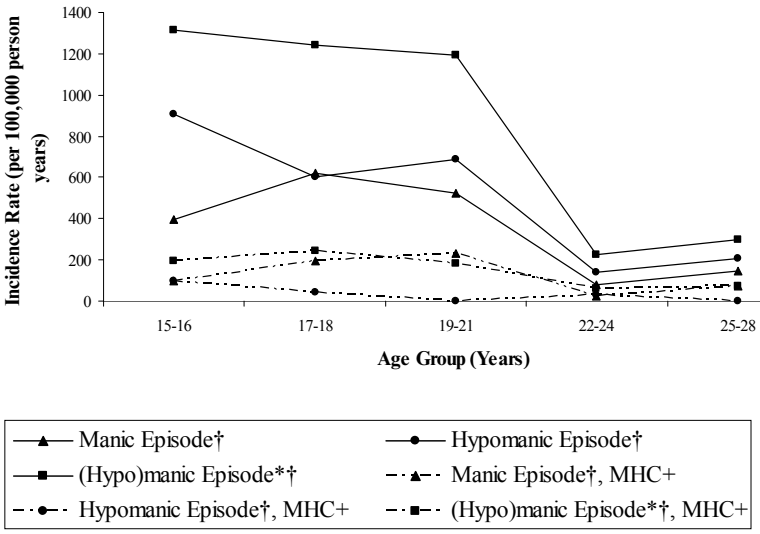
Abbreviations: MHC+, episodes in combination with mental health care; DEP+, with depressive episode; DEP-, without depressive episode; *(Hypo)manic episode: either hypomanic or manic episode; † In participants with at least four (hypo)manic symptoms; ‡ Total: total group, independent of having lifetime depressive episodes; § Values are expressed as percentage (number) of cases; ‖ Values are expressed as number of cases per 100,000 person-years; ¶ Values are expressed as denominator population of person-years

Age, sex, and urbanicity

A strong association existed between age and IRs (Table 2.2, Fig. 2.1, Fig. 2.2), with IRs decreasing as age increased, which was significant for hypomanic episodes (HR 0.65; 95% CI 0.50-0.85, p=0.001) and (hypo)manic episodes (HR 0.67; 95% CI 0.54-0.84, p=0.000). Post-hoc analyses showed the IRs of these episodic phenotypes, compared to the age group 15-21 years, decreased very strongly after the age of 21 years (HR 0.021; 95% CI 0.0024-0.18, p=0.000 for hypomanic episode, HR 0.031; 95% CI 0.0050-0.19, p=0.000 for (hypo)manic episode). Restriction to episodes plus mental health care showed a similar decline in IRs of manic and (hypo)manic episodes after the age of 21 years, although statistically inconclusive. Subsequent CMSA showed similar associations (see Table 1-C and Fig 2-B at www.mania.homestead.com).

The incidence of manic episodes was 14 times lower in women compared to men (HR 0.072; 95% CI 0.065-0.79, p=0.031). However, no sex differences were present for hypomanic episodes or (hypo)manic episodes and there was no association with urbanicity. In the CMSA, male preponderance in incidence of manic episodes remained of similar effect size (HR 0.08; 95% CI 0.070-0.86, p=0.037).

Fig 2.1. Incidence of (Hypo)manic Disorder, Stratified by Age and Care



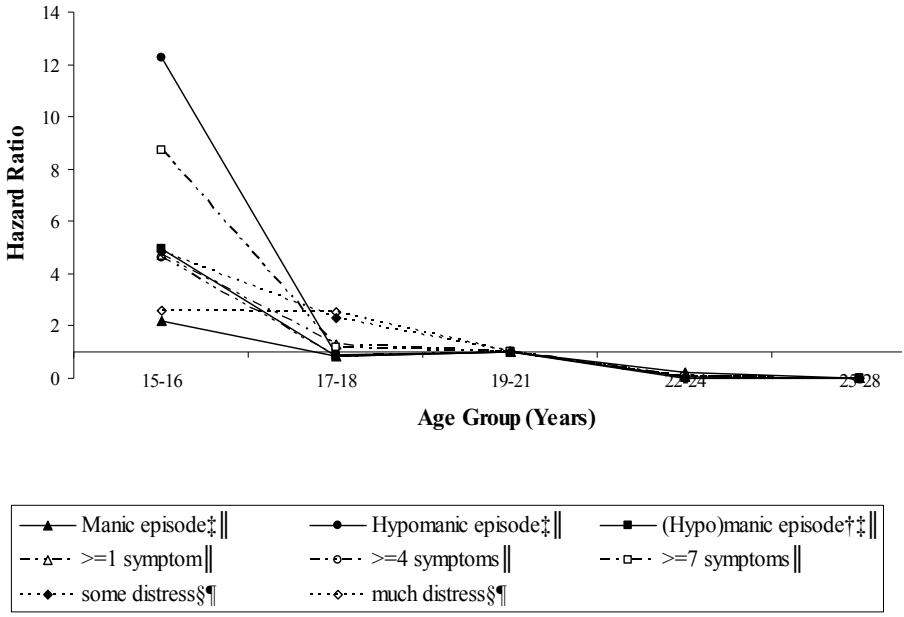
Abbreviations: MHC+, episodes in combination with mental health care; *(Hypo)manic episode: either hypomanic or manic episode; † Independent of having lifetime depressive episodes.

Table 2.2. Predictors of Incident (Hypo)manic Phenotypes

	Risk of Incident (Hypo)manic Phenotype, Hazard Ratio 95%CI			
	Age‖	**Female vs. Male**¶	**City vs. Rural**#	**Childhood Disorder***,**
Manic episode‡	0.74 (0.50-1.10)	0.07 (0.065-0.79) ††	1.55 (0.37-6.57)	3.65 (0.92-14.45)
Hypomanic episode‡	0.65 (0.50-0.85) ‡‡	1.55 (0.62-3.85)	1.08 (0.42-2.77)	7.82 (1.94-31.60) ††
(Hypo)manic episode†‡	0.67 (0.54-0.84) ‡‡	0.75 (0.36-1.56)	1.21 (0.55-2.66)	5.29 (2.01-13.91) ‡‡
≥1 symptom‡	0.63 (0.55-0.72) ‡‡	1.40 (0.94-2.08)	1.15 (0.75-1.77)	0.83 (0.36-1.92)
≥4 symptoms‡	0.60 (0.51-0.72) ‡‡	1.46 (0.88-2.43)	1.10 (0.64-1.89)	1.06 (0.38-2.92)
≥7 symptoms‡	0.61 (0.45-0.85) ††	0.40 (0.13-1.18)	4.51 (0.94-21.72)	2.38 (0.50-11.31)
≥10 symptoms‡	0.34 (0.11-1.06)	0.60 (0.05-6.79)	5.44 (0.28-107.42)	NA
Some Distress§	0.66 (0.49-0.89) ††	0.99 (0.38-2.61)	1.10 (0.43-2.80)	0.95 (0.24-3.71)
Much distress§	0.69 (0.43-1.10)	NA	0.56 (0.07-4.46)	1.23 (0.19-8.16)
Considerable distress§	0.87 (0.34-2.21)	NA	0.93 (0.03-26.96)	NA
Psychiatric Help§	0.34 (0.13-0.86) ††	2.73 (0.20-36.77)	NA	NA

Abbreviations: CI, confidence interval; NA, data not applicable; * Childhood disorder: oppositional-defiant disorder, conduct disorder or attention deficit hyperactivity disorder; † (Hypo)manic episode: either hypomanic or manic episode; ‡ Results adjusted for age, sex, urbanicity, depression and childhood disorders ; § Results adjusted for age, sex, urbanicity, depression, childhood disorders and number of (hypo)manic symptoms ; ‖ Reference category: 15 years age group; ¶ Reference category: male sex; # Reference category: rural environment; ** Reference category: no childhood disorder; †† $p \leq 0.05$; ‡‡ $p \leq 0.001$

Fig. 2.2. Hazard Ratios of Incident (Hypo)manic Phenotypes, Stratified by Age Group*



* Reference category: 19-21 years age group; † (Hypo)manic episode: either hypomanic or manic episode; ‡ Independent of having lifetime depressive episodes; § In participants with at least four (hypo)manic symptoms; ‖ Results adjusted for sex, urbanicity, depression and childhood disorders (oppositional defiant disorder (OD), conduct disorder (CD) or attention-deficit hyperactivity disorder (ADHD)); ¶ Results adjusted for sex, urbanicity, depression, childhood disorders (ODD, CD or ADHD) and number of (hypo)manic symptoms.

Incidence of (hypo)manic symptoms

Rates

The number of participants steadily declined with increasing level of symptoms (Table 2.1). For participants experiencing ≥1 symptom, the CLI was 6 times higher before restriction of the group to participants with symptoms plus mental health care (Table 2.1). This discrepancy decreased as the number of symptoms increased, and in the group of participants experiencing ≥10 symptoms, CLI was only twice as high before restriction to symptoms plus mental health care. Participants diagnosed with a childhood disorder had a 31.6% risk of developing (hypo)manic symptoms, compared with a 25.4% risk in participants without childhood disorder (see Table 1-D at www.mania.homestead.com).

This association was close to statistical significance (OR 1.65; 95% CI 0.99-2.75, p=0.057). Subsequent CMSA showed similar distributions of participants across symptom groups (see Table 1-C at www.mania.homestead.com).

Age, sex, and urbanicity

In all symptom categories, IRs were associated negatively with age (HR 0.63; 95% CI 0.55-0.72, *p*=0.000 for ≥1 symptom, HR 0.60; 95% CI 0.51-0.72, *p*=0.000 for ≥4 symptoms, HR 0.61; 95% CI 0.45-0.85, *p*=0.003 for ≥7 symptoms) (Table 2.2, Fig. 2.2). Results remained the same in the CMSA (see Fig 2-B at www.mania.homestead.com). No significant differences in IRs were found with respect to urbanicity or sex (Table 2.2). However, in the CMSA, female preponderance was seen both in the group with ≥1 symptom as in the group with ≥4 symptoms, albeit only significantly in the group with ≥1 symptom (HR 1.51; 95% CI 1.01-2.26, *p*=0.045 and HR 1.61; 95% CI 0.97-2.69, *p*=0.068 respectively).

Incidence of distress

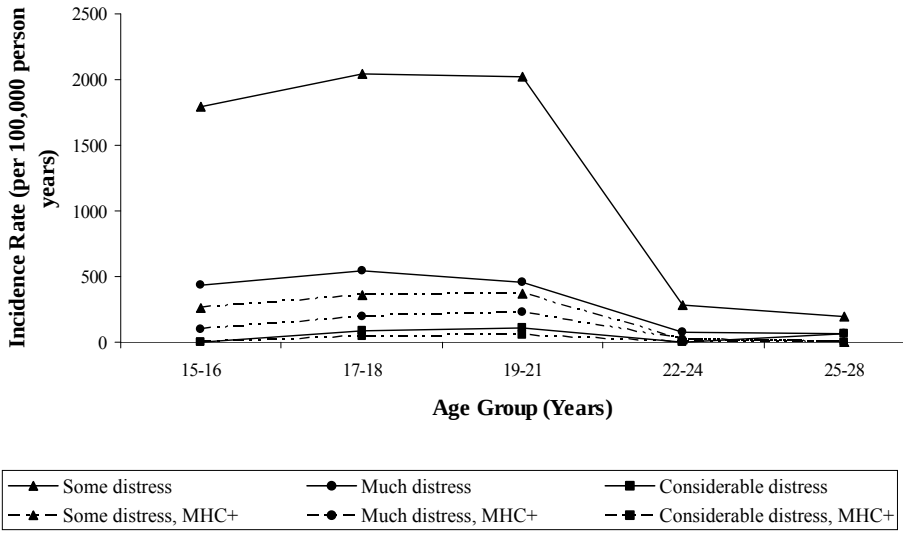
Rates

CLI and IRs of distress are described in table 2.1. Higher rates of distress were experienced by fewer people. The majority of people with "some distress" remained outside care, and the majority of people with "much distress" was in care. Participants diagnosed with a childhood disorder had a 25.0% risk of experiencing distress at T0 (if suffering from ≥4 symptoms), compared with 24.1% in those without (see Table 1-E at www.mania.homestead.com). This association was not significant (OR 0.97; 95% CI 0.20-4.71, p=0.972). Subsequent CMSA decreased CLI and IRs by approximately a factor 1.5-2, irrespective of mental health care (see Table 1-C at www.mania.homestead.com).

Age, sex, and urbanicity

For the group experiencing "some distress", a negative association was found with age (Table 2.2, Fig. 2.2, Fig. 2.3), which was independent of number of symptoms (HR 0.66; 95% CI 0.49-0.89, *p*=0.006). The incidence of distress was independent of sex and urbanicity. In the CMSA, the association with age remained (see Fig 2-B and Fig 3-B at www.mania.homestead.com).

Fig. 2.3. Incidence of Experienced Distress*, Stratified by Age and Care



Abbreviations: MHC+, distress in combination with mental health care; *In participants with at least four (hypo)manic symptoms.

DISCUSSION

Findings

In this large prospective study of over 1000 adolescents and young adults, results show that incidence rates of both (hypo)manic episodes and (hypo)manic symptoms are far higher than previously thought, and that the risk of developing a disorder was very low after the age of 21 years, independent of childhood disorders such as ADHD. In addition, results demonstrate a continuous distribution of (hypo)manic symptoms and distress, thus supporting the hypothesis that a dimensional representation may usefully describe the (hypo)manic phenotype (Allardyce et al., 2007). Furthermore, only a small fraction of adolescents and young adults experiencing these phenomena was receiving psychiatric care and co-occurrence of (hypo)manic episodes with depression was rather low compared to most literature. The incidence of the bipolar phenotype, in particular phenotypes at the level of clinical morbidity, was strongly associated with previous childhood disorders and male sex.

Cumulative incidence and person-year incidence rates

Incidence rates in this study are much higher than those reported previously (Bebbington and Ramana, 1995). A partial explanation for this discrepancy is the use of clinical samples in previous work, which results in loss of all individuals not in contact with mental health services. The effect sample type has on observed IRs is clearly shown in the current data, in which stratification for mental health care decreased IRs. However, the elevated IRs cannot be explained entirely this way, since even for participants receiving mental health care, IRs were still 7-50 times higher than previously reported estimates, while CLI estimates did yield estimates comparable to those in previous reports (Lish et al., 1994). A likely reason for the higher IRs, given similar CLI estimates, is that the current sample consisted of adolescents, who display the highest risk of developing mental disorders (Kessler et al., 2005). Therefore, all studies focusing on adults are likely to report much lower IRs. The focus on clinical samples also forms a plausible explanation for the low co-occurrence of depressive episodes with (hypo)manic episodes, since both types of episodes, independently of each other, increase need for care and help-seeking, resulting in more "comorbid" psychopathology at the level of mental health care ("Berkson's bias") (Regeer et al., in press). Accordingly, the co-occurrence of depressive episodes in the current study was higher in participants receiving mental health care, and was comparable to the comorbidity rate reported by Judd and colleagues in a 10-year follow-up study of bipolar-I patients (Judd et al., 2003).

Bipolar disease as a developmental disorder

The greatest risk of developing (hypo)manic disorder was before age 22 years, after which it decreased to the point of almost disappearing, while the risk of experiencing (hypo)manic symptoms for the first time decreased more gradually as age increased. These findings are supported by other studies in which the most common age of onset for bipolar disorder appeared to be between 15-19 years (Szádóczky et al., 1998). Findings similarly concur with studies in which substantial numbers of adult patients retrospectively reported first experiencing symptoms in childhood or adolescence (Joyce 1984). Evidence exists of considerable psychopathological, longitudinal and familial/genetic overlap between bipolar disorder and childhood disorders (Henin et al., 2007; Nierenberg et al., 2005). The findings in the current sample show low levels of cross-sectional comorbidity at T0, but very high longitudinal comorbidity between childhood disorders and new, incident bipolar phenotypes, in particular at the level of

clinical morbidity, over time. CMSA in which these disorders were excluded did not change the pattern of association with age. The pattern of findings therefore suggests that the ontogenesis of (hypo)manic symptoms and (hypo)manic disorder may be traced to the adolescent developmental period and that expression of certain childhood disorders increases the risk for later expression of bipolar morbidity. This is in line with the hypothesis that adult mental disorders are the result of long-term alterations in neurodevelopment (Rich et al., 2006) and connected to developmental pathways with partial phenotypic expression in childhood (Leibenluft et al., 2003). It has been suggested that during adolescence, a reorganization of frontally based neural systems involved in affective processes causes a baseline difference of positive valence affect which in turn may lead to extreme fluctuations in behavioural state. Secondly, developmental changes in reward processes or in associated cognitive parameters may result in an increased propensity of adolescents to experience high arousal positive states, thus causing a higher probability to experience more markedly positive moods and greater fluctuations in mood states (Leibenluft et al., 2003).

Continuity

Current results indicate (hypo)manic symptoms are a common phenomenon in the general population, with over 25% of the study sample reporting 4 or more (hypo)manic symptoms. Symptoms and clinical morbidity showed dose-response relationships, in that more cases of clinical morbidity arose as the number of symptoms increased, supporting continuity between subclinical and clinical phenotypes. Longitudinal evidence for continuity was provided by Regeer and colleagues, who showed dose-response relationships between number of symptoms and transition over time to DSM-IV bipolar disorder in a population sample (Regeer et al., 2006). However, Lewinsohn and colleagues reported adolescent subthreshold bipolar disorder was not associated with an increased incidence of bipolar disorder, and concluded that the tendency to develop periods of elated mood might be transient and limited to adolescence (Lewinsohn et al., 2000). Later, however, the authors concluded, using the same data, a continuum may exist extending down to elevated levels of hypomanic personality traits, to subthreshold and mild forms of the disorder (Lewinsohn et al., 2003). Moreover, Angst and colleagues demonstrated that having manic symptoms below the diagnostic threshold for hypomanic episode was relevant in identifying bipolar-II disorder (Angst et al., 2003a). Therefore, it is suggested that a continuous relationship exists between (hypo)manic symptoms and bipo-

lar disorder. However, as evidenced by findings in the current study, while symptoms appear to be distributed in the population and continuous with disorder, the vast majority of those individuals with expression at the symptom level never develop bipolar disorder. Thus, (hypo)manic symptoms may be conceived partially as pertaining to normal adolescent development. If, however, symptoms persist over time, individuals may be at risk of a possible transition to bipolar disorder. Thus, future work must investigate whether adolescents with persistent subclinical bipolar phenotypes are at risk of making the transition to bipolar disorder, and which factors drive such transitions. Possible factors are symptom factors, like intrusiveness, frequency and comorbidity of symptoms, but also personal and cultural factors, such as coping, illness behaviour, societal tolerance and the development of functional impairments, as well as known risk factors such as a positive family history of bipolar disorder, exposure to life events, or an interaction between these factors (Hillegers et al., 2004; Lapalme et al., 1997; Van Os and Verdoux, 2003).

Risk factors

Male sex was a risk factor for the onset of manic episodes. This appears inconsistent with studies finding equal sex distributions (Lloyd et al., 2005). However, the finding does concur with several studies in which it was suggested that male sex is associated with earlier onset of mania (Carlson et al., 2000; Kennedy et al., 2005). Thus, Carlson and colleagues (2000) found subjects with onset of mania before the age of 21 years were more likely to be male, and Kennedy and colleagues (2005) demonstrated incidence for males peaked between 16-25 years, to fall dramatically afterwards, whereas incidence for females was lower and did not fall as dramatically. Male preponderance in incidence was not seen for subclinical bipolar phenotypes, suggesting male sex specifically increases the risk for clinical morbidity within the bipolar spectrum. The link between male sex and poor outcome is well known for other types of psychotic illness, in particular schizophrenia (Castle and Murray, 1991).

Urbanicity generally did not increase the risk for (hypo)manic phenotypes. The absence of a consistent effect of urbanicity in (hypo)manic disorder concurs with previous findings (Krabbendam and Van Os, 2005). A recent study showed any association between (hypo)manic disorder and urbanicity is likely mediated by positive psychotic symptoms (Kaymaz et al., 2007).

Limitations

Several limitations need to be considered.
First, although a prospective design was used, the study became partly retrospective by implementing questions regarding time intervals between waves. Therefore, the possibility of recall bias cannot be excluded although arguably this would likely contribute more to false negatives than false positives as remote episodes of illness may often be forgotten, especially among patients with milder/less recurrent illness or those who did not receive treatment (Simon and VonKorff, 1995).
Second, exclusion of individuals at T0 and exclusion of the older cohort means results are based on a limited age range with associated decrease in statistical power. This theoretically could have caused the incidence to drop after the age of 21 years. However, similar results were found after the oldest 2 age groups were collapsed, thus increasing statistical power.
Third, the age range of participants is limited as follow-up of participants did not begin until the age of 14 years. Future studies should examine whether adolescent bipolar symptoms, relevant to adult clinical morbidity, are present also in younger samples.

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LITERATURE

Akiskal HS, Bourgeois ML, Angst J, Post R, Möller H, Hirschfeld R. (2000) Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J Affect Disord*, 59 Suppl 1:S5-S30.

Allardyce J, Suppes T, Van Os J. (2007) Dimensions and the psychosis phenotype. *Int J Methods Psychiatr Res*, 16 Suppl 1 2007:S34-40.

Angst J. (1998) The emerging epidemiology of hypomania and bipolar II disorder. *J Affect Disord*, 50(2-3):143-151.

Angst J, Marneros A. (2001) Bipolarity from ancient to modern times: conception, birth and rebirth. *J Affect Disord*, 67(1-3):3-19.

Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rössler W. (2003a) Toward a re-definition of subthreshold bipolarity: epidemiology and proposed criteria for bipolar-II, minor bipolar disorders and hypomania. *J Affect Disord*, 73(1-2):133-146.

Angst J, Gamma A, Benazzi F, Ajdacic V, Eich D, Rössler W. (2003b) Diagnostic issues in bipolar disorder. *Eur Neuropsychopharmacol*, 13 Suppl 2:S43-50.

Bebbington P, Ramana R. (1995) The epidemiology of bipolar affective disorder. *Soc Psychiatry Psychiatr Epidemiol*, 30(6):279-292.

Birmaher B, Axelson D. (2006) Course and outcome of bipolar spectrum disorder in children and adolescents: a review of the existing literature. *Dev Psychopathol*, 18(4):1023-1035.

Carlson GA, Kashani JH. (1988) Manic symptoms in a non-referred adolescent population. *J Affect Disord*, 15(3):219-226.

Carlson GA, Bromet EJ, Sievers S. (2000) Phenomenology and outcome of subjects with early- and adult-onset psychotic mania. *Am J Psychiatry*, 157(2):213-219.

Castle DJ, Murray RM. (1991) The neurodevelopmental basis of sex differences in schizophrenia. *Psychol Med*, 21(3):565-575.

Egeland JA, Hostetter AM, Pauls DL, Sussex JN. (2000) Prodromal symptoms before onset of manic-depressive disorder suggested by first hospital admission histories. *J Am Acad Child Adolesc Psychiatry*, 39(10):1245-1252.

First MB. (2006) Beyond clinical utility: broadening the DSM-V research appendix to include alternative diagnostic constructs. *Am J Psychiatry*, 163(10):1679-1681.

Ghaemi SN, Ko JY, Goodwin FK. (2002) "Cade's disease" and beyond: misdiagnosis, antidepressant use, and a proposed definition for bipolar spectrum disorder. *Can J Psychiatry*, 47(2):125-134.

Hanssen M, Bak M, Bijl R, Vollebergh W, Van Os J. (2005) The incidence and outcome of subclinical psychotic experiences in the general population. *Br J Clin Psychol*, 44(Pt 2):181-191.

Henin A, Biederman J, Mick E, Hirshfeld-Becker DR, Sachs GS, Wu Y, Yan L, Ogutha J, Nierenberg AA. (2007) Childhood antecedent disorders to bipolar disorder in adults: a controlled study. *J Affect Disord*, 99(1-3):51-57.

Hillegers MH, Burger H, Wals M, Reichart CG, Verhulst FC, Nolen WA, Ormel J. (2004) Impact of stressful life events, familial loading and their interaction on the onset of mood disorders: study in a high-risk cohort of adolescent offspring of parents with bipolar disorder. *Br J Psychiatry*, 185:97-101.

Joyce PR. (1984) Age of onset in bipolar affective disorder and misdiagnosis as schizophrenia. *Psychol Med*, 14(1):145-149.

Judd LL, Akiskal HS. (2003) The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *J Affect Disord*, 73(1-2):123-131.

Judd LL, Akiskal HS, Schettler PJ, Coryell W, Maser J, Rice JA, Solomon DA, Keller MB. (2003) The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders? *J Affect Disord*, 73(1-2):19-32.

Kaymaz N, Van Os J, De Graaf R, Ten Have M, Nolen W, Krabbendam L. (2007) The impact of subclinical psychosis on the transition from subclinicial mania to bipolar disorder. *J Affect Disord*, 98(1-2):55-64.

Kennedy N, Boydell J, Kalidindi S, Fearon P, Jones PB, Van Os J, Murray RM. (2005) Gender differences in incidence and age at onset of mania and bipolar disorder over a 35-year period in Camberwell, England. *Am J Psychiatry*, 162(2):257-262.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. (1994) Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry*, 51(1):8-19.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. (2005) Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*, 62(6):593-602.

Krabbendam L, Van Os J. (2005) Schizophrenia and urbanicity: a major environmental influence--conditional on genetic risk. *Schizophr Bull*, 31(4):795-799.

Lapalme M, Hodgins S, LaRoche C. (1997) Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. *Can J Psychiatry*, 42(6):623-631.

Leibenluft E, Charney DS, Pine DS. (2003) Researching the pathophysiology of pediatric bipolar disorder. *Biol Psychiatry*, 53(11):1009-1020.

Lewinsohn PM, Klein DN, Seeley JR. (1995) Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry*, 34(4):454-463.

Lewinsohn PM, Klein DN, Seeley JR. (2000) Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disord*, 2(3 Pt 2):281-293.

Lewinsohn PM, Seeley JR, Klein DN. (2003) Bipolar disorders during adolescence. *Acta Psychiatr Scand Suppl*, (418):47-50.

Lieb R, Isensee B, Von Sydow K, Wittchen HU. (2000) The Early Developmental Stages of Psychopathology Study (EDSP): a methodological update. *Eur Addict Res*, 6(4):170-182.

Lish JD, Dime-Meenan S, Whybrow PC, Price RA, Hirschfeld RM. (1994) The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. *J Affect Disord*, 31(4):281-294.

Lloyd T, Kennedy N, Fearon P, Kirkbride J, Mallett R, Leff J, Holloway J, Harrison G, Dazzan P, Morgan K, Murray RM, Jones PB. (2005) Incidence of bipolar affective disorder in three UK cities: results from the AESOP study. *Br J Psychiatry*, 186:126-131.

Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC. (2007) Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*, 64(5):543-552.

Murray CJL, Lopez AD. (1996) The global burden of disease : a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. In: Health HSoP, ed. *Global burden of disease and injury series*. Cambridge: World Health Organization. Harvard School of Public Health.

Nierenberg AA, Miyahara S, Spencer T, Wisniewski SR, Otto MW, Simon N, Pollack MH, Ostacher MJ, Yan L, Siegel R, Sachs GS. (2005) Clinical and diagnostic implications of lifetime attention-deficit/hyperactivity disorder comorbidity in adults with bipolar disorder: data from the first 1000 STEP-BD participants. *Biol Psychiatry*, 57(11):1467-1473.

Pfister H, Wittchen HU. (1995) M-CIDI Computerprogramm. München: Max-Planck-Institut für Psychiatrie, Klinisches Institut.

Reed V, Gander F, Pfister H, Steiger A, Sonntag H, Trenkwalder C, Hundt W, Wittchen HU. (1998) To what degree does the Composite International Diagnostic Interview (CIDI) correctly identify DSM-IV disorders? Testing validity issues in a clinical sample. *Int J Methods Psychiatr Res*, 7:142-155.

Regeer E, Krabbendam L, De Graaf R, Ten Have M, Nolen W, Van Os J. (in press) Berkson's bias and the mood dimensions of bipolar disorder. *Int J Methods Psychiatr Res*.

Regeer EJ, Krabbendam L, De Graaf R, Ten Have M, Nolen WA, Van Os J. (2006) A prospective study of the transition rates of subthreshold (hypo)mania and depression in the general population. *Psychol Med*, 36(5):619-627.

Regier DA, Boyd JH, Burke JD, Jr., Rae DS, Myers JK, Kramer M, Robins LN, George LK, Karno M, Locke BZ. (1988) One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. *Arch Gen Psychiatry*, 45(11):977-986.

Rich BA, Vinton DT, Roberson-Nay R, Hommer RE, Berghorst LH, McClure EB, Fromm SJ, Pine DS, Leibenluft E. (2006) Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. *Proc Natl Acad Sci U S A*, 103(23):8900-8905.

Simon GE, VonKorff M. (1995) Recall of psychiatric history in cross-sectional surveys: implications for epidemiologic research. *Epidemiol Rev*, 17(1):221-227.

Spauwen J, Krabbendam L, Lieb R, Wittchen HU, Van Os J. (2006) Evidence that the outcome of developmental expression of psychosis is worse for adolescents growing up in an urban environment. *Psychol Med*, 36(3):407-415.

Statacorp. (2005) STATA Statistical Software. Release 9.2 ed. Texas: College Station.

Szádóczky E, Papp Z, Vitrai J, Ríhmer Z, Füredi J. (1998) The prevalence of major depressive and bipolar disorders in Hungary. Results from a national epidemiologic survey. *J Affect Disord*, 50(2-3):153-162.

Van Os J, Verdoux H. (2003) Diagnosis and classification of schizophrenia: categories versus dimensions, distributions versus disease. In: Murray RM, Jones P, Susser E, Van Os J, Cannon M, eds. *The epidemiology of Schizophrenia*. first ed. Cambridge, United Kingdom: Cambridge University Press;364-410.

Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, Joyce PR, Karam EG, Lee CK, Lellouch J, Lepine JP, Newman SC, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen H, Yeh EK. (1996) Cross-national epidemiology of major depression and bipolar disorder. *Jama*, 276(4):293-299.

WHO. (1990) Composite International Diagnostic Interview (CIDI), Version 1.0. Geneva, Switzerland: World Health Organisation.

Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. (1991) Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *Br J Psychiatry*, 159:645-653, 658.

Wittchen HU. (1994) Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res*, 28(1):57-84.

Wittchen HU, Lachner G, Wunderlich U, Pfister H. (1998a) Test-retest reliability of the computerized DSM-IV version of the Munich-Composite International Diagnostic Interview (M-CIDI). *Soc Psychiatry Psychiatr Epidemiol*, 33(11):568-578.

Wittchen HU, Perkonigg A, Lachner G, Nelson CB. (1998b) Early developmental stages of psychopathology study (EDSP): objectives and design. *Eur Addict Res*, 4(1-2):18-27.

Wittchen HU, Mühlig S, Pezawas L. (2003) Natural course and burden of bipolar disorders. *Int J Neuropsychopharmacol*, 6(2):145-154.

Wittchen HU, Pfister H. (1997) DIA-X-Interviews: Manual für Screening-Verfahren und Interview; Interviewheft Längsschnittuntersuchung (DIA-X-Lifetime); Ergänzungsheft (DIA-X-Lifetime); Interviewheft Querschnittsuntersuchung (DIA-X-12 Monatsversion); Ergänzungsheft (DIA-X-12 Monatsversion); PC-Programm zur Durchführung der Interviews (Längs- und Querschnittsuntersuchung). Auswertungsprogramm. In: Zeitlinger Sa, ed. Frankfurt, Germany.

Chapter 3

Prediction of transition from common adolescent bipolar experiences to bipolar disorder

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ABSTRACT

Background. Although (hypo)manic symptoms are common in adolescence, transition to adult bipolar disorder is infrequent.
Aims. To examine whether the risk of transition to bipolar disorder is conditional on the extent of persistence of subthreshold affective phenotypes
Method. In an 8-year prospective community cohort study of 3021 adolescents and young adults, the association between persistence of affective symptoms over the first 3 years and the 8-year clinical outcomes of (i) incident DSM-IV (hypo)manic episodes and (ii) incident use of mental health care was assessed.
Results. Transition to clinical outcome was associated with prior persistence of symptoms in a dose-dependent manner. Around 30-43% of clinical outcomes could be traced to prior persistence of a combination of (hypo)manic and depressive symptoms.
Conclusions. In a substantial proportion of cases, onset of clinical bipolar disorder may be seen as the poor outcome of a developmentally common and usually transitory non-clinical bipolar phenotype.

Declaration of interest
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INTRODUCTION

Although categorical ordering is clinically useful, the type of distribution expected for mental disorders of multifactorial interactive aetiologies is continuous (Johns and van Os, 2001). Accordingly, most mental disorders have been shown to exist along a spectrum including subthreshold expressions as shown for, for example, depression (Anderson et al., 1993) and psychosis (Johns and van Os, 2001). Bipolar disorder similarly may be best described as part of a continuum (Akiskal et al., 2000; Birmaher et al., 2006). Recent research in adolescents and young adults has indicated that subthreshold phenotypes consisting of (hypo)manic symptoms are a common phenomenon in the general population, with more than a fourth of the population experiencing 4 or more (hypo)manic symptoms at some point in time before the age of 28 years (Tijssen et al., submitted). (Hypo)manic symptoms that are not meeting the criteria for disorder may nevertheless have some clinical relevance. First, (hypo)manic symptoms may be associated with significant disability and maladjustment, although less severe than the impairments seen in clinical disorders (Judd and Akiskal, 2003). Second, the subthreshold phenotype predicts transition to bipolar disorder (Akiskal et al., 2000; Birmaher et al., 2006), as prospective studies have demonstrated a dose-response relationship between the number of (hypo)manic symptoms and likelihood of later transition to DSM-IV bipolar disorder (Regeer et al., 2006). Finally, there is evidence of familial co-aggregation of bipolar subthreshold and clinical phenotypes (Hantouche and Akiskal, 2006).

Although it has been established that the common developmental expression of (hypo)manic symptoms predicts adult onset bipolar disorder (Egeland et al., 2000), much less is known about what characteristics determine poor outcome in only a small minority of all those with (hypo)manic symptoms (Lewinsohn et al., 2000). One of the missing pieces of information regarding the prediction-onset cycle in bipolar disorder is that due to the lack of prospective-longitudinal data, little is known about the dynamics of the course of subthreshold phenotypes in relation to later onset of disorder. Recent work in *psychosis* has suggested that course characteristics of the subthreshold phenotype are crucial in terms of prediction to clinical disorder (Dominguez et al., submitted), in that it was shown that subthreshold phenotypes that tended to persist at the subclinical level over longer periods of time (i.e. years) carried the greatest risk for transition in a dose-response fashion. It has recently been argued that the onset of

psychotic disorders can be traced to gene-environment interactions that cause normally transient psychopathological experiences in adolescence to first persist and subsequently give rise to clinical disorder (Dominguez et al., submitted). In the current paper, therefore, the hypothesis was tested that differential course of *(hypo)manic* symptoms in adolescence would be associated with differential risk for transition to full-blown bipolar disorder, greater levels of persistence over time predicting greater likelihood of transition (Angst et al., 2005). Secondly, as bipolar disorder is often preceded by depressive symptoms, it was hypothesized that the course and level of persistence of *depressive* symptoms would be equally relevant in predicting transition. Both hypotheses were tested in a large representative cohort of adolescents followed over a period of up to 10 years. Given previous evidence of the effect of number of symptoms (symptom loading) on risk of transition (Regeer et al., 2006), the effect of persistence of (hypo)manic and depressive symptoms was analysed in relation to symptom loading as well.

PARTICIPANTS AND METHODS

Sample

This study is part of the Early Developmental Stages of Psychopathology study (EDSP), a prospective-longitudinal cohort community study. Detailed information about the design, sample, instruments, procedures and statistical methods of the EDSP is presented elsewhere (Lieb et al., 2000; Wittchen et al., 1998b). Data were collected in a random representative population sample of adolescents and young adults living in the Munich area (Germany), aged 14-24 years at baseline. The study sample was randomly drawn from the 1994 government population registers and comprised residents in Munich and its surrounding area.

Study design

The study consists of a baseline survey (T0, *n*=3021) and 3 follow-up investigations (T1, T2, T3), covering a time period of approximately 1.6 years (T0-T1, SD = 0.2), 3.4 years (T0-T2, SD = 0.3) and 8.3 years (T0-T3, range 7.4-10.6 years, SD = 0.7) respectively. Since the older cohort of adolescents, aged 18-24 years at baseline, was not interviewed at T1, the current results are based on the time periods T0-T2 and T2-T3. Response rates were 84% at T2 (*n*=2548) and 73% at T3 (*n*=2210). For the younger cohort (*n*=1228), the time periods T0-T1 and T1-T2 were aggregated to represent the interval T0-T2. For the current

report, appropriate risk sets were formed which were defined as the set of individuals at risk of developing, for the first time, the clinical outcome at T3. Risk sets consisted of all individuals who i) had post-baseline DIA-X/M-CIDI interviews with complete data at both T2 and T3 (2029 of 3021 participants) ii) had never been diagnosed before T3 with the clinical outcome as defined below (DSM (hypo)manic episodes and/or Mental Health Care Use respectively). Thus, for the analyses of transition to T3 DSM (hypo)manic episodes, all participants with a (hypo)manic episode at T0 and/or at T2 were excluded (n=127), yielding a risk set of 1920 (2029-127); for the analyses pertaining to the T3 outcome of Any Mental Health Care Use, all participants with Any Mental Health Care Use at T0 and/or T2 were excluded (n=381), yielding a risk set of 1648 (2029-381). After exclusion of both DSM (hypo)manic episodes prior to T3 and Any Mental Health Care Use prior to T3 (i.e. *any* clinically relevant outcome, n=464), a risk set of 1565 (2029-464) participants remained.

Instruments

Interviews were conducted using the Computer-Assisted Personal Interview (CAPI) version of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen and Pfister, 1997), an updated version of the World Health Organization's CIDI version 1.2 (WHO 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 DSM-IV. The interview additionally allows, by coverage of additional ICD-10 items, the computation of ICD-10 diagnoses, although the respective algorithms for ICD-10 were not used in the present paper. High interrater and test-retest reliability of the CIDI have been established (Wittchen et al., 1991; Wittchen et al., 1998a), as well as validity (Reed et al., 1998). DIA-X/M-CIDI test-retest reliability (kappa) was 0.68 (p<0.001) for DSM-IV major depressive disorder and 0.64 (p<0.001) for DSM-IV bipolar disorder. Since the assessment of severe mental disorders with CIDI interviews by lay interviewers may not be entirely reliable (Anthony et al., 1985), fully trained and experienced psychologists who were allowed to probe with 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.

Assessment of affective symptom groups

Affective symptoms were assessed at T0 and T2 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) 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. Depressive symptoms were only rated if present for at least two weeks; (hypo)manic 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 or core (hypo)manic symptoms was present. Only participants having core (hypo)manic symptoms that were either noticed by others or because of which participants experienced problems were included.
Guided by previous work (Krabbendam et al., 2004; Regeer et al., 2006), two sum scores of symptom ratings were formed: (i) a sum score of depressive symptoms with a minimum of 0, and a maximum score of 28 endorsements (ii) a sum score of (hypo)manic symptoms with a minimum of 0, and a maximum score of 11 endorsements. Subsequently, in both symptom groups, progressively stricter and overlapping subcategories of these sum scores, indicating the degree of symptom loading, were created (Krabbendam et al., 2004; Regeer et al., 2006) (0: no symptoms; 1: at least 2 symptoms; 2: at least 4 symptoms; 3: at least 6 symptoms).
Because of the known co-occurrence of (hypo)manic symptoms and depressive symptoms in bipolar disorder (Regeer et al., in press), a third symptom group of 'bipolar symptom sum score' with corresponding subcategories of symptom loading was formed. In this group, both the depressive symptom sum score as well as the (hypo)manic symptom sum score were taken into account by adding both scores together, but only if the participant suffered from at least one (hypo)manic symptom at any time point. Thus, a minimum of 0 and a maxi-

mum of 39 (28+11) endorsements was theoretically possible. Subcategories of symptom loading of the bipolar symptom sum score were similar to the (hypo)manic and depressive symptom sum score (i.e. ≥2, ≥4 and ≥6 bipolar symptoms).

Assessment of persistence

For each of the symptom groups, a persistence variable was created. "Persistence" was defined as the number of times at the T0 and T2 interviews that subjects scored positive on having depressive and/or manic symptoms, irrespective of which particular depressive and/or manic symptoms were present. The persistence variable thus had 3 levels: (0) level 0, no symptoms at T0 and T2; (1) level 1, occurrence of symptoms only once at T0 or T2; (2) level 2, occurrence of symptoms twice both at T0 and T2.

Assessment of clinical outcome

In order to predict transition to clinical disorder, two clinical outcomes were used in the analyses. The first was defined as suffering from either a DSM-IV manic or a DSM-IV hypomanic episode (hereafter: DSM (hypo)manic episode) and the second as need for mental health care due to affective symptoms (hereafter: Mental Health Care Use). Participants suffering from DSM (hypo)manic episodes were defined, irrespective of presence of depressive episodes, using the DIA-X/M-CIDI DSM-IV diagnostic algorithms (Pfister and Wittchen, 1995), as follows: (i) participants suffering from neither hypomanic nor manic episodes (ii) participants suffering from either hypomanic or manic episodes.
In order to assess need for Mental Health Care Use, data from two DIA-X/M-CIDI sections were used. First, participants were asked, in the course of the DIA-X/M-CIDI interview on (hypo)manic symptoms, whether they were ever treated in a hospital or spoke to a professional because of their (hypo)manic symptoms. Second, in another section of the DIA-X/M-CIDI interview, participants were shown a list of several types of outpatient, inpatient or day patient institutions for mental health problems, ranging from a general practitioner or a school psychologist to psychiatric sheltered housing, after which they were asked if they had ever sought help at any of these institutions because of any *mental health* problems. All participants who responded positively to one or both of these questions in the respective DIA-X/M-CIDI sections were considered to have the Mental Health Care Use outcome.

Statistical Analysis

The association (expressed as Odds Ratio, OR) between persistence as independent variable (0, 1, 2) and clinical outcome (DSM (hypo)manic episodes and Mental Health Care Use) as dependent variable (0, 1) was analysed for each symptom group ((hypo)manic, depressive and bipolar symptoms respectively) and each symptom loading (2, 4 and 6 symptoms respectively) using logistic regression in STATA, version 9.2 (Statacorp 2005). First, in order to test for a monotonic trend in the association between level of persistence and transition to the clinical outcome, an ordinal variable was created that represented the level of persistence of each symptom group (values ranging from 0-2 for level 0, level 1, and level 2 of persistence respectively). Second, in order to test for a monotonic trend in the association between number of symptoms and transition to the clinical outcome, an ordinal variable was created that represented the number of symptoms present in each symptom group (values ranging from 0-3 for 0, 2, 4 and 6 symptoms respectively). In order to assess whether any effect of persistence was independent of age, odds ratios for all phenotypes were adjusted for age.

RESULTS

Analyses regarding the development of DSM (hypo)manic episodes were conducted in a sample of 1902 adolescents. Sex distribution was approximately equal (52.3% males). Mean age at baseline was 18.3 years (SD 3.3; range 14-24 years). In this risk set, 1.1% (n=21) developed an incident DSM (hypo)manic episode at T3.

Analyses regarding Mental Health Care Use were conducted in a sample of 1648 adolescents. Sex distribution was approximately equal (53.9% males). Mean age at baseline was 18.2 years (SD 3.3; range 14-24 years) In this risk set, 10.4% (n=172) had incident Mental Health Care Use at T3.

Drop-out rates at T3 (after excluding all participants without complete data at both T2 and T3, yielding a dataset of 2029 participants) were almost equal for the different levels of persistence for i) (hypo)manic symptoms (18.8% persistence level 0 vs. 21.1% level 1 vs. 23.1% level 2), ii) depressive symptoms (19.1% level 0 vs. 19.2% level 1 vs. 22.2% level 2), and iii) bipolar symptoms (14.9% level 0, 22.6% level 1, 24.3% level 2).

Presence of (hypo)manic symptoms and transition to clinical outcome

More than a fourth (25.1%, n=392) of 1565 participants displayed (hypo)manic symptoms once at T0 or T2, while 2.6% (n=41) experienced symptoms twice (Table 3.1, third column). The number of affected subjects decreased with increasing level of symptom loading. Thus, while 404 participants (25.8%) experienced at least 2 (hypo)manic symptoms, only 258 participants (16.5%) experienced ≥4 (hypo)manic symptoms and 81 participants (5.2%) experienced ≥6 (hypo)manic symptoms (Table 3.2, third column).

Participants who *never* experienced 2 or more (hypo)manic symptoms (n=1160) had an 0.7% risk of developing DSM (hypo)manic episodes and a 9.4% risk for Mental Health Care Use in the final follow-up. With greater levels of persistence, the risk of developing DSM (hypo)manic episodes increased from 0.7% to 2.0%-3.2%, and the risk of Mental Health Care Use from 9.4% to 12.3%-14.1% (Table 3.1, columns 4 and 8). Similarly, with greater levels of symptom loading, the risk of developing DSM (hypo)manic episodes increased to 1.9%-3.3% and the risk of Mental Health Care Use to 11.5%-12.8% (Table 3.2, columns 4 and 8).

Within the different categories of symptom loading (Table 3.2, columns 5 and 9), an association was found with persistence level for both transition to DSM (hypo)manic episodes (summary increase in risk per unit increase in persistence level ranging from 2.10-3.13 depending on category of symptom loading) and transition to Mental Health Care Use (summary increase in risk ranging from 1.22-1.36), which was significant for all comparisons related to DSM (hypo)manic episodes (Table 3.2, columns 5 and 9). Likewise, within each level of persistence, a dose-response relationship was seen between the level of symptom loading and the risk of transition (Table 3.1, columns 5 and 9).

Depicting level of persistence and level of symptom loading together (Fig. 3.1A and Fig. 3.1B) revealed that level of persistence became increasingly relevant as the number of symptoms persisting increased. For example, a level 2 persistence of ≥2 (hypo)manic symptoms was associated with a 4.14 times increased risk of developing DSM (hypo)manic episodes (95% CI: 0.89-19.24, p=0.070), while a level 2 persistence of ≥4 (hypo)manic symptoms was associated with a 12.52 times increased risk of developing DSM (hypo)manic episodes (95% CI: 2.63-59.61, p=0.001) (Fig. 3.1A).

Table 3.1. Odds Ratios Monotonic Trend for Impairment Associated with Symptom Loading* by Level of Persistence and Symptom Group

Symptom Group	Persistence Level †	Total % (No.) §	(Hypo)manic Episodes ‡,‖				Mental Health Care Use ¶			
			% (No.)	OR *	95% CI	*P*	% (No.)	OR *	95% CI	*P*
(Hypo)manic	1	25.1 (392)	2.0 (10)	1.62	1.13-2.33	0.009	12.3 (56)	1.06	0.91-1.25	0.448
	2	2.6 (41)	3.2 (2)	2.37	1.11-5.05	0.026	14.1 (9)	1.42	0.98-2.06	0.063
Depressive	1	45.1 (706)	0.9 (8)	1.00	0.72-1.40	0.996	11.9 (89)	1.20	1.06-1.35	0.003
	2	14.5 (227)	2.4 (8)	1.58	1.12-2.24	0.010	20.2 (53)	1.50	1.29-1.74	0.000
Bipolar	1	39.7 (621)	1.2 (9)	1.13	0.81-1.57	0.460	11.4 (76)	1.14	1.01-1.29	0.039
	2	16.6 (259)	2.4 (9)	1.71	1.22-2.39	0.002	17.0 (52)	1.42	1.22-1.64	0.000

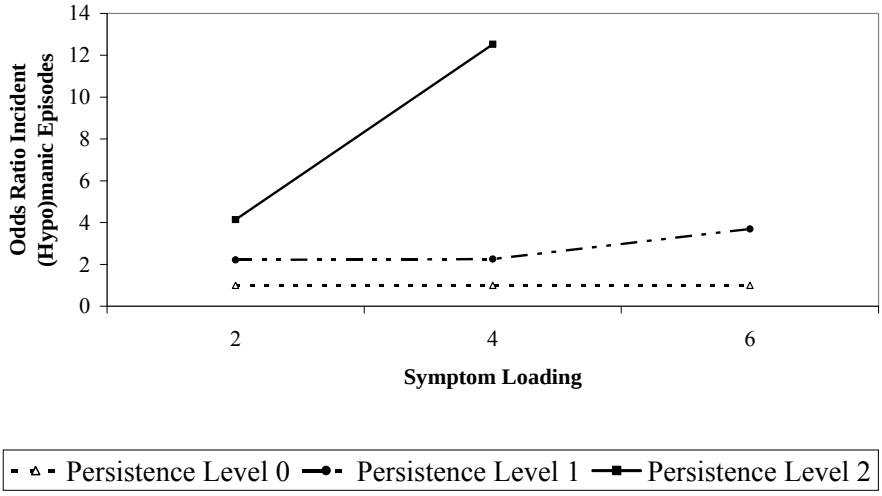
Abbreviations: OR, Odds Ratio; CI, Confidence Interval; * The ORs express summary increase in risk with 1 unit change in symptom loading (0: no symptoms; 1: at least 2 symptoms; 2: at least 4 symptoms; 3: at least 6 symptoms); † Level 1, symptoms at one time (T0 or T2); level 2, symptoms twice (T0 and T2); ‡ (Hypo)manic Episodes: either hypomanic or manic episodes; § Risk Set: All participants with data at T0, T2 and T3 and no kind of impairment at both T0 and T2 (n=1565); ‖ Risk Set: All participants with data at T0, T2 and T3 and no (hypo)manic episodes at both T0 and T2 (n=1902); Risk Set: All participants with data at T0, T2 and T3 and no Mental Health Care Use at both T0 and T2 (n=1648)

Table 3.2. Odds Ratios Monotonic Trend for Impairment Associated with Persistence* by Symptom Loading and Symptom Group

Symptom Group	Symptom Loading	Total % (No.) ‡	(Hypo)manic Episodes †,§				Mental Health Care Use ‖			
			% (No.)	OR *	95% CI	*P*	% (No.)	OR *	95% CI	*P*
(Hypo)manic	2	25.8 (404)	1.9 (10)	2.10	1.10-4.01	0.024	12.8 (61)	1.30	1.00-1.70	0.053
	4	16.5 (258)	2.3 (8)	2.92	1.44-5.93	0.003	11.5 (38)	1.22	0.88-1.69	0.224
	6	5.2 (81)	3.3 (4)	3.13	1.12-8.76	0.030	11.9 (15)	1.36	0.83-2.23	0.222
Depressive	2	51.5 (806)	1.2 (13)	1.58	0.90-2.76	0.108	13.1 (114)	1.77	1.44-2.18	0.000
	4	40.3 (630)	1.5 (13)	1.77	1.02-3.08	0.041	14.6 (101)	1.79	1.45-2.21	0.000
	6	27.7 (434)	1.9 (12)	2.29	1.31-4.01	0.004	16.3 (78)	1.90	1.51-2.39	0.000
Bipolar	2	46.6 (729)	1.6 (15)	2.03	1.19-3.46	0.009	12.8 (103)	1.59	1.30-1.93	0.000
	4	38.4 (601)	1.7 (14)	2.24	1.31-3.81	0.003	13.9 (94)	1.67	1.36-2.05	0.000
	6	27.8 (435)	2.3 (14)	2.85	1.65-4.91	0.000	14.8 (74)	1.76	1.40-2.22	0.000

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; * The ORs express the summary increase in risk with 1 unit change in level of persistence (variable has 3 levels: (0) level 0, no symptoms at T0 and T2; (1) level 1, occurrence of symptoms only once at T0 or T2; (2) level 2, occurrence of symptoms twice both at T0 and T2); † (Hypo)manic Episodes: either hypomanic or manic episodes; ‡ Risk Set: All participants with data at T0, T2 and T3 and no kind of impairment at both T0 and T2 (n=1565); § Risk Set: All participants with data at T0, T2 and T3 and no (hypo)manic episodes at both T0 and T2 (n=1902); ‖ Risk Set: All participants with data at T0, T2 and T3 and no Mental Health Care Use at both T0 and T2 (n=1648)

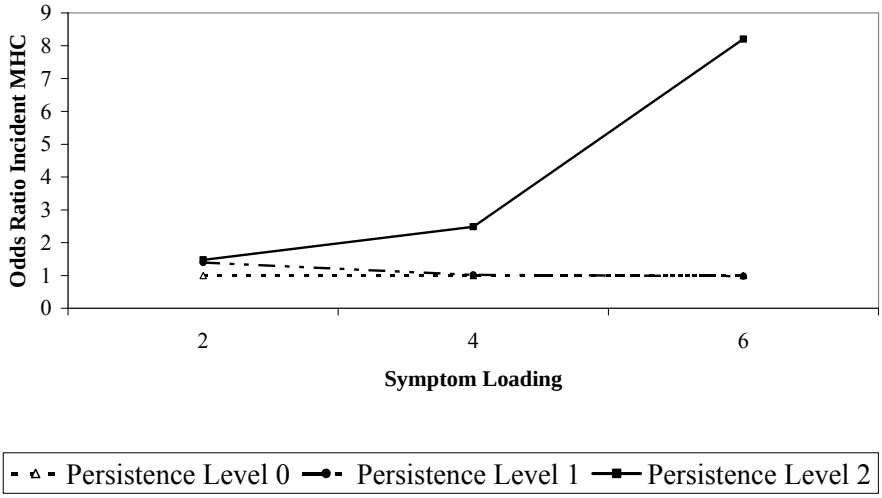
Fig. 3.1A. Risk of Incident (Hypo)manic Episodes* following Persistence† of (Hypo)manic Symptoms (odds ratios in figure quantified in table below figure)‡§



Persistence Level	Symptom Loading		
	2	4	6
	OR (95% CI)		
0	1.00	1.00	1.00
1	2.22 (0.89-5.55)	2.26 (0.85-5.99)	3.70 (1.22-11.19)
2	4.14 (0.89-19.24)	12.52 (2.63-59.61)	--

* (Hypo)manic episodes: either hypomanic or manic episodes; † Persistence: Level 0, symptoms not present at T0 or T2; Level 1, symptoms at one time (T0 or T2); level 2, symptoms twice (T0 and T2); ‡ Reference category: level of persistence = 0; § Results adjusted for age; ‖ Results not applicable if level of persistence=2 and no. of (hypo)manic symptoms=≥6 as all participants already became impaired *before* T3.

Fig. 3.1B. Risk of Incident Mental Health Care Use (MHCU) following Persistence* of (Hypo)manic Symptoms (odds ratios in figure quantified in table below figure)† ‡



Persistence Level	Symptom Loading		
	2	4	6
	OR (95% CI)		
0	1.00	1.00	1.00
1	1.39 (0.98-1.98)	1.01 (0.67-1.53)	0.98 (0.53-1.83)
2	1.47 (0.71-3.07)	2.49 (1.05-5.89)	8.21 (1.64-41.14)

* Persistence: Level 0, symptoms not present at T0 or T2; Level 1, symptoms at one time (T0 or ;); level 2, symptoms twice (T0 and T2); Reference category: level of persistence = 0; ‡ Results adjusted for age.

Presence of depressive symptoms and transition to clinical outcome

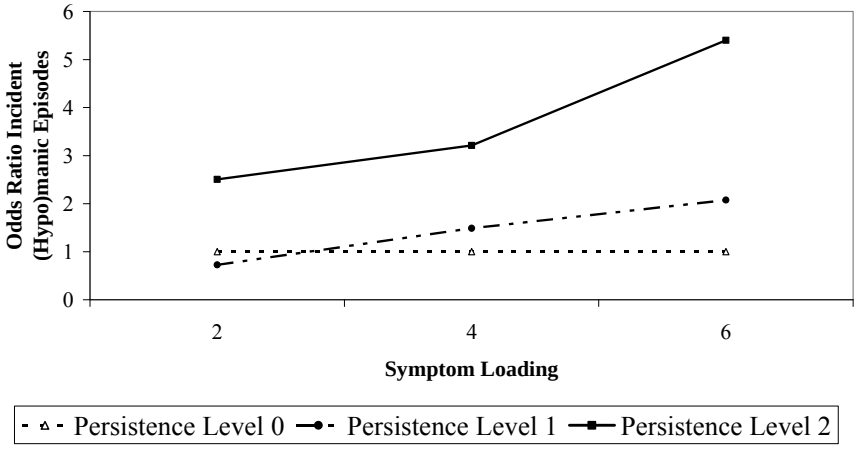
Nearly half (45.1%, n=706) of 1565 participants displayed depressive symptoms once at T0 or T2, while slightly less than 15 percent (14.5%, n=227) experienced symptoms twice (Table 3.1, column 3). The number of affected subjects decreased with increasing level of symptom loading. Thus, while 806 participants (51.5%) experienced at least 2 depressive symptoms, 630 participants (40.3%) experienced ≥4 depressive symptoms and 434 participants (27.7%) experienced ≥6 depressive symptoms (Table 3.2, column 3).

Participants who *never* experienced 2 or more depressive symptoms (n=759) had an 0.9% risk of developing DSM (hypo)manic episodes and a 7.6% risk for Mental Health Care Use.

The risk of developing DSM (hypo)manic episodes was similar for persistence level zero and one (0.9%), but increased to 2.4% for persistence level two, while the risk of Mental Health Care Use increased with increasing persistence level from 7.6% to 11.9-20.2% (Table 3.1, columns 4 and 8). Similarly, with increasing level of symptom loading, the risk of developing DSM (hypo)manic episodes increased to 1.2%-1.9% and the risk of Mental Health Care Use to 13.1%-16.3% (Table 3.2, columns 4 and 8). Within the different categories of symptom loading (Table 3.2, columns 5 and 9), an association was found with persistence level for both transition to DSM (hypo)manic episodes (summary increase in risk per unit increase in persistence level ranging from 1.58-2.29 depending on symptom category) and transition to Mental Health Care Use (summary increase in risk ranging from 1.77-1.90), which was significant for all but one comparison (Table 3.2, columns 5 and 9). Similarly, within each level of persistence, a dose-response relationship was seen between the level of symptom loading and the risk of transition (Table 3.1, columns 5 and 9).

Depicting level of persistence and level of symptom loading together (Figs 3.2A and 3.2B) revealed that level of persistence became increasingly relevant as the number of symptoms persisting increased, but only for the outcome of DSM (hypo)manic episodes (Fig. 3.2A) and not for the Mental Health Care Use outcome (Fig. 3.2B). For example, a level 2 persistence of depressive symptoms was associated with a 2.51 times increased risk of developing DSM (hypo)manic episodes for ≥2 depressive symptoms (95% CI: 0.93-6.75, p=0.069), a 3.21 times increased risk for ≥4 depressive symptoms (95% CI: 1.10-9.37, p=0.033), and a 5.40 times increased risk for ≥6 depressive symptoms (95% CI: 1.77-16.44, p=0.003) (Fig. 3.2A).

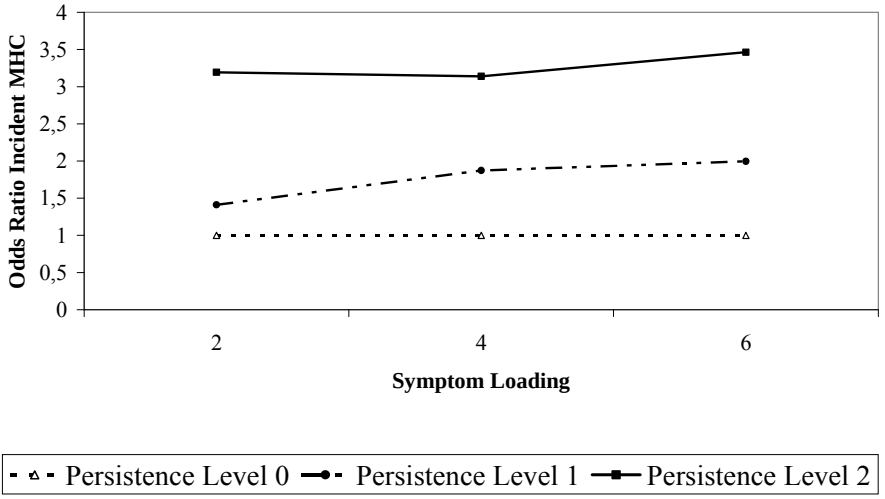
Fig. 3.2A. Risk of Incident (Hypo)manic Episodes* following Persistence† of Depressive Symptoms (odds ratios in figure quantified in table below figure)‡§



Persistence Level	Symptom Loading		
	2	4	6
	OR (95% CI)		
0	1.00	1.00	1.00
1	0.73 (0.24-2.23)	1.49 (0.54-4.13)	2.07 (0.77-5.61)
2	2.51 (0.93-6.75)	3.21 (1.10-9.37)	5.40 (1.77-16.44)

* (Hypo)manic episodes: either hypomanic or manic episodes; † Persistence: Level 0, symptoms not present at T0 or T2; Level 1, symptoms at one time (T0 or T2); level 2, symptoms twice (T0 and T2); ‡ Reference category: level of persistence = 0; § Results adjusted for age.

Fig. 3.2B. Risk of Incident Mental Health Care Use (MHCU) following Persistence* of Depressive Symptoms (odds ratios in figure quantified in table below figure)† ‡



Persistence Level	Symptom Loading		
	2	4	6
	OR (95% CI)		
0	1.00	1.00	1.00
1	1.41 (0.97-2.06)	1.87 (1.31-2.67)	1.99 (1.40-2.84)
2	3.19 (2.13-4.79)	3.14 (2.02-4.89)	3.46 (2.05-5.84)

* Persistence: Level 0, symptoms not present at T0 or T2; Level 1, symptoms at one time (T0 or T2); level 2, symptoms twice (T0 and T2); † Reference category: level of persistence = 0; ‡ Results adjusted for age.

Presence of bipolar symptoms and transition to clinical outcome

Almost fourty percent (39.7%, n=621) of 1565 participants displayed bipolar symptoms (for definition see above) once at T0 or T2, while 16.6% (n=259) experienced symptoms twice (Table 3.1, column 3). The number of affected subjects decreased with increasing level of symptom loading. Thus, while 729 participants (46.6%) experienced at least 2 bipolar symptoms, 601 participants (38.4%) experienced ≥4 bipolar symptoms and 435 participants (27.8%) experienced ≥6 bipolar symptoms (Table 3.2, column 3).

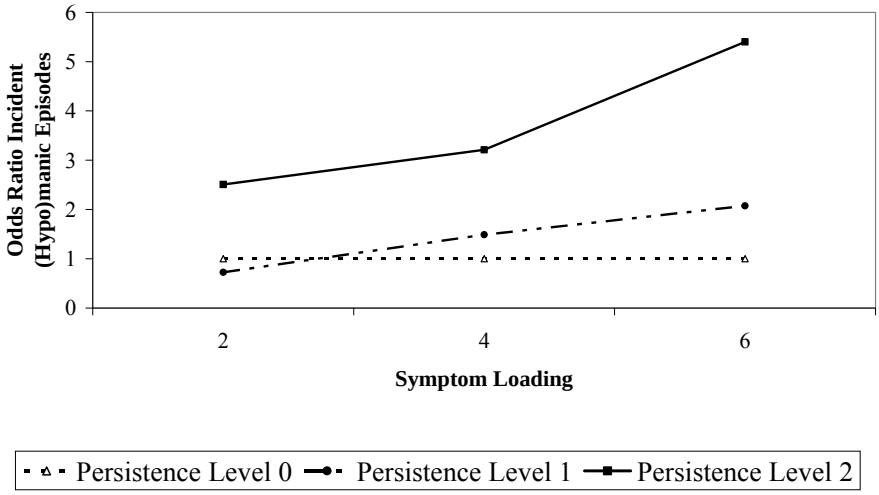
Participants who *never* experienced 2 or more bipolar symptoms (n=836) had an 0.6% risk of developing DSM (hypo)manic episodes and an 8.3% risk for Mental Health Care Use.
With increasing levels of persistence, the risk of developing DSM (hypo)manic episodes increased from 0.6% to 1.2%-2.4%, and the risk of Mental Health Care Use increased from 8.3% to 11.4%-17.0% (Table 3.1, columns 4 and 8). Similarly, with increasing level of symptom loading, the risk of developing DSM (hypo)manic episodes increased to 1.6%-2.3% and the risk of Mental Health Care Use to 12.8%-14.8% (Table 3.2, columns 4 and 8). Again, within the different categories of symptom loading, an association was found with persistence level for both transition to DSM (hypo)manic episodes (summary increase in risk per unit increase in persistence level ranging from 2.03-2.85 depending on symptom category) and transition to Mental Health Care Use (summary increase in risk ranging from 1.59-1.76), which was significant for all comparisons (Table 3.2, columns 5 and 9). Likewise, within each level of persistence, a dose-response relationship was seen between the level of symptom loading and the risk of transition (Table 3.1, columns 5 and 9).

Depicting level of persistence and symptom loading together (Fig. 3.3A and Fig. 3.3B) revealed that level of persistence became increasingly relevant as the number of symptoms persisting increased. For example, a level 2 persistence of bipolar symptoms was associated with a 4.04 times increased risk of developing DSM (hypo)manic episodes for ≥2 bipolar symptoms (95% CI: 1.39-11.72, p=0.010), a 4.94 times increased risk for ≥4 bipolar symptoms (95% CI: 1.75-13.97, p=0.003), and an 8.03 times increased risk for ≥6 bipolar symptoms (95% CI: 2.61-24.75, p=0.000) (Fig. 3.3A).

Proportion of clinical outcome with prior affective symptoms
Of the participants who developed DSM (hypo)manic episodes at T3 (n=21), 47.6% had experienced 2 or more (hypo)manic symptoms prior to T2, of which 9.5% more than once. This compares to 61.9% and 38.1% of those who had experienced 2 or more depressive symptoms at least once or twice respectively and 71.4% and 42.9% of those who had experienced 2 or more bipolar symptoms at least once or twice respectively.
Of the participants who developed a need for Mental Health Care Use (n=172), 35.5% had experienced 2 or more (hypo)manic symptoms, of which 5.2% more than once. This compares to 66.3% and 30.8% of those who had experi-

enced 2 or more depressive symptoms at least once or twice respectively and 59.9% and 30.2% of those who had experienced 2 or more bipolar symptoms at least once or twice respectively.

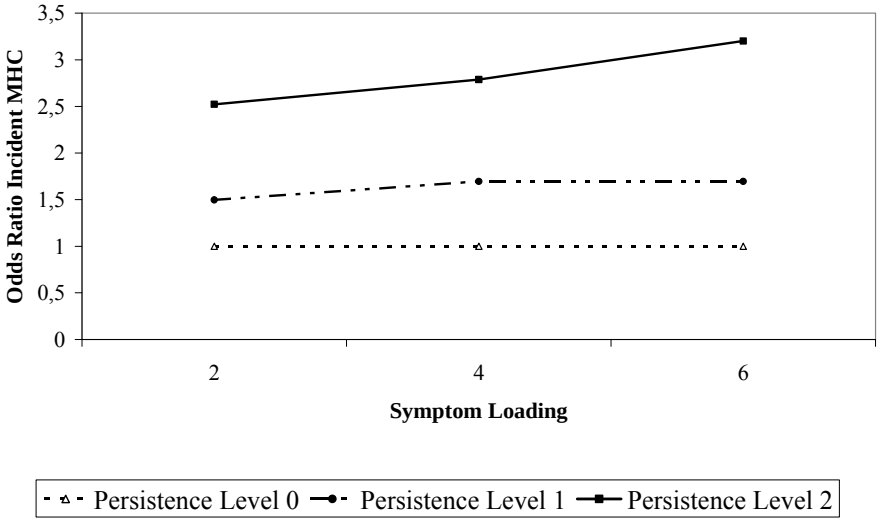
Fig. 3.3A. Risk of Incident (Hypo)manic Episodes* following Persistence† of Depressive Symptoms (odds ratios in figure quantified in table below figure)‡§



Persistence Level	Symptom Loading		
	2	4	6
	OR (95% CI)		
0	1.00	1.00	1.00
1	1.79 (0.55-5.86)	1.86 (0.60-5.70)	3.44 (1.22-9.68)
2	4.04 (1.39-11.72)	4.94 (1.75-13.97)	8.03 (2.61-24.75)

* (Hypo)manic episodes: either hypomanic or manic episodes; † Persistence: Level 0, symptoms not present at T0 or T2; Level 1, symptoms at one time (T0 or T2); level 2, symptoms twice (T0 and T2); ‡ Reference category: level of persistence = 0; § Results adjusted for age and number of bipolar symptoms at T3.

Fig. 3.3B. Risk of Incident Mental Health Care Use (MHCU) following Persistence* of Bipolar Symptoms (odds ratios in figure quantified in table below figure)† ‡



Persistence Level	Symptom Loading		
	2	4	6
	OR (95% CI)		
0	1.00	1.00	1.00
1	1.50 (1.00-2.24)	1.69 (1.16-2.47)	1.69 (1.17-2.45)
2	2.52 (1.70-3.74)	2.79 (1.83-4.24)	3.20 (1.95-5.25)

Persistence: Level 0, symptoms not present at T0 or T2; Level 1, symptoms at one time (T0 or T2); level 2, symptoms twice (T0 and T2); † Reference category: level of persistence = 0; ‡ Results adjusted for age.

DISCUSSION

The risk of transition to bipolar phenotype/health care use associated with persistence of affective symptoms was greatest if both persistence level and symptom loading were high. Thus, depending on persistence level and symptom loading category, the risk of transition to DSM (hypo)manic episodes varied between 1.62 to 12.52 for (hypo)manic symptoms, between 0.73 to 5.40 for depressive symptoms, and between 1.13 to 8.03 for the combination of (hypo)manic and depressive symptoms ('bipolar symptoms'). Similarly, the risk of transition to Mental Health Care Use varied between 0.98-8.21 for (hypo)manic symptoms, between 1.20-3.46 for depressive symptoms, and be-

tween 1.14-3.20 for bipolar symptoms. Transition of both (hypo)manic and/or depressive symptoms to a clinically relevant outcome of bipolar disorder was dependent on the level of persistence of symptoms in a dose-response fashion. The effect of persistence (i.e. the difference in risk between symptoms once or symptoms twice present over time) on transition was even greater than the effect of symptoms themselves (i.e. the difference between no symptoms and symptoms once) for both (hypo)manic and/or depressive symptoms. This suggests that particularly *persistence* of symptoms, relative to having symptoms *per se*, is predictive for transition to clinically relevant outcomes. Second, the dose-response association between persistence and clinical outcomes became stronger as the number of symptoms persisting increased. Thus, not simply the number of symptoms, but -more importantly- the number of symptoms persisting may predict transition to clinically relevant outcomes. (Hypo)manic symptoms displayed the highest predictive values, albeit with the lowest attributable risk fraction of 5-10%, whereas bipolar symptoms displayed the lowest predictive value, but the highest attributable risk fraction of 30-43%.

Theoretical implications

Many adolescents experience (hypo)manic symptoms (Tijssen et al., submitted) and the current results confirm the hypothesis that having (hypo)manic symptoms is a relatively frequently occurring phenomenon in adolescence, most of which will disappear over time (Lewinsohn et al., 2000). However, the results also demonstrate that in some adolescents, (hypo)manic symptoms become persistent, representing a risk state which may progress to full-blown, clinically relevant bipolar disorder. The results of this study are thus in accordance with similar findings in people with depressive symptoms (Garrison et al., 1989) and psychotic symptoms (Cougnard et al., 2007; Dominguez et al., submitted). Moreover, results concur with longitudinal evidence relating to the development of bipolar disorder (Kaymaz et al., 2007; Regeer et al., 2006). Regeer and colleagues (2006) reported a dose-response relationship between the number of (hypo)manic symptoms and transition to bipolar disorder whereas Kaymaz and colleagues (2007) concluded that subthreshold symptoms and comorbidity with psychotic symptoms at a subthreshold level are predictive of a future diagnosis of bipolar disorder.

The role of persistence of symptoms, in terms of clinical relevance, may be viewed in the light of the kindling-sensitization model put forward by Post (Post 1992). According to this model, neurotransmitter pathways are activated

by events and produce not only intermediate short-term effects, but also a series of events (i.e. intracellular changes at the level of gene transcription) that have long-lasting consequences for the organism. It is postulated that the type, magnitude and frequency of repetition of the event may be critical to these long-term effects. Thus, every time a person experiences an affective episode, the associated neurotransmitter and peptide alterations may leave behind memory traces that predispose to further episodes, a process referred to as 'sensitization' (Post 1992).

Therefore, a next logical step would be to examine what causes the persistence of bipolar symptoms in a small minority of adolescents, while most experience symptoms only temporarily. Furthermore, in view of the growing literature regarding the symptomatic overlap and possible cosegregation with ADHD and other externalizing childhood disorders (Faraone et al., 1997), it would be interesting to examine whether the persistence of (hypo)manic symptoms during adolescence could in some cases be traced back to a process that started already in childhood, taking on the form of, for example, ADHD during that developmental stage. However, given the fact that also persistence of much more common depressive symptoms increased the risk of transition to clinical disorder, childhood ADHD cannot account for all or the majority of the findings. In the literature, several explanations are given as to why (hypo)manic symptoms might develop during adolescence, with a focus on both neurodevelopmental changes (Leibenluft et al., 2003) as well as on environmental changes (Alloy et al., 2005) during this phase of life. According to an interactive developmental model, the course of developmental subclinical expression of psychopathology is affected by interactions between the individual and the environment; exposure to additional environmental risk factors may thus explain why a minority of individuals deviate from a trajectory of good outcome of transient subclinical expressions to progression to full-blown disorder (Cougnard et al., 2007). It is recognised that genetic factors play an important role in the development of bipolar disorder (Lapalme et al., 1997; Lieb et al., 2002). Other identified risk factors are the occurrence of life events (Johnson 2005), the use of substances like alcohol and cannabis (Henquet et al., 2006; Strakowski et al., 2000) and personality factors (Angst et al., 2003) as well as interactions between these risk factors (Alloy et al., 2005). Thus, it is attractive to speculate that some of the identified risk factors act by causing persistence of symptoms and subsequent transition from subthreshold expression to a clinical disorder, as this may create a possibility to intervene early. Given the fact that adolescence represents a pe-

riod in which the most critical stages of educational, occupational and social development are completed, consequences often lead to lifelong disability (Merikangas et al., 2007). Thus, the importance of early intervention is evident.

Limitations

Several limitations need to be considered when interpreting the results. First, although a prospective design was used, the study necessarily became partly retrospective by implementing questions regarding time intervals between waves. Therefore, the possibility of recall bias cannot be excluded although arguably this would likely contribute more to false negatives than to false positives as remote episodes of illness may often be forgotten, especially among subjects with milder or less recurrent illness or those who did not receive treatment (Simon and VonKorff, 1995). Second, although trained interviewers at the level of psychologist were used and care was taken to distinguish between (hypo)mania and feelings of euphoria, detecting (hypo)manic symptoms still remains difficult. False positives and false negatives are likely to have occurred, but given the design and interview procedures, their rate is also likely low. Third, the possibility exists that subjects that dropped out from follow-up had more psychopathology than the ones who remained for all longitudinal evaluations. However, this would probably not have influenced the results as drop-out rates were similar across the different levels of persistence. Furthermore, previous analyses showed that mood disorders were not affected by selective attrition (Wittchen et al 2005, available upon request). Fourth, exclusion of individuals with bipolar impairment at T0 and T2, necessary to ensure that associations between persistence and impairment were truly predictive, resulted in a small number of individuals with a T3 clinical outcome and a decrease in statistical power. Therefore, it is possible that due to loss of power the statistical significance of some associations was affected. The fact that effect sizes, albeit some non-significant, are in the expected direction and show dose-response relationships as expected, supports the validity of the results.

Fifth, in establishing persistence of symptoms, duration of symptoms was not taken into account. Thus, a participant who had symptoms shortly twice will have a higher level of persistence than a participant who had symptoms only once but over a longer period of time. Although this may have influenced the results, these two types of manifestation (tendency to recurrence and tendency to persist) are likely correlated and unlikely to denote entirely different groups. To the degree that the above depicted scenario may have been present though,

it would arguably only have served to decrease effect sizes whilst leaving the direction of effects intact, thus not affecting the validity of the current results.

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LITERATURE

Akiskal HS, Bourgeois ML, Angst J, Post R, Möller H, Hirschfeld R. (2000) Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J Affect Disord*, 59 Suppl 1:S5-S30.

Alloy LB, Abramson LY, Urosevic S, Walshaw PD, Nusslock R, Neeren AM. (2005) The psychosocial context of bipolar disorder: environmental, cognitive, and developmental risk factors. *Clin Psychol Rev*, 25(8):1043-1075.

Anderson J, Huppert F, Rose G. (1993) Normality, deviance and minor psychiatric morbidity in the community. A population-based approach to General Health Questionnaire data in the Health and Lifestyle Survey. *Psychol Med*, 23(2):475-485.

Angst J, Gamma A, Endrass J. (2003) Risk factors for the bipolar and depression spectra. *Acta Psychiatr Scand Suppl*, (418):15-19.

Angst J, Sellaro R, Stassen HH, Gamma A. (2005) Diagnostic conversion from depression to bipolar disorders: results of a long-term prospective study of hospital admissions. *J Affect Disord*, 84(2-3):149-157.

Anthony JC, Folstein M, Romanoski AJ, Von Korff MR, Nestadt GR, Chahal R, Merchant A, Brown CH, Shapiro S, Kramer M, et al. (1985) Comparison of the lay Diagnostic Interview Schedule and a standardized psychiatric diagnosis. Experience in eastern Baltimore. *Arch Gen Psychiatry*, 42(7):667-675.

Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Keller M. (2006) Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry*, 63(2):175-183.

Cougnard A, Marcelis M, Myin-Germeys I, De Graaf R, Vollebergh W, Krabbendam L, Lieb R, Wittchen HU, Henquet C, Spauwen J, Van Os J. (2007) Does normal developmental expression of psychosis combine with environmental risk to cause persistence of psychosis? A psychosis proneness-persistence model. *Psychol Med*, 37(4):513-527.

Dominguez M, Wichers M, Lieb R, Wittchen HU, Van Os J. (submitted) Evidence that onset of clinical phenotypes is the outcome of progressively more persistent subclinical psychotic experiences: an 8 year cohort study. *Am J Psychiatry*.

Egeland JA, Hostetter AM, Pauls DL, Sussex JN. (2000) Prodromal symptoms before onset of manic-depressive disorder suggested by first hospital admission histories. *J Am Acad Child Adolesc Psychiatry*, 39(10):1245-1252.

Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T. (1997) Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? *J Am Acad Child Adolesc Psychiatry*, 36(10):1378-1387; discussion 1387-1390.

Garrison CZ, Schluchter MD, Schoenbach VJ, Kaplan BK. (1989) Epidemiology of depressive symptoms in young adolescents. *J Am Acad Child Adolesc Psychiatry*, 28(3):343-351.

Hantouche EG, Akiskal HS. (2006) Toward a definition of a cyclothymic behavioral endophenotype: which traits tap the familial diathesis for bipolar II disorder? *J Affect Disord*, 96(3):233-237.

Henquet C, Krabbendam L, De Graaf R, Ten Have M, Van Os J. (2006) Cannabis use and expression of mania in the general population. *J Affect Disord*, 95(1-3):103-110.

Johns LC, van Os J. (2001) The continuity of psychotic experiences in the general population. *Clin Psychol Rev*, 21(8):1125-1141.

Johnson SL. (2005) Life events in bipolar disorder: towards more specific models. *Clin Psychol Rev*, 25(8):1008-1027.

Judd LL, Akiskal HS. (2003) The prevalence and disability of bipolar spectrum disorders in the US population: re-analysis of the ECA database taking into account subthreshold cases. *J Affect Disord*, 73(1-2):123-131.

Kaymaz N, Van Os J, De Graaf R, Ten Have M, Nolen W, Krabbendam L. (2007) The impact of subclinical psychosis on the transition from subclinicial mania to bipolar disorder. *J Affect Disord*, 98(1-2):55-64.

Krabbendam L, Myin-Germeys I, De Graaf R, Vollebergh W, Nolen WA, Iedema J, Van Os J. (2004) Dimensions of depression, mania and psychosis in the general population. *Psychol Med*, 34(7):1177-1186.

Lapalme M, Hodgins S, LaRoche C. (1997) Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. *Can J Psychiatry*, 42(6):623-631.

Leibenluft E, Charney DS, Pine DS. (2003) Researching the pathophysiology of pediatric bipolar disorder. *Biol Psychiatry*, 53(11):1009-1020.

Lewinsohn PM, Klein DN, Seeley JR. (2000) Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disord*, 2(3 Pt 2):281-293.

Lieb R, Isensee B, Von Sydow K, Wittchen HU. (2000) The Early Developmental Stages of Psychopathology Study (EDSP): a methodological update. *Eur Addict Res*, 6(4):170-182.

Lieb R, Isensee B, Hofler M, Pfister H, Wittchen HU. (2002) Parental major depression and the risk of depression and other mental disorders in offspring: a prospective-longitudinal community study. *Arch Gen Psychiatry*, 59(4):365-374.

Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC. (2007) Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*, 64(5):543-552.

Pfister H, Wittchen HU. (1995) M-CIDI Computerprogramm. München: Max-Planck-Institut für Psychiatrie, Klinisches Institut.

Post RM. (1992) Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry*, 149(8):999-1010.

Reed V, Gander F, Pfister H, Steiger A, Sonntag H, Trenkwalder C, Hundt W, Wittchen HU. (1998) To what degree does the Composite International Diagnostic Interview (CIDI) correctly identify DSM-IV disorders? Testing validity issues in a clinical sample. *Int J Methods Psychiatr Res*, 7:142-155.

Regeer E, Krabbendam L, De Graaf R, Ten Have M, Nolen W, Van Os J. (in press) Berkson's bias and the mood dimensions of bipolar disorder. *Int J Methods Psychiatr Res*.

Regeer EJ, Krabbendam L, De Graaf R, Ten Have M, Nolen WA, Van Os J. (2006) A prospective study of the transition rates of subthreshold (hypo)mania and depression in the general population. *Psychol Med*, 36(5):619-627.

Simon GE, VonKorff M. (1995) Recall of psychiatric history in cross-sectional surveys: implications for epidemiologic research. *Epidemiol Rev*, 17(1):221-227.

Statacorp. (2005) STATA Statistical Software. Release 9.2 ed. Texas: College Station.

Strakowski SM, DelBello MP, Fleck DE, Arndt S. (2000) The impact of substance abuse on the course of bipolar disorder. *Biol Psychiatry*, 48(6):477-485.

Tijssen MJA, Van Os J, Wittchen HU, Lieb R, Beesdo K, Mengelers R, Krabbendam L, Wichers MC. (submitted) Evidence that bipolar disorder is the poor outcome fraction of a common developmental phenotype: an 8-year cohort study in young people.

WHO. (1990) Composite International Diagnostic Interview (CIDI), Version 1.0. Geneva, Switzerland: World Health Organisation.

Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. (1991) Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *Br J Psychiatry*, 159:645-653, 658.

Wittchen HU, Lachner G, Wunderlich U, Pfister H. (1998a) Test-retest reliability of the computerized DSM-IV version of the Munich-Composite International Diagnostic Interview (M-CIDI). *Soc Psychiatry Psychiatr Epidemiol*, 33(11):568-578.

Wittchen HU, Perkonigg A, Lachner G, Nelson CB. (1998b) Early developmental stages of psychopathology study (EDSP): objectives and design. *Eur Addict Res*, 4(1-2):18-27.

Wittchen HU, Pfister H. (1997) DIA-X-Interviews: Manual für Screening-Verfahren und Interview; Interviewheft Längsschnittuntersuchung (DIA-X-Lifetime); Ergänzungsheft (DIA-X-Lifetime); Interviewheft Querschnittsuntersuchung (DIA-X-12 Monatsversion); Ergänzungsheft (DIA-X-12 Monatsversion); PC-Programm zur Durchführung der Interviews (Längs- und Querschnittsuntersuchung). Auswertungsprogramm. In: Zeitlinger Sa, ed. Frankfurt, Germany.

Chapter 4

Risk factors predicting onset and persistence of subthreshold expression of bipolar psychopathology among youth from the community

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ABSTRACT

Introduction. Previous work suggests that transitory subthreshold expressions of hypo(manic) psychopathology are common in the general population and that a subgroup with persistence of these symptoms over time is particularly at risk of making the transition to full-blown bipolar disorder. The current study examines factors that (i) increase the risk of experiencing these subthreshold expressions for the first time (onset) and (ii) increase the risk that transitory subthreshold expressions become persistent (persistence).

Methods. In a prospective cohort community study of 1395 adolescents aged 14-17 years at baseline, the association between risk factors (a positive family history of mood disorders, negative life events (early trauma/loss of parent), substance use (alcohol/cannabis), ADHD and temperamental/personality traits) and onset of (hypo)manic symptoms and 'bipolar symptoms' (depressive symptoms occurring in the context of (hypo)mania) over an 8-year follow-up period was determined. In order to study the effect of risk factors on persistence of mood symptoms, the interaction between baseline risk factors and baseline symptoms in predicting 8-year follow-up symptoms was tested.

Results. Both cannabis use and novelty seeking increased the risk of onset of (hypo)manic symptoms, while novelty seeking *decreased* the risk of persistence. Novelty seeking was similarly associated with onset of bipolar symptoms as were early trauma and harm avoidance, whereas reward dependence was associated with persistence of bipolar symptoms.

Conclusion. Mood abnormalities in the context of bipolar disorder may arise stepwise, with different risk factors operating in the phase of onset and the phase of persistence of subthreshold expressions before the development of full-blown illness. In addition, the early precursors of depression and mania dimensions in the context of bipolar disorder in part show differential associations with environmental exposures and personality traits, suggesting different underlying biological and psychological mechanisms for these dimensions.

INTRODUCTION

There is evidence that bipolar disorder, similar to depression and psychosis (Johns and van Os, 2001; Whittington and Huppert, 1996), is expressed in the general population as a continuum (Merikangas et al., 2007; Tijssen et al., submitted-a). The occurrence of full-blown bipolar disorder is frequently preceded by subthreshold expressions of psychopathology, with initially low levels of distress, that may be traced back to the period of early adolescence. However, experience of (hypo)manic symptoms in adolescents does not necessarily indicate future psychopathology (Lewinsohn et al., 2000; Tijssen et al., submitted-b), as in the majority of cases these symptoms run a benign course, disappearing by the time adulthood is reached, without being associated with threshold mood disorders. Nevertheless, a subgroup of adolescents with subthreshold expression of bipolar psychopathology does make the transition to bipolar disorder (Tijssen et al., submitted-b). There is evidence suggesting that an important factor differentiating between those who make the transition and those who do not may be the level of persistence of subthreshold expression of bipolar psychopathology over time: previous work has shown that those with persisting subthreshold expression had the greatest risk of transition in a dose-response fashion with level of persistence (Tijssen et al., submitted-b).

Little is known about the factors that influence persistence of subthreshold expression of bipolar psychopathology. Insights into the causes of persistence would facilitate the identification of subjects at risk in an early stage of the development of psychopathology and make early intervention possible. There are indications that the onset and course of bipolar disorder are affected by complex person-environment interactions (Johnson et al., 2000; Post et al., 2001). In the current study, therefore, it was hypothesised that the role of established risk factors could be productively examined in relation to the subthreshold expression of bipolar psychopathology, differentiating between risk factors for *onset* of subthreshold bipolar psychopathology and risk factors for *persistence* of subthreshold bipolar psychopathology (Fig. 4.1).

The choice of risk factors was guided by previous research. Thus, much research has emphasized the role of a positive family history of mood disorders in the development of bipolar illness (Lapalme et al., 1997; Lieb et al., 2002; Weissman et al., 2006). Recent work has also shown that attention-deficit/hyperactivity disorder (ADHD) in both children and/or their relatives increased the risk of a later diagnosis of bipolar disorder (Chang et al., 2000;

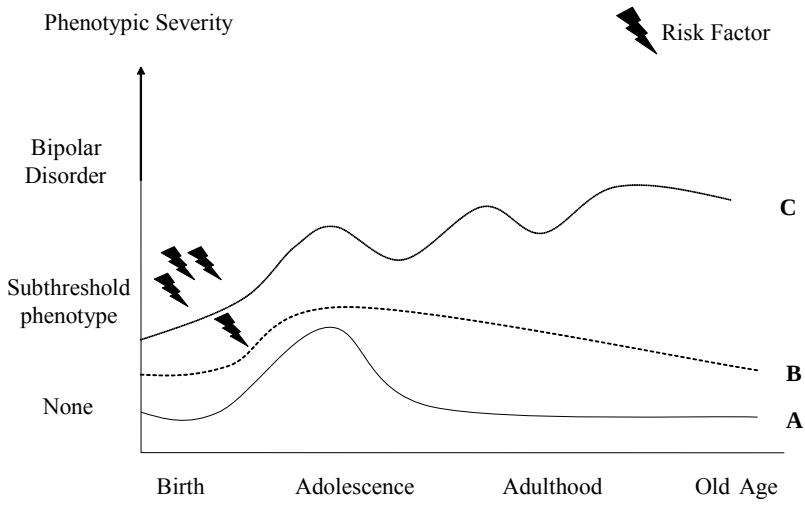

Fig. 4.1. Development of Bipolar Disorder: Abnormal Persistence of Developmental; Expression of Subthreshold Bipolar Experiences Expression of Subthreshold Bipolar Experiences. Person A has "normal" developmental expression of subthreshold bipolar experiences that are transient. Person B has similar expression, but longer persistence due to additional but mild environmental exposure. Person C has longer persistence due to severe repeated environmental exposures and eventual transition to clinical bipolar disorder.

Faraone et al., 1997; Henin et al., 2007). An environmental risk factor for mood disorder, discussed extensively in the literature, is the experience of traumatic or stressful life events (Alloy et al., 2005; Marchand et al., 2005). In particular negative life events such as 'early parental loss' (Agid et al., 1999; Tsuchiya et al., 2005) and 'severe childhood abuse' (Garno et al., 2005; Leverich et al., 2002) have been found to increase the risk for later bipolar disorder. There is also evidence that substance abuse is a risk factor for bipolar disorder. For example, Strakowski and DelBello (2000) concluded that substance abuse precedes the onset of mood disorder in approximately 60% of patients (Strakowski and DelBello, 2000) and Henquet et al. (2006) reported that cannabis use increases the risk of mania by nearly a factor 3 (Henquet et al., 2006). Finally, certain temperamental respectively personality traits likely represent risk factors for bipolar disorder. Young et al. (1995) suggest that a harm avoidant personal-

ity is related to mood disorders in general and that novelty seeking is associated with bipolar disorder (Young et al., 1995), while Osher et al. (1996) conclude levels of harm avoidance and reward dependence are elevated in euthymic bipolar patients compared to controls (Osher et al., 1996).
Given evidence that the "comorbid" dimensions of depression and mania in bipolar disorder may be in part spurious and related to the phenomenon of morbidity concentration associated with Berkson bias (Regeer et al., in press), analyses were conducted separately for any symptom of (hypo)mania and for symptoms of depression occurring in the context of mania (i.e. 'bipolar symptoms'). This allowed for the assessment of possible separate risk mechanisms associated with depression comorbidity.
Thus, risk factors were examined in relation to onset and persistence of subthreshold expression of both manic and bipolar psychopathology in a large representative cohort of adolescents followed over a period of up to 10 years.

PARTICIPANTS AND METHODS

Sample

This study is part of the Early Developmental Stages of Psychopathology study (EDSP), a prospective-longitudinal cohort study. Detailed information about design, sample, instruments, procedures, and statistical methods of the EDSP is presented elsewhere (Lieb et al., 2000; Wittchen et al., 1998b). Data were collected in a random representative population sample of adolescents and young adults living in the Munich area (Germany), aged 14-24 years at baseline. The study sample was randomly drawn from the 1994 government population registers and comprised residents in Munich and its surrounding area.

Study design

The present study is based on a subset of EDSP respondents, aged 14-17 years at the outset of study (T0, *n*=1395, response rate 75%). Participants completed a baseline survey (T0) and 3 follow-up investigations (T1, T2, T3), covering a time period of approximately 1.6 years (T0-T1, SD = 0.2), 3.4 years (T0-T2, SD = 0.3) and 8.3 years (T0-T3, range 7.4-10.6 years, SD = 0.7) respectively. Response rates (conditional on T0 completion) were respectively 88% at T1 (*n*=1228), 83% at T2 (*n*=1169) and 73% at T3 (*n*=1022).

Instruments

Interviews were conducted using the computerized version of the Munich-Composite International Diagnostic Interview (DIA-X/M-CIDI) (Wittchen and Pfister, 1997), an updated version of the World Health Organization's CIDI version 1.2 (WHO 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 DSM-IV. High interrater and test-retest reliability of the CIDI have been established (Wittchen et al., 1991; Wittchen 1994), as well as validity (Reed et al., 1998). Test-retest reliability (kappa) of the DIA-X/M-CIDI was 0.68 (p<0.001) for DSM-IV major depressive disorder and 0.64 (p<0.001) for DSM-IV bipolar disorder (Wittchen et al., 1998a). Since the assessment of mental disorders with CIDI interviews by lay interviewers may not be entirely reliable (Anthony et al., 1985), fully trained and experienced psychologists who were allowed to probe with follow-up questions conducted the interviews. At baseline, the lifetime version of the DIA-X/M-CIDI was used, for subsequent investigations the DIA-X/M-CIDI interval version.

Assessment of mood symptoms

Mood symptoms were assessed using 28 items 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 suicide ideation) and 11 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). Items were rated either 'present' or 'absent'. Depressive symptoms were only rated if any of the core items (depressed mood, loss of interest, loss of energy) were endorsed having been present for at least two weeks; (hypo)manic symptoms were only assessed if the core items of irritability and elevated mood were present for at least 4 successive days. In addition, upon completion of the symptom assessment, consistent with DSM-IV differential diagnostic rules, only those mood symptoms were counted towards subthreshold or threshold mood episodes, that were not always and entirely explained as a direct result of alcohol or drug use or somatic conditions. However, the substance-related and somatic related exclusion rules did not need to be employed except for a few subjects.

Furthermore, symptoms were only rated if at least one of the M-CIDI core depressive or core (hypo)manic symptoms was present. Only participants having core (hypo)manic symptoms that were either noticed by others or because of which participants experienced problems were included. Guided by previous work using the CIDI (Krabbendam et al., 2004; Regeer et al., 2006), two sum scores of symptom ratings were formed: (1) a sum score of depressive symptoms with a minimum of 0, and a maximum score of 28 positive ratings; (2) a sum score of (hypo)manic symptoms with a minimum of 0, and a maximum score of 11 positive ratings. A symptom group of 'bipolar symptom sum score' was formed. In this group, both the depressive symptom sum score as well as the (hypo)manic symptom sum score were taken into account by adding both scores together if the participant suffered from at least one core (hypo)manic symptom at any time point. Thus, a minimum of 0 and a maximum of 39 (28+11) positive ratings was theoretically possible. For reasons described earlier, symptom sum scores used for the current analyses were '(hypo)manic symptom sum score' and 'bipolar symptom sum score'. These scores contrast a phenotype of (hypo)manic symptoms and a phenotype of depressive symptoms arising in the context of (hypo)mania.
The number of 'baseline mood symptoms' of the different symptom groups (i.e. (hypo)manic and bipolar symptoms) was determined by calculating the symptom sum score of the respective symptom group at baseline (T0).
The number of 'follow-up mood symptoms' of the different symptom groups was defined for each participant as the highest symptom sum score of the respective symptom group at follow-up (either T1, T2 or T3).

Risk Factors

Family history of mood episodes
Family history of either (hypo)manic episodes (first or second degree relatives) or depressive episodes (first degree relatives) was assessed using several different methods.
First, at baseline, participants provided family history information on all relatives using an M-CIDI family history module. Family history items were designed using a modified version of the Family History Research Diagnostic Criteria (Merikangas et al., 1998) as a model. Second, parallel to T1, face-to-face interviews were carried out with participants' parents. In this interview, i) the M-CIDI EDSP family supplement was used to collect direct information

regarding family history of psychiatric disease of the interviewed parent (in which interviewers were blinded to the diagnostic findings of the respective offspring), and ii) a module was used that provided family history data of the non-interviewed parent as well as of other family members of the participant (Lachner and Wittchen, 1997). Direct information was mostly based on maternal responses (97.4%). Response rate of parents was 86% (n=1053). A positive response, from any of the three measurements concerning relatives, to a current or past (hypo)manic or depressive episode, was considered as a positive diagnosis in relatives, indicating a level of diagnostic certainty of "probable". Two variables of genetic risk were created: (1) a positive family history of (hypo)manic episodes in first- or second- degree relatives; (2) a positive family history of depressive episodes in first degree relatives. For both variables, a positive family history was rated either absent or present.

Negative life events

In order to assess exposure to lifetime, potentially traumatic events, participants were shown at baseline a list with several traumatic events, for example having a terrible war experience, having experienced physical threat, having been sexually abused as a child, having been raped, having experienced a natural catastrophe, having been in a serious accident, having been imprisoned, or witnessing any of these events. All participants who responded positively to this question were considered exposed to trauma.

In addition, the negative life event 'parental loss' was defined as either (0) no death of parents or (1) death of father and/or mother.

Substance use

Use of substances was assessed with the DIA-X/M-CIDI substance use module. Guided by previous work (Zimmermann et al., 2003), an alcohol use variable was created. Alcohol use status was defined dichotomously by combining four commonly used quantity-frequency categories and was defined as either: (0) 'No/seldom'/'occasional' use (abstinent or use <3 times a week in the peak period and not qualifying for higher use categories) or (1) 'Regular'/'hazardous' use (using at least 3 times a week in the period of peak lifetime use or an average use of more than 40g/day (men) or 20g/day (women) of ethanol in the period of peak lifetime use). Second, a cannabis use variable was created in which participants were only considered to have lifetime cannabis use in case

they reported at baseline that they had used cannabis five times or more, consistent with previous work (Henquet et al., 2006).

ADHD

The face-to-face interviews with participants' parents were used to collect information regarding ADHD. This childhood disorder was assessed with questions covering the criteria defined by the DSM-IV and was coded either absent or present.

Personality

The Tridimensional Personality Questionnaire (TPQ), a 100-item, self-report, true-false instrument, was used to assess personality at T3. The TPQ was developed by Cloninger (Cloninger 1987) and examines one of the most widely adopted models proposed for classifying temperament and personality (Miettunen et al., 2004). The TPQ has demonstrated good validity (Bagby et al., 1992) as well as good test-retest reliability (Cloninger 1988). The 100 items of the TPQ are grouped along 12 subscales that are used to scale participants on 3 higher-order personality dimensions: (i) Novelty Seeking (NS), the tendency to respond with intense excitement to novel stimuli or cues for potential rewards or potential relief of punishment; (ii) Harm Avoidance (HA), the tendency to respond intensively to signals of aversive stimuli; (iii) Reward Dependence (RD), the tendency to respond intensely to signals of rewards, especially social approval, sentiment and succour. For each dimension (NS or HA or RD), a continuous scale was created using Cloninger's scoring keys that represented the adherence of participants to the respective dimension. Subsequently, for the purpose of the analyses, a cut-off score for each dimension was *a priori* defined dichotomously as the group of participants with the highest 10% of scores in that dimension.

Statistical Analysis

The risk set was defined as all participants who (i) had post-baseline DIA-X/M-CIDI interviews at T1 and T2 and T3, (ii) had complete documentation of risk factors and (iii) had no '(hypo)manic episodes' (i.e. manic or hypomanic episodes) at baseline. Thus, the risk set consists of 705 participants.

Risk of development of symptoms

The association between risk factors and *onset* of (hypo)manic or bipolar symptoms respectively was calculated as the strength of the association between risk factors at baseline and follow-up (hypo)manic/bipolar symptoms, given absence of (hypo)manic/bipolar symptoms at baseline. Risk factors included: (i) family history of mood episodes ((hypo)manic episodes or depressive episodes respectively); (ii) exposure to trauma; (iii) loss of a parent; (iv) alcohol use; (v) cannabis use; (vi) ADHD; (vii) personality style (NS, HA or RD respectively). Analyses for (hypo)manic symptom score were carried out using ordered logistic regression (values ranging from 0-3 for 0, 1-2, 3-4 and ≥5 symptoms respectively; to account for the continuous yet extremely skewed distribution of (hypo)manic symptoms), and for bipolar symptom score using multiple linear regression in STATA (Statacorp 2005). Effect sizes are presented as odds ratios (ORs) and standardized beta coefficients (β) respectively. In order to assess the independence of risk factors, all risk factors were included in the same model. Estimates were adjusted for age at baseline (in years), sex (reference category = male sex) and socio-economic status ('SES'). The variable 'SES' was created consistent with previous work (Spauwen et al., 2006) by combining the items 'social status' and 'financial status' of the M-CIDI demographic section, and was defined as either 'low' (low social status/low financial status), 'middle' (low social status/high financial status or high social status/low financial status or any combination with either middle social status or middle financial status), or 'high' (high social status/high financial status).

Risk of persistence of symptoms

The risk of *persistence* of mood symptoms was defined as the strength of the association between baseline mood symptoms and follow-up mood symptoms.
In the case that this association is significantly different depending on the presence of a risk factor (i.e. there is a statistical interaction between baseline mood symptoms and this risk factor), the hypothesis that the risk factor affects the persistence of baseline mood symptoms is supported. Thus, the moderating effects of risk factors on the association between baseline mood symptoms and follow-up mood symptoms were tested in ordered logistic regression and multiple linear regression models of (hypo)manic and bipolar symptoms respectively. Interactions were tested for the same risk factors and taking into consideration the same confounders as described above for onset of symptoms. In order to

assess the independence of interaction effects, all interactions were included in the same model.

RESULTS

Subject characteristics

Analyses were conducted in a sample of 705 adolescents. Sex distribution was approximately equal (52.8% males). Mean age at baseline was 15.1 years (SD 1.1). Approximately 4.1% of participants had low SES, compared to 62.3% middle and 33.6% high SES.
Of all participants, 5.4% had a positive family history of (hypo)manic episodes and 39.0% of depressive episodes. More than a tenth (12.2%) had ever experienced some kind of potential traumatic event, and 3.1% had lost at least one parent. About 1.6% met criteria for regular alcohol use and 4.4% had lifetime cannabis use (5+ times). ADHD was present in 3.6% of participants (Table 4.1).

More than a fifth (23.0%, n=162) of 705 participants had ever experienced (hypo)manic symptoms at baseline. Thus, for the analyses of *onset* of (hypo)manic symptoms, the risk set consisted of 543 (705-162) participants. In this risk set, 79 participants (14.5%) developed (hypo)manic symptoms for the first time at follow-up. The mean number of (hypo)manic symptoms experienced by these participants was 3.9 (S.D. 1.9, range 1-10).
As regards persistence, 46 of 705 participants (6.5%) had (hypo)manic symptoms both at baseline and follow-up. The mean number of (hypo)manic symptoms experienced by these participants was 3.7 (S.D. 2.1, range 1-9). (Table 4.2).
More than fourty percent (44.4%, n=313) of participants experienced bipolar symptoms at baseline. Thus, for the analyses of *onset* of bipolar symptoms, the risk set consisted of 392 (705-313) participants. In this risk set, 239
participants (61.0%) developed bipolar symptoms for the first time at follow-up. The mean number of bipolar symptoms experienced by these participants was 5.4 (S.D. 3.6, range 1-20).
As regards persistence, 243 of 705 participants (34.5%) had bipolar symptoms both at baseline and follow-up. The mean number of bipolar symptoms experienced by these participants was 6.8 (S.D. 4.4, range 1-23). (Table 4.2).

Table 4.1. Number of Participants with Risk Factors at Baseline*

Risk Factor †	Number of cases (%)	Number of cases (N)
Family History (Hypo)mania ‡	5.4	38
Family History Depression §	39.0	275
Trauma	12.2	86
Loss of Parent	3.1	22
Alcohol Use ‖	1.6	11
Cannabis Use ¶	4.4	31
ADHD	3.6	25
Novelty Seeking #	11.4	80
Harm Avoidance #	7.1	50
Reward Dependence #	7.2	51

Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; * Risk Set: All participants with (1) post-baseline interviews at T0, T1, T2 and T3; (2) complete documentation of risk factors at T0; (3) no (hypo)manic episodes at T0 (n=705); † Presence of risk factors determined at baseline (T0) except for personality (T3); ‡ Defined as having one or more first or second degree relatives with (hypo)manic episodes; § Defined as having one or more first degree relatives with depressive episodes; ‖ Defined as 'regular use' (as using at least 3 times a week in the period of peak lifetime use) or 'hazardous use' (an average use of more than 40g/day (men) or 20g/day (women) of ethanol in the period of peak lifetime use); Defined as having used cannabis five times or more; # Defined as the group of participants with the highest 10% of scores in the personality dimension.

Table 4.2. Presence and Persistence of Mood Symptoms*

Symptom Group	Baseline Symptoms	Follow-up Symptoms †		
		No	Yes	Total
(Hypo)manic	No	65.8 (464)	11.2 (79)	77.0 (543)
	Yes	16.5 (116)	6.5 (46)	23.0 (162)
Bipolar ‡	No	21.7 (153)	33.9 (239)	55.6 (392)
	Yes	9.9 (70)	34.5 (243)	44.4 (313)

* Risk Set: All participants with (1) post-baseline interviews at T0, T1, T2 and T3; (2) complete documentation of risk factors at T0; (3) no (hypo)manic episodes at T0 (n=705); † Values are expressed as percentage (number) of cases; ‡ A combination of (hypo)manic and depressive symptoms.

Associations between Risk Factors and Onset/Persistence of (Hypo)manic Symptoms

Onset

Participants who had *no* risk factors at baseline (n=233 of 543) had an 11.2% risk of post-baseline onset of (hypo)manic symptoms. Depending on the risk factor present, this risk varied from 8.3%-35.3% (Table 4.3, column 2).

The risk factors cannabis use and novelty seeking were associated with post-baseline onset of (hypo)manic symptoms (OR 4.26; 95% CI 1.42-12.76, p=0.010 and OR 3.47; 95% CI 1.75-6.89, p=0.000 respectively) (Table 4.3).

Persistence

Participants who had *no* risk factors at baseline (n=271 of 705) had a 4.1% risk of persistence of (hypo)manic symptoms. Depending on the risk factor present, this risk varied from 0%-13.2% (Table 4.3, column 6).

None of the risk factors were associated positively with persistence of (hypo)manic symptoms. However, a *negative* association with persistence was observed for the personality trait novelty seeking (OR 0.64; 95% CI 0.48-0.85, p=0.002) (Table 4.3).

Table 4.3. Risk of (Hypo)manic Symptoms Associated with Selected Factors*

Risk Factor †	Risk (Hypo)manic Symptoms ‡							
	Onset §				Persistence			
	% (N)	OR	95% CI	*P*	% (N)	*OR*	95% CI	*P*
Fam. History (Hypo)mania ‖	9.1 (2)	0.61	0.13-2.81	0.523	13.2 (5)	1.17	0.83-1.67	0.372
Fam. History Depression	13.7 (25)	0.74	0.43-1.27	0.270	9.1 (25)	1.06	0.87-1.29	0.592
Trauma	20.0 (12)	1.48	0.71-3.11	0.295	10.5 (9)	0.94	0.75-1.19	0.620
Loss of Parent	11.1 (2)	0.91	0.19-4.31	0.908	4.6 (1)	0.68	0.31-1.48	0.330
Alcohol Use #	22.2 (2)	2.18	0.39-12.39	0.377	0 (0)	-	-	-
Cannabis Use **	35.3 (6)	4.26	1.42-12.76	0.010	12.9 (4)	0.86	0.62-1.20	0.384
ADHD	9.5 (2)	0.49	0.10-2.35	0.374	8.0 (2)	1.11	0.72-1.73	0.628
Personality: Novelty Seeking ††	26.8 (15)	3.47	1.75-6.89	0.000	6.3 (5)	0.64	0.48-0.85	0.002
Personality: Harm Avoidance ††	23.1 (9)	1.74	0.76-3.99	0.191	8.0 (4)	1.18	0.85-1.65	0.319
Personality: Reward Dependence ††	8.3 (3)	0.54	0.16-1.86	0.326	7.8 (4)	0.96	0.65-1.40	0.814

Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; OR, Odds Ratio; CI, Confidence Interval; * Risk Set: All participants with (1) post-baseline interviews at T0, T1, T2 and T3; (2) complete documentation of risk factors at T0; (3) no (hypo)manic episodes at T0 (n=705); † Presence of risk factors determined at baseline (T0) except for personality (T3); ‡ Results adjusted for age, sex, and socio-economic status; § Participants with (hypo)manic symptoms at baseline excluded (n=162), leaving 543 (705-162) participants for; analyses; Table 4.3. Risk of (Hypo)manic Symptoms Associated with Selected Factors* "cont."; ‖ Defined as having one or more first or second degree relatives with (hypo)manic episodes; Defined as having one or more first degree relatives with depressive episodes; # Defined as 'regular use' (as using at least 3 times a week in the period of peak lifetime use) or 'hazardous use' (an average use of more than 40g/day (men) or 20g/day (women) of ethanol in the period of peak lifetime use); ** Defined as having used cannabis five times or more; †† Defined as the group of participants with the highest 10% of scores in the personality dimension.

Associations between Risk Factors and Onset/Persistence of Bipolar Symptoms

Onset

Participants who had *no* risk factors at baseline (n=188 of 392) had a 56.4% risk of post-baseline onset of bipolar symptoms. Depending on the risk factor present, this risk varied from 42.9%-80.0% (Table 4.4, column 2).

The risk factor trauma was associated with post-baseline onset of bipolar symptoms (β=0.12, *p*=0.019), as were the personality traits Novelty Seeking (β=0.12, *p*=0.015) and Harm Avoidance (β=0.18, *p*=0.000) (Table 4.4).

Persistence

Participants who had *no* risk factors at baseline (n=271 of 705) had a 20.3% risk of persistence of bipolar symptoms. Depending on the risk factor present, this risk varied from 36.4%-67.7% (Table 4.4, column 5).

The personality trait Reward Dependence was associated with persistence of bipolar symptoms (β=0.11, *p*=0.031). None of the other investigated risk factors showed an association (Table 4.4).

Proportion of participants with symptoms with prior risk factors

Of the participants with first onset of (hypo)manic symptoms during follow-up (n=79), 67.1% had experienced any risk factor at baseline; for the participants with persistence of (hypo)manic symptoms from baseline through follow-up (n=46), this proportion was 76.1%.

Of the participants with first onset of bipolar symptoms during follow-up (n=239), 55.7% had experienced any risk factor at baseline; for the participants with persistence of bipolar symptoms from baseline through follow-up (n=243), this proportion was 77.4%.

Table 4.4. Risk of Bipolar Symptoms Associated with Selected Factors*

Risk Factor †	Risk Bipolar Symptoms ‡,§					
	Onset ‖			Persistence		
	% (N)	Beta	*P*	% (N)	Beta	*P*
Fam. History (Hypo)mania ¶	42.9 (6)	-0.030	0.560	55.3 (21)	0.039	0.482
Fam. History Depression #	60.3 (70)	-0.036	0.467	46.9 (129)	-0.006	0.927
Trauma	70.6 (24)	0.120	0.019	52.3 (45)	-0.064	0.226
Loss of Parent	66.7 (6)	0.077	0.119	36.4 (8)	-0.074	0.107
Alcohol Use **	80.0 (4)	0.018	0.721	54.6 (6)	-0.009	0.858
Cannabis Use ††	62.5 (5)	0.039	0.436	67.7 (21)	0.031	0.582
ADHD	53.9 (7)	0.009	0.854	44.0 (11)	0.085	0.062
Personality: Novelty Seeking ‡‡	69.4 (25)	0.123	0.015	41.3 (33)	0.017	0.733
Personality: Harm Avoidance ‡‡	80.0 (16)	0.181	0.000	58.0 (29)	-0.003	0.958
Personality: Reward Dependence ‡‡	61.5 (16)	-0.041	0.408	45.1 (23)	0.105	0.031

Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; * Risk Set: All participants with (1) post-baseline interviews at T0, T1, T2 and T3; (2) complete documentation of risk factors at T0; (3) no (hypo)manic episodes at T0 (n=705); † Presence of risk factors determined at baseline (T0) except for personality (T3); ‡ Results adjusted for age, sex, and socio-economic status; § A combination of (hypo)manic and depressive symptoms; ‖ Participants with bipolar symptoms at baseline excluded (n=313), leaving 392 (705-313) participants for analyses; Defined as having one or more first or second degree relatives with (hypo)manic episodes; # Defined as having one or more first degree relatives with depressive episodes; ** Defined as 'regular use' (as using at least 3 times a week in the period of peak lifetime use) or 'hazardous use' (an average use of more than 40g/day (men) or 20g/day (women) of ethanol in the period of peak lifetime use); †† Defined as having used cannabis five times or more; ‡‡ Defined as the group of participants with the highest 10% of scores in the personality dimension.

DISCUSSION

Associations with risk factors for bipolar disorder were different depending on 1) the group of symptoms analysed (i.e. (hypo)manic symptoms or depressive symptoms in the context of (hypo)mania), and 2) the developmental phase analysed (i.e. onset of symptoms versus persistence of symptoms). More specifically, the results suggest cannabis use and novelty seeking are associated with the onset of (hypo)manic symptoms, while the onset of bipolar symptoms, or depressive symptoms occurring in the context of mania, was associated with trauma, novelty seeking and harm avoidance. Persistence of (hypo)manic symptoms was *negatively* associated with novelty seeking; persistence of bipolar symptoms was associated with reward dependence. The fact that novelty seeking was positively associated with onset of (hypo)mania and negatively associated with

its persistence strongly suggests a critical developmental window of risk consumption, so that those with higher levels of novelty that put them at risk for (hypo)mania have their risk consumed early in life, after which the remaining individuals with higher levels show a "survival" effect, yielding the observed negative association. These findings should be interpreted in the light of our previous finding that the risk for expression of bipolarity in the general population appears to be consumed almost entirely during the adolescent developmental period (Tijssen et al., submitted-a). The novelty seeking component of the TPQ may be sensitive to the early changes that precede and give rise to adolescent expression of (hypo)mania.

Mechanisms

(Hypo)manic dimension

The results agree with the hypothesis that the course of bipolar disorder is affected by interactions between the individual and the environment. Moreover, they provide clues regarding possible mechanisms involved in the development of the different psychopathological domains.

First, the fact that both cannabis use and novelty seeking were associated with the onset of (hypo)manic symptoms may point to an underlying pathway involving alterations in dopaminergic neurotransmission. Cannabis use is associated with symptoms of psychosis (Henquet et al., 2005) and mania (Henquet et al., 2006) and its psychotogenic effect is thought to be mediated in part by alterations in meso-limbic dopamine signalling (D'Souza et al., 2005; Linszen and Van Amelsvoort, 2007; Pisanu et al., 2006; Voruganti et al., 2001). Similarly, animal, pharmacological and genetic studies have implied dopaminergic mechanisms underlying variation in novelty seeking (Boileau et al., 2006; Cloninger et al., 1993; Laine et al., 2001; Leyton et al., 2002; Munafo et al., 2008). There are indications that the level of dopamine signalling is already physiologically increased during adolescence (Arnsten and Shansky, 2004; Chambers et al., 2003; Spear 2000), suggesting that the observed developmental time window of (hypo)mania expression in adolescence may be the result of developmental alterations in dopamine signalling interacting with alterations in dopamine neurotransmission associated with cannabis and temperament. This hypothesis would fit well with the observed high prevalence of (hypo)manic symptoms reported in adolescents that are transitory for the great majority of individuals. Thus, when the baseline level of dopamine signalling decreases after

adolescence, the threshold for experiencing (hypo)manic symptoms would become higher resulting in reduced expression (Fig 4.2.). There is evidence of underlying dopamine dysregulation in mania. Thus, several brain imaging studies report an association between dopamine activity and mania/euphoria (Anand et al., 2000; Drevets et al., 2001), and both Murray and colleagues (2004) and Ketter and coworkers (2004) summarise evidence indicating that pharmacological agents can induce/reduce mania by altering dopaminergic activity (Ketter et al., 2004; Murray et al., 2004).

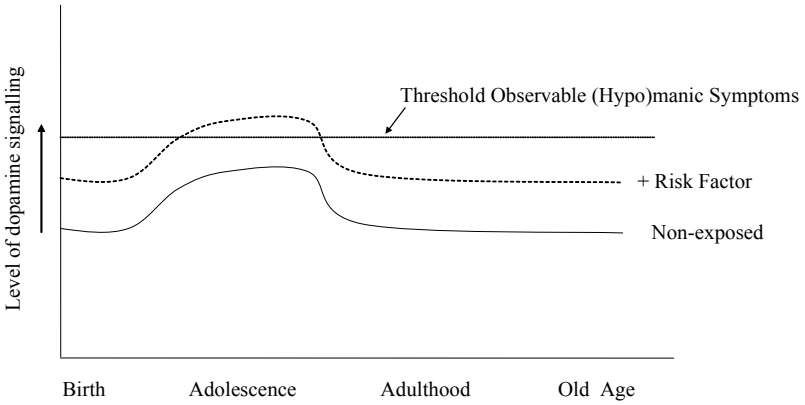

Fig. 4.2. Presence of (Hypo)manic Symptoms: Association with Level of Dopamine Signalling. During adolescence, a developmental alteration in dopamine signalling occurs, approaching the threshold for observable (hypo)manic symptoms for all adolescents. If during this developmental time window risk factors are present that affect dopaminergic neurotransmission, the threshold is exceeded and (hypo)manic symptoms may arise. After adolescence, the baseline level of dopamine signalling is reduced, resulting in decreased expression of (hypo)manic symptoms.

Bipolar dimension

In contrast, the association between trauma and harm avoidance on the one hand and onset of depressive symptoms in the context of (hypo)mania on the other as well as the association between reward dependence and persistence of these symptoms could point to an underlying mechanism involving the Hypothalamic-Pituitary-Adrenal axis (HPA-axis). The HPA-axis is part of the central stress response system and hyperactivation of this axis is associated with depressive disorder and anxiety disorder (Heim and Nemeroff, 1999; Mello et al., 2003). It is hypothesized that early life trauma can result in hyperactivation of the HPA-axis, and that exposure to persistent or repetitive stress may lead to persistent increases in stress hormones and eventually psychopathology (Heim

and Nemeroff, 1999; Mello et al., 2003). Harm avoidance and reward dependence may act as a mediator, influencing the likelihood of exposure to stressors or conferring sensitivity to stressors (Davidson 2000; Tyrka et al., 2006). Given the high prevalence of depressive symptoms in bipolar disorder, HPA-axis abnormalities have also been described in bipolar depression (Dinan 2001; Rybakowski and Twardowska, 1999; Watson et al., 2004). Indeed, the connection with bipolar disorder may be more prominent than the connection with unipolar depression (Rybakowski and Twardowska, 1999). Therefore, the association between trauma, harm avoidance and reward dependence on the one hand and depressive symptoms in the context of mania on the other may point to hyperactivation and subsequent sensitisation of the HPA-axis associated with childhood trauma (hyperactivation) and personality factors (hyperactivation, sensitisation) (Fig. 4.3).

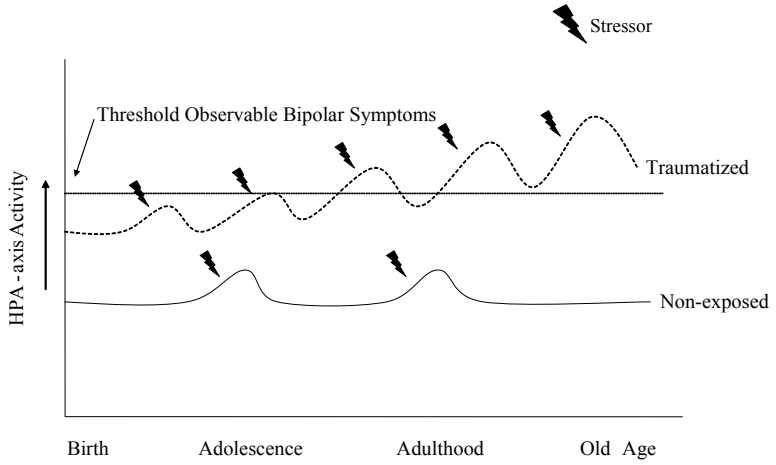

Fig. 4.3. Presence of Bipolar Symptoms: Association with HPA-axis activity. Physiologically, exposure to stressors results in transient increases in HPA-axis activity and feelings of distress. In traumatized individuals, HPA-axis hyperactivity may occur, resulting in more sensitive and intense reactions to stressors exceeding the threshold for observable bipolar symptoms. Persistent exposure to stressors (e.g. related to personality) may eventually result in persistent HPA-axis activity with persistence of bipolar symptoms.

Limitations

Several limitations need to be considered when interpreting the results. First, although a prospective design and analyses procedure was used, the study necessarily became partly retrospective by implementing questions regarding time

intervals between waves. Therefore, the possibility of recall bias cannot be excluded. Second, exclusion of individuals with (hypo)manic and bipolar symptoms at baseline, necessary to ensure that associations between risk factors and follow-up symptoms were truly predictive, resulted in a decrease of statistical power. Therefore, it is possible that due to loss of power the statistical significance of some associations was affected. Furthermore, this has likely resulted in lower associations between risk factors and the onset of symptoms, given the fact that some of the risk associated with the factors examined would already have been consumed at baseline. Third, findings regarding family history should be interpreted with caution since prevalence rates are high compared to other studies (Nelson et al., 1995). Fourth, in order to examine the effects of all relevant risk factors for bipolar disorder, multiple testing was necessary. This increased the possibility of type I errors. However, the fact that the pattern of associations was coherent in terms of underlying biological pathways supports the validity of the results.

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LITERATURE

Agid O, Shapira B, Zislin J, Ritsner M, Hanin B, Murad H, Troudart T, Bloch M, Heresco-Levy U, Lerer B. (1999) Environment and vulnerability to major psychiatric illness: a case control study of early parental loss in major depression, bipolar disorder and schizophrenia. *Mol Psychiatry*, 4(2):163-172.

Alloy LB, Abramson LY, Urosevic S, Walshaw PD, Nusslock R, Neeren AM. (2005) The psychosocial context of bipolar disorder: environmental, cognitive, and developmental risk factors. *Clin Psychol Rev*, 25(8):1043-1075.

Anand A, Verhoeff P, Seneca N, Zoghbi SS, Seibyl JP, Charney DS, Innis RB. (2000) Brain SPECT imaging of amphetamine-induced dopamine release in euthymic bipolar disorder patients. *Am J Psychiatry*, 157(7):1108-1114.

Anthony JC, Folstein M, Romanoski AJ, Von Korff MR, Nestadt GR, Chahal R, Merchant A, Brown CH, Shapiro S, Kramer M, et al. (1985) Comparison of the lay Diagnostic Interview Schedule and a standardized psychiatric diagnosis. Experience in eastern Baltimore. *Arch Gen Psychiatry*, 42(7):667-675.

Arnsten AF, Shansky RM. (2004) Adolescence: vulnerable period for stress-induced prefrontal cortical function? Introduction to part IV. *Ann N Y Acad Sci*, 1021:143-147.

Bagby RM, Parker JDA, Joffe R. (1992) Confirmatory factor analysis of the Tridimensional Personality Questionnaire. *Pers Individ Diff*, 3:1245-1246.

Boileau I, Dagher A, Leyton M, Gunn RN, Baker GB, Diksic M, Benkelfat C. (2006) Modeling sensitization to stimulants in humans: an [11C]raclopride/positron emission tomography study in healthy men. *Arch Gen Psychiatry*, 63(12):1386-1395.

Chambers RA, Taylor JR, Potenza MN. (2003) Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *Am J Psychiatry*, 160(6):1041-1052.

Chang KD, Steiner H, Ketter TA. (2000) Psychiatric phenomenology of child and adolescent bipolar offspring. *J Am Acad Child Adolesc Psychiatry*, 39(4):453-460.

Cloninger CR. (1987) A systematic method for clinical description and classification of personality variants. A proposal. *Arch Gen Psychiatry*, 44(6):573-588.

Cloninger CR. (1988) A unified biosocial theory of personality and its role in the development of anxiety states: a reply to commentaries. *Psychiatr Dev*, 6(2):83-120.

Cloninger CR, Svrakic DM, Przybeck TR. (1993) A psychobiological model of temperament and character. *Arch Gen Psychiatry*, 50(12):975-990.

D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, Gueorguieva R, Cooper TB, Krystal JH. (2005) Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry*, 57(6):594-608.

Davidson RJ. (2000) Affective style, psychopathology, and resilience: brain mechanisms and plasticity. *Am Psychol*, 55(11):1196-1214.

Dinan TG. (2001) Psychoneuroendocrinology of mood disorders. *Curr Opin Psychiatry*, 14:51-55.

Drevets WC, Gautier C, Price JC, Kupfer DJ, Kinahan PE, Grace AA, Price JL, Mathis CA. (2001) Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol Psychiatry*, 49(2):81-96.

Faraone SV, Biederman J, Mennin D, Wozniak J, Spencer T. (1997) Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? *J Am Acad Child Adolesc Psychiatry*, 36(10):1378-1387; discussion 1387-1390.

Garno JL, Goldberg JF, Ramirez PM, Ritzler BA. (2005) Impact of childhood abuse on the clinical course of bipolar disorder. *Br J Psychiatry*, 186:121-125.

Heim C, Nemeroff CB. (1999) The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biol Psychiatry*, 46(11):1509-1522.

Henin A, Biederman J, Mick E, Hirshfeld-Becker DR, Sachs GS, Wu Y, Yan L, Ogutha J, Nierenberg AA. (2007) Childhood antecedent disorders to bipolar disorder in adults: a controlled study. *J Affect Disord*, 99(1-3):51-57.

Henquet C, Murray R, Linszen D, van Os J. (2005) The environment and schizophrenia: the role of cannabis use. *Schizophr Bull*, 31(3):608-612.

Henquet C, Krabbendam L, De Graaf R, Ten Have M, Van Os J. (2006) Cannabis use and expression of mania in the general population. *J Affect Disord*, 95(1-3):103-110.

Johns LC, van Os J. (2001) The continuity of psychotic experiences in the general population. *Clin Psychol Rev*, 21(8):1125-1141.

Johnson L, Andersson-Lundman G, Åberg-Wistedt A, Mathé AA. (2000) Age of onset in affective disorder: its correlation with hereditary and psychosocial factors. *J Affect Disord*, 59(2):139-148.

Ketter TA, Wang PW, Becker OV, Nowakowska C, Yang Y. (2004) Psychotic bipolar disorders: dimensionally similar to or categorically different from schizophrenia? *J Psychiatr Res*, 38(1):47-61.

Krabbendam L, Myin-Germeys I, De Graaf R, Vollebergh W, Nolen WA, Iedema J, Van Os J. (2004) Dimensions of depression, mania and psychosis in the general population. *Psychol Med*, 34(7):1177-1186.

Lachner G, Wittchen HU. (1997) Münchener Composite International Diagnostic Interview: Familiengenetische Version (M-CIDI-FG). Munich, Germany: Max Planck Institut für Psychiatrie Eigendruck.

Laine TP, Ahonen A, Räsänen P, Tiihonen J. (2001) Dopamine transporter density and novelty seeking among alcoholics. *J Addict Dis*, 20(4):91-96.

Lapalme M, Hodgins S, LaRoche C. (1997) Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. *Can J Psychiatry*, 42(6):623-631.

Leverich GS, McElroy SL, Suppes T, Keck PE, Jr., Denicoff KD, Nolen WA, Altshuler LL, Rush AJ, Kupka R, Frye MA, Autio KA, Post RM. (2002) Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biol Psychiatry*, 51(4):288-297.

Lewinsohn PM, Klein DN, Seeley JR. (2000) Bipolar disorder during adolescence and young adulthood in a community sample. *Bipolar Disord*, 2(3 Pt 2):281-293.

Leyton M, Boileau I, Benkelfat C, Diksic M, Baker G, Dagher A. (2002) Amphetamine-induced increases in extracellular dopamine, drug wanting, and novelty seeking: a PET/[11C]raclopride study in healthy men. *Neuropsychopharmacology*, 27(6):1027-1035.

Lieb R, Isensee B, Von Sydow K, Wittchen HU. (2000) The Early Developmental Stages of Psychopathology Study (EDSP): a methodological update. *Eur Addict Res*, 6(4):170-182.

Lieb R, Isensee B, Hofler M, Pfister H, Wittchen HU. (2002) Parental major depression and the risk of depression and other mental disorders in offspring: a prospective-longitudinal community study. *Arch Gen Psychiatry*, 59(4):365-374.

Linszen D, Van Amelsvoort T. (2007) Cannabis and psychosis: an update on course and biological plausible mechanisms. *Curr Opin Psychiatry*, 20(2):116-120.

Marchand WR, Wirth L, Simon C. (2005) Adverse life events and pediatric bipolar disorder in a community mental health setting. *Community Ment Health J*, 41(1):67-75.

Mello AA, Mello MF, Carpenter LL, Price LH. (2003) Update on stress and depression: the role of the hypothalamic-pituitary-adrenal (HPA) axis. *Rev Bras Psiquiatr*, 25(4):231-238.

Merikangas KR, Stevens DE, Fenton B, Stolar M, O'Malley S, Woods SW, Risch N. (1998) Comorbidity and familial aggregation of alcoholism and anxiety disorders. *Psychol Med*, 28(4):773-788.

Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC. (2007) Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry*, 64(5):543-552.

Miettunen J, Kantojärvi L, Ekelund J, Veijola J, Karvonen JT, Peltonen L, Jarvelin MR, Freimer N, Lichtermann D, Joukamaa M. (2004) A large population cohort provides normative data for investigation of temperament. *Acta Psychiatr Scand*, 110(2):150-157.

Munafo MR, Yalcin B, Willis-Owen SA, Flint J. (2008) Association of the dopamine D4 receptor (DRD4) gene and approach-related personality traits: meta-analysis and new data. *Biol Psychiatry*, 63(2):197-206.

Murray RM, Sham P, Van Os J, Zanelli J, Cannon M, McDonald C. (2004) A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophr Res*, 71(2-3):405-416.

Nelson E, Rice J, Rochberg N, Endicott J, Coryell W, Akiskal HS. (1995) Affective illness in family members and matched controls. *Acta Psychiatr Scand*, 91(3):146-151.

Osher Y, Cloninger CR, Belmaker RH. (1996) TPQ in euthymic manic-depressive patients. *J Psychiatr Res*, 30(5):353-357.

Pisanu A, Acquas E, Fenu S, Di Chiara G. (2006) Modulation of Delta(9)-THC-induced increase of cortical and hippocampal acetylcholine release by micro opioid and D(1) dopamine receptors. *Neuropharmacology*, 50(6):661-670.

Post RM, Leverich GS, Xing G, Weiss RB. (2001) Developmental vulnerabilities to the onset and course of bipolar disorder. *Dev Psychopathol*, 13(3):581-598.

Reed V, Gander F, Pfister H, Steiger A, Sonntag H, Trenkwalder C, Hundt W, Wittchen HU. (1998) To what degree does the Composite International Diagnostic Interview (CIDI) correctly identify DSM-IV disorders? Testing validity issues in a clinical sample. *Int J Methods Psychiatr Res*, 7:142-155.

Regeer E, Krabbendam L, De Graaf R, Ten Have M, Nolen W, Van Os J. (in press) Berkson's bias and the mood dimensions of bipolar disorder. *Int J Methods Psychiatr Res*.

Regeer EJ, Krabbendam L, De Graaf R, Ten Have M, Nolen WA, Van Os J. (2006) A prospective study of the transition rates of subthreshold (hypo)mania and depression in the general population. *Psychol Med*, 36(5):619-627.

Rybakowski JK, Twardowska K. (1999) The dexamethasone/corticotropin-releasing hormone test in depression in bipolar and unipolar affective illness. *J Psychiatr Res*, 33(5):363-370.

Spauwen J, Krabbendam L, Lieb R, Wittchen HU, Van Os J. (2006) Impact of psychological trauma on the development of psychotic symptoms: relationship with psychosis proneness. *Br J Psychiatry*, 188:527-533.

Spear LP. (2000) The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev*, 24(4):417-463.

Statacorp. (2005) STATA Statistical Software. Release 9.2 ed. Texas: College Station.

Strakowski SM, DelBello MP. (2000) The co-occurrence of bipolar and substance use disorders. *Clin Psychol Rev*, 20(2):191-206.

Tijssen MJA, Van Os J, Wittchen HU, Lieb R, Beesdo K, Mengelers R, Krabbendam L, Wichers MC. (submitted-a) Evidence that bipolar disorder is the poor outcome fraction of a common developmental phenotype: an 8-year cohort study in young people.

Tijssen MJA, Van Os J, Wittchen HU, Lieb R, Beesdo K, Mengelers R, Wichers MC. (submitted-b) Prediction of transition from common adolescent bipolar experiences to bipolar disorder.

Tsuchiya KJ, Agerbo E, Mortensen PB. (2005) Parental death and bipolar disorder: a robust association was found in early maternal suicide. *J Affect Disord*, 86(2-3):151-159.

Tyrka AR, Mello AF, Mello MF, Gagne GG, Grover KE, Anderson GM, Price LH, Carpenter LL. (2006) Temperament and hypothalamic-pituitary-adrenal axis function in healthy adults. *Psychoneuroendocrinology*, 31(9):1036-1045.

Voruganti LN, Slomka P, Zabel P, Mattar A, Awad AG. (2001) Cannabis induced dopamine release: an in-vivo SPECT study. *Psychiatry Res*, 107(3):173-177.

Watson S, Gallagher P, Ritchie JC, Ferrier IN, Young AH. (2004) Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. *Br J Psychiatry*, 184:496-502.

Weissman MM, Wickramaratne P, Nomura Y, Warner V, Pilowsky D, Verdeli H. (2006) Offspring of depressed parents: 20 years later. *Am J Psychiatry*, 163(6):1001-1008.

Whittington JE, Huppert FA. (1996) Changes in the prevalence of psychiatric disorder in a community are related to changes in the mean level of psychiatric symptoms. *Psychol Med*, 26(6):1253-1260.

WHO. (1990) Composite International Diagnostic Interview (CIDI), Version 1.0. Geneva, Switzerland: World Health Organisation.

Wittchen HU, Robins LN, Cottler LB, Sartorius N, Burke JD, Regier D. (1991) Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *Br J Psychiatry*, 159:645-653, 658.

Wittchen HU. (1994) Reliability and validity studies of the WHO--Composite International Diagnostic Interview (CIDI): a critical review. *J Psychiatr Res*, 28(1):57-84.

Wittchen HU, Lachner G, Wunderlich U, Pfister H. (1998a) Test-retest reliability of the computerized DSM-IV version of the Munich-Composite International Diagnostic Interview (M-CIDI). *Soc Psychiatry Psychiatr Epidemiol*, 33(11):568-578.

Wittchen HU, Perkonigg A, Lachner G, Nelson CB. (1998b) Early developmental stages of psychopathology study (EDSP): objectives and design. *Eur Addict Res*, 4(1-2):18-27.

Wittchen HU, Pfister H. (1997) DIA-X-Interviews: Manual für Screening-Verfahren und Interview; Interviewheft Längsschnittuntersuchung (DIA-X-Lifetime); Ergänzungsheft (DIA-X-Lifetime); Interviewheft Querschnittsuntersuchung (DIA-X-12 Monatsversion); Ergänzungsheft (DIA-X-12 Monatsversion); PC-Programm zur Durchführung der Interviews (Längsund Querschnittsuntersuchung). Auswertungsprogramm. In: Zeitlinger Sa, ed. Frankfurt, Germany.

Young LT, Bagby RM, Cooke RG, Parker JD, Levitt AJ, Joffe RT. (1995) A comparison of Tridimensional Personality Questionnaire dimensions in bipolar disorder and unipolar depression. *Psychiatry Res*, 58(2):139-143.

Zimmermann P, Wittchen HU, Höfler M, Pfister H, Kessler RC, Lieb R. (2003) Primary anxiety disorders and the development of subsequent alcohol use disorders: a 4-year community study of adolescents and young adults. *Psychol Med*, 33(7):1211-1222.

Chapter 5

Discussion

There is fairly little knowledge about the natural course of bipolar disorders. However, the amount of research on this disorder has increased dramatically in the last few years. Following these investigations, the idea has arisen that bipolar patients might present with subclinical expressions of bipolar psychopathology years before the development of full-blown bipolar disorder (e.g. Akiskal et al., 2000; Birmaher et al., 2006; Cassano et al., 1999; Egeland et al., 1987). It appears that bipolar disorder might not only be more common than once assumed, but also develop far earlier. However, the lack of prospective longitudinal research in general population samples prevents us from getting a clear answer (Wittchen et al., 2003). Therefore, for this thesis, bipolar phenotypes were investigated in a general population sample of adolescents in the EDSP study. In this final chapter, an interactive developmental model is presented and a further discussion of possible theoretical backgrounds is given. Finally, clinical implications and directions for future research are presented.

An Interactive Developmental Model

It was hypothesized in the introduction that bipolar disorder might be (1) a continuous disorder, (2) a developmental disorder and (3) a multifactorial disorder. In retrospect, all three hypotheses seem to be true. First, it was shown that besides full-blown bipolar disorder, subclinical expressions are common in the general population (Chapter 2). Moreover, it appeared that these subclinical expressions can precede full-blown bipolar disorder (Chapter 3). Thus, in this sample, indications for two criteria that assume continuity of subclinical expressions of bipolar disorder with full-blown bipolar disorder are present, namely phenomenological continuity and aetiological continuity (Flett et al., 1997). This is similar to the evidence for continuity seen for depression (Flett et al., 1997), and it seems possible that bipolar disorder, like depressive disorder, may be better conceptualized as distributed along a continuum. Second, it was shown in Chapter 2 that subclinical expressions of bipolar disorder were already present during adolescence and were in some cases preceded by childhood disorders. This implies that the first expressions of bipolar disorder can be seen as early as during adolescence, if not earlier. However, the longitudinal course of these subclinical expressions differed between participants. Thus, while some adolescents experienced subclinical expressions of bipolar disorder persistently and had a higher risk of transition to bipolar disorder, these subclinical expressions were transient in most of the adolescents (Chapter 3). Third, with respect to the multifactorial nature of bipolar disorder, it was shown that differences in

environmental exposure and personality were responsible for the difference in initial experience and longitudinal course of these subclinical expressions. In other words, the onset and longitudinal course were determined at least partly by (1) exposure to risk factors and (2) personality traits (Chapter 4).

An interactive developmental model by which all these results can be explained was introduced in Chapter 4. Briefly, it is presumed that subclinical expressions of bipolar disorder are reasonably common in the general population and in fact are part of a normal development, in which the extent to which individuals experience these subclinical expressions depends on the initial exposure to particular risk factors. In time, the expression of these subclinical phenotypes will disappear in most individuals, with no obvious increase in psychopathology in these individuals compared to individuals who did not experience subclinical expressions of bipolar disorder. However, when individuals are exposed to additional risk factors, it is possible that subclinical expressions of bipolar disorder will be present for a longer period of time. The risk of developing a full-blown bipolar disorder increases with an increase in the severity of these additional risk factors and in the level of persistence. Thus, after the onset of subclinical expressions of bipolar disorder, the level of persistence of these subclinical expressions determines the risk of transition to full-blown bipolar disorder, whereas the level of persistence is determined by the extent to which an individual is exposed to risk factors (Fig. 5.1).

This model is able to explain all the findings of this study. Moreover, it agrees with a post-hoc analysis in which Novelty Seeking and Harm Avoidance significantly increase the risk of developing (hypo)manic episodes or depressive episodes respectively. Unfortunately, except for personality factors, none of the risk factors analysed could be linked to persistence of symptoms. Furthermore, the model is purely descriptive. In order to increase the validity of the model, a biopsychological mechanism must be recognized that can account for all its characteristics (Lewinsohn et al., 2000). In other words, a common biopsychological mechanism should be indicated that is able to explain (1) why there are quantitative differences in bipolar symptom expression between individuals, (2) why adolescence is a period during which there is an increased risk for the expression of bipolar symptoms, (3) why persistence of bipolar symptom expression can increase the risk of transition to bipolar disorder and (4) why certain risk factors can influence the degree of bipolar symptom expression.

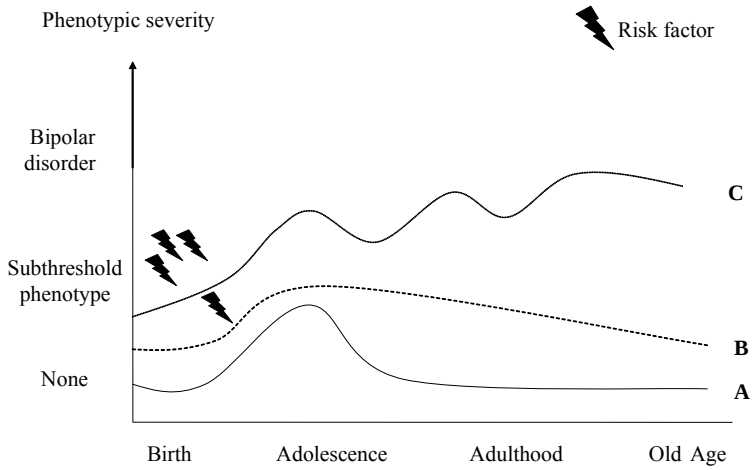

Fig. 5.1. Development of Bipolar Disorder: Abnormal Persistence of Developmental Expression of Subthreshold Bipolar Experiences. Person A has 'normal' developmental expression of subthreshold bipolar experiences that are transient. Person B has increased expression and longer persistence due to additional but mild environmental exposure. Person C has longer persistence due to severe repeated environmental exposures and eventual transition to clinical bipolar disorder.

It was assumed previously in this thesis that the biopsychological mechanisms that might meet these requirements are not the same for (hypo)manic symptoms and for depressive symptoms (Chapter 4). Thus, while briefly reviewing normal physiology as well as pathological findings in bipolar patients to determine whether there might be a biopsychological basis for the interactive developmental model, the emphasis will be on separate systems for each dimension. It must be remarked, however, that a possible involvement of these systems in the pathophysiology of bipolar disorder might very well be related to disturbances in the regulation of these systems (e.g. excitability/tonicity) rather than to a disturbance in the system itself (Askland and Parsons, 2006). Furthermore, while differentiating between systems that cause (hypo)manic symptoms and depressive symptoms, it is possible that a unitary (regulatory?) system might cause extreme mood fluctuations and thus explain the increased symptom expression within both dimensions. There is an ongoing debate concerning the status of bipolar disorder, namely whether it is a separate entity within the categorization of mood disorders or merely a result of high comorbidity of (hypo)manic and depressive episodes (Cuellar et al., 2005). Extensive research

on this issue is required in order to resolve this debate. Although it is not the intention of this thesis to resolve it, a suggestion will be made that might explain both the similarities and the differences between unipolar and bipolar mood disorders.

However, before elaborating further on the model and its characteristics, another result of the study should be mentioned shortly, as it was rather surprising. In chapter 4, it was shown that ADHD was not associated with the onset or persistence of (hypo)manic symptoms. This is inconsistent with the work of Biederman and colleagues (2005), who found that up to 77% of adolescents with mania (aged 13-18 years old) had comorbid ADHD (Biederman et al., 2005). There might be several explanations for this discrepancy. First, a substantial part of it might be explained by the use of different sample types. While Biederman and colleagues used a clinical sample, a community sample was used in the EDSP. As explained by Berkson's bias, both ADHD and (hypo)manic episodes can, independently of each other, increase need for care and help-seeking, resulting in more "comorbid" psychopathology at the level of mental health care (Regeer et al., in press). Indeed, when a post-hoc analysis of participants *in care* was performed, the comorbidity rates of (hypo)manic episodes with childhood disorders more than doubled. Secondly, as Biederman and colleagues only considered the diagnosis of mania positive if a consensus was achieved that the diagnosis was of a clinical concern due to the quality and severity of symptoms, the associated impairment and the coherence of the clinical picture, it is very well possible that Biederman and colleagues have included only the most severe cases of mania, in which comorbidity might be more common.

Theoretical Backgrounds: Normal Physiology

A continuum of symptom expressions

The presence of a continuum of bipolar phenotypes presumes that a distinction between 'healthy persons' and bipolar patients can be made purely on quantitative grounds (Lewinsohn et al., 2000). Thus, if bipolar disorder is indeed a continuous disorder, the pathophysiology of bipolar disorder reflects the exaggerated expression of normal physiology. The core symptoms of both (hypo)manic and depressive episodes are related to extreme mood valence. Therefore, the identification of the physiological systems underlying the normal

expressions of mood (positive affect/happiness and negative affect/sadness) might give an indication of what has gone awry in bipolar disorder.

Happiness

A meta-analysis by Phan and colleagues (2002) showed that nearly 70% of happiness induction studies reported activation in the basal ganglia, a group of subcortical brain structures that includes the striatum (putamen, caudate nucleus, nucleus accumbens), pallidum, subthalamic nucleus and substantia nigra. Activation of the basal ganglia was observed in response to happy faces, pleasant pictures, happiness-induced recall, pleasant sexual arousal and successful competitive arousal (Phan et al., 2002). The existence of a relationship between basal ganglia activation and happiness is supported by work that showed that this structure is an important component of the 'reward circuit' (Gold 2003; Knutson et al., 2001), while the experience of reward has been shown to cause happiness (Knutson et al., 2001). Because of this important link between the reward system and happiness, it has also been hypothesized that dopamine – the neurotransmitter most commonly linked to the reward system – might induce happiness (Ashby et al., 1999).

Sadness

Negative affect ensues from negative, stressful life events (Van Eck et al., 1998). However, although several systems have been hypothesized to underlie the association between negative affect and stress (Van Praag 2004b), it is not yet known which system is responsible for it. Thus, for instance, in line with the evidence that was found for studies on happiness induction, several investigators have suggested a link with the reward system (e.g. Alloy et al., 2006a). On the other hand, links have been made with the neurotransmitter serotonin (Young et al., 1985) and with cortisol and the hypothalamic-pituitary-adrenal (HPA) axis (Brown et al., 1993; Buchanan et al., 1999; Peeters et al., 2003), which implies that systems other than the reward system might be active when experiencing sadness.

To conclude, both happiness and sadness develop after exposure to minor life events: pleasant, rewarding events typically cause happiness, while negative, stress-inducing events typically cause sadness. Physiologically, happiness has been linked to the reward circuit, in which an important role might be allocated

to the neurotransmitter dopamine and the basal ganglia. As regards sadness, however, several systems have been hypothesized to be relevant.
A continuum of 'normal happiness' with (hypo)manic symptoms and 'normal sadness' with depressive symptoms seems possible, in which the extent to which the reward system and a stress-related system are activated could determine the level of (hypo)manic/depressive symptom expression.

Adolescence as a risk period

As stated in the model, adolescence represents a developmental stage during which individuals have an increased risk of experiencing (hypo)manic and depressive symptoms compared to both younger and older individuals. Thus, to be compliant with our hypothesis, adolescence should be physiologically associated with temporary changes in the innervation of emotional systems that may give rise to expression of bipolar symptoms.

In general, adolescence represents a time of transitions. Not only is it a time during which individuals make the transition from the dependence of youth to the independence of adulthood, but it is also a time during which numerous changes take place, for instance developmental changes, bodily changes and changes in socio-environmental contexts (Spear 2000). Not surprisingly, having to endure all these transitions has several consequences for the adolescent. First, to be able to attain the necessary skills for independence, adolescents as a group possess certain behavioural features. Thus, the number of peer-directed social interactions increases during this time and there is an elevation in novelty-seeking and risk-taking behaviours, in which the last two have been linked to a diminished ability to experience pleasurable activities followed by a search for additional appetitive reinforcers (Chambers et al., 2003; Spear 2000). Second, the number of stressful life events adolescents are faced with increases dramatically. This is all the more important as it seems that the perception of events as stressful (i.e. 'stress sensitivity') may be elevated during this period (Spear 2000).
Biologically, adolescence is associated with prominent neural alterations in the brain (Chambers et al., 2003; Spear 2000), and an adolescent brain has been said to be in 'a constant state of flux', undergoing numerous regressive and progressive changes in mesocorticolimbic regions (Leibenluft et al., 2003; Spear 2000). Briefly, during adolescence, 'pruning' of (mostly excitatory) synapses takes place, resulting in a major decline in the amount of excitatory stimulation

reaching the cortex, presumably to effectively accommodate environmental needs. Indeed, a substantial synapse elimination of presumed glutaminergic excitatory input in prefrontal cortex (PFC) occurs during adolescence, and while the volume of the PFC declines, function seems to improve (Spear 2000). Furthermore, a substantial reorganization of dopamine systems occurs during adolescence. Thus, research suggests a developmental shift in balance among different forebrain dopamine terminal regions and a difference in dopamine tone between adolescents and adults (Chambers et al., 2003; Spear 2000). Grossly simplified, dopamine tone in PFC is enhanced during adolescence, while there are indications that basal dopamine activity in the nucleus accumbens (NAcc) might be decreased. Grace and colleagues (1991) suggested that the level of tonic dopamine regulates the amplitude of the phasic dopamine response to stimuli, in which an increase in tonic dopamine results in decreased phasic dopamine release, while a decrease in tonic dopamine leads to increased phasic dopamine release (Grace 1991). Therefore, the low tonic dopamine levels in the NAcc might result in increased amplitude of phasic dopamine in response to stimuli and thus increased response of the reward system.
Stress sensitivity of adolescents might increase in relation to the increase in cognitive ability and reasoning capacity, in other words, to the increased capacity to reflect on the developing self (Petersen et al., 1993). Furthermore, research in rats has shown that stress-induced HPA axis activation increases to reach a peak around adolescence (Spear 2000), which might increase the level of distress that is experienced.

In conclusion, adolescence is a period of transition in which behavioural, environmental and biological changes take place. All these changes may contribute to increased instability of emotional systems as expressed by increased innervation of the reward system and increased sensitivity to stress, and thus to an increased level of both (hypo)manic and depressive symptom expression during this period.

Persistence

It is stated in the interactive developmental model that persistence of symptoms somehow increases the risk of transition to bipolar disorder. For this to be true, individuals who experience symptoms persistently should shift upwards along the continuum of bipolar disorder more easily than individuals who experience symptoms only once. A reasonable explanation for this, as discussed in Chapter

3, seems to be provided by Post (1992) in the kindling-sensitization model. Post hypothesized that neurotransmitter pathways are activated by events and produce not only intermediate short-term effects, but also a series of events (i.e. intracellular changes at the level of gene transcription) that have long-lasting consequences for the organism. Thus, every time a person experiences an affective episode, the associated neurotransmitter and peptide alterations may leave behind memory traces, and as a result less stressors are required to precipitate recurrences of the affective episode than were required to precipitate the first onset (Post 1992).

Although data from the Stanley Foundation Bipolar Network (SFBN) suggest that early psychosocial stressors can interact with the neurobiology of bipolar disorder (Leverich et al., 2002), it seems that no investigations have focused on possible sensitization of specific neurotransmitter pathways in (hypo)mania. Nevertheless, dopamine sensitization has been hypothesized to increase the risk of developing full-blown psychotic disorder (Tsapakis et al., 2003) and thus might prove to be important in the development of (hypo)mania as well.

In regard to depressive symptomatology, however, this model has been abundantly investigated. Several investigations have shown that early exposure to major stressful life events such as childhood trauma is an important predictor of onset of depression (see e.g. Heim and Nemeroff, 1999; Van Praag 2004a). Furthermore, it is reported that the previous exposure to stressors results in increased stress sensitivity (the negative affect reactivity towards minor life events) (Harkness et al., 2006; Wichers et al., submitted), whereas stress sensitivity is suggested to express the liability to develop a major depressive disorder (Wichers et al., 2007). Moreover, the observation that traumatic events predict the onset of depressive symptoms but not the persistence (Chapter 4) could be explained by the kindling-sensitization model, as minor life events might be sufficient to trigger symptom expression in this phase of the development of the disorder (i.e. persistence of symptoms). In conclusion, Post suggests in the kindling-sensitization model that long-term changes in neurotransmitter pathways might accompany affective symptoms. This might explain why the level of persistence of symptoms determines the risk of transition to bipolar disorder.

Influence of risk factors

In this study, cannabis use and novelty seeking were shown to increase the risk of developing (hypo)manic symptoms, while trauma, harm avoidance and reward dependence were related to increased experience of depressive symptoms.

According to the interactive developmental model, these risk factors should thus activate the related biopsychological system (i.e. cannabis use and novelty seeking activate the reward system, while trauma, harm avoidance and reward dependence are related to the increased activity of a stress response system).

Several lines of evidence have suggested that cannabis, similar to other drugs of abuse, exerts its effect by interacting with the brain reward system (see e.g. Bardo et al., 1996; Maldonado and Rodriguez de Fonseca, 2002; Tsapakis et al., 2003), in which the main effect might be a stronger response to natural rewards and/or a response to this drug as though it were a natural reward (Schultz 2002). Indeed, although the precise mechanism of action is not yet clear, it is supposed that cannabis and more specifically its main psychoactive component delta-9-tetrahydrocannabinol enhances mesolimbic dopaminergic activity by influencing dopaminergic CB_1 receptors that are densely diffused in regions involved in the processing of rewarding stimuli (D'Souza et al., 2005; Van Laar et al., 2007; Wenger et al., 2003). Similarly, a growing body of evidence indicates that novelty seeking is mediated by the mesolimbic dopamine system. For instance, animal studies have shown that dopamine antagonists block novelty seeking in rats and mice (Bardo et al., 1996), while several genetic studies found a connection between novelty seeking and the D4 dopamine receptor gene (Munafo et al., 2008).
To summarize, both the risk factor cannabis use and the personality trait novelty seeking seem to interact with the brain reward system, thereby perhaps increasing the level of expression of (hypo)manic symptoms.

As mentioned before, early exposure to trauma might result in increased stress sensitivity (Wichers et al., submitted). Indeed, animal studies have shown a relation between early life trauma and hyperactivation of the HPA axis (Ladd et al., 1996; Plotsky and Meaney, 1993), and it seems possible that exposure to early trauma subsequently heightens an individual's experience of stress. Personality has similarly been hypothesized to confer sensitivity to stressors (Davidson 2000; Tyrka et al., 2006). Thus, personality might influence the likelihood of exposure to stressors (Tyrka et al., 2006), which might prove important in light of the above-mentioned kindling-sensitization model. Furthermore, it is suggested by Davidson (2000) that individuals who have difficulty regulating negative affect might have an increased reactivity to stressful events (Davidson 2000), while Alloy and colleagues (2005, 2006) hypothesize that maladaptive

cognitive patterns underlie a failure to recover from negative events (Alloy et al., 2005; Alloy et al., 2006b).
To conclude, both trauma and personality seem to heighten stress sensitivity. Therefore, the presence of these risk factors could lead to both higher expressions and longer persistence of depressive symptoms. Other factors that might prove to increase the risk of persistence of symptoms are lack of social support and comorbidity with other psychiatric disorders or physical illness, as suggested by other studies (Spijker and Nolen, 1998; Spijker et al., 2004).

Theoretical Backgrounds: Pathological Findings about Bipolar Disorder

A connection was made with both the reward system and a stress response system in normal physiology that accounted for all characteristics of the model, emphasizing the possible importance of this model. It would be even more convincing, however, if changes in components of these systems were found in bipolar patients.
Unfortunately, neuroimaging studies in bipolar disorder do not present us with clear answers, as many different structures are investigated and reports on these structures are often conflicting. Nevertheless, several studies of bipolar patients have shown alterations in the basal ganglia, more specifically increased activity in the caudate during mania (Blumberg et al., 2000; Caligiuri et al., 2006; O'Connell et al., 1995). An association between dopamine activity and mania/euphoria was shown by Anand and colleagues (2000) as well as by Drevets and co-workers (2001) (Anand et al., 2000; Drevets et al., 2001). Finally, several investigations have shown a link between the behavioural approach system and bipolar disorder (e.g. Alloy et al., 2006a). Thus, the reward system might indeed be affected in bipolar disorder.
As regards alterations in stress sensitivity, most literature focuses on unipolar depression (Peeters et al., 2004; Van Praag 2004b; Wichers et al., 2007). However, the finding of HPA axis abnormalities in bipolar depression implies that stress response systems might be affected in bipolar disorder as well (Rybakowski and Twardowska, 1999; Watson et al., 2004). Furthermore, data from Zahn and colleagues (1991) showed a more intense response of the autonomic nervous system in response to anxiety in the offspring of bipolar patients compared to controls, and it was suggested that the salience of stressful events and the sensitization to stress might be increased in these individuals (Zahn et al., 1991). Thus, to summarize, alterations in the stress response system might be associated with depressive symptoms in bipolar disorder.

A Possible Explanation for Similarities and Differences Between Mood Disorders

So far, the development of both (hypo)manic and depressive symptoms could be explained by the interactive developmental model, in which the model seems to comply with normal physiology and with pathology. However, as explained, separate biopsychological systems were described to underlie the development of (hypo)manic symptoms and depressive symptoms, whereas the construct of a 'bipolar' disorder suggests a unitary system might underlie both dimensions (although it should be remembered that Berkson's bias might explain part of the co-occurrence of these dimensions (Regeer et al., in press)). Although premature, I suggest that the involvement of separate biopsychological systems for both dimensions does not necessarily exclude the presence of one overarching, shared mechanism. For example, it has been hypothesized that the partial genetic and comorbidity overlap between schizophrenia and bipolar disorder (Ketter et al., 2004; Murray et al., 2004) as well as the overlap between depressive disorders and anxiety disorders (Baldwin et al., 2002; Overbeek et al., 2002; Overbeek et al., 2005) might result from the exposure to common risk factors, while the exposure to unique risk factors for each disorder might differentiate between the disorders (Baldwin et al., 2002; Murray et al., 2004). The same might be true for bipolar disorder and might thus explain the overlap between bipolar disorder and unipolar disorder (McGuffin et al., 2003). In theory, a shared vulnerability as represented in the common characteristic 'mood instability' might be the result of exposure to common risk factors, while it is the additional exposure to unique risk factors that might explain the extent to which the separate mood dimensions are affected, which then determines the number of (hypo)manic and/or depressive symptoms an individual experiences and thus the diagnosis '(hypo)manic episode' or 'depressive episode'. Indeed, this might explain the frequent occurrence of mixed episodes (Suppes et al., 2005) and perhaps explain why depressive episodes are three times as common as (hypo)manic episodes in treated outpatients with bipolar I or bipolar II disorder (Kupka et al., 2007), as risk factors that elicit depressive episodes might be more commonly encountered or less frequently treated than risk factors that elicit (hypo)manic episodes.

Clinical Implications

The present findings have several implications for clinical practice.

First, they provide clarity regarding the development and longitudinal course of bipolar disorder. For example, it was shown that bipolar disorder is presented in the general population as a continuum and that the first expressions of this disorder can develop as early as adolescence. This information can be used to initiate aimed prevention programmes. For instance, prevention programmes aimed at adolescents might prevent the progression of bipolar symptoms and thus the development of a full-blown disorder in later life. This is especially important since adolescence represents a time of transitions in which expressions of psychopathology can have major consequences for later life. On the other hand, these results show that one need not panic when adolescents present with bipolar symptoms, because for most of them the outcome will be rather favourable. Perhaps a risk profile could be created to enable mental health care givers to estimate the chances that an adolescent with bipolar symptoms will develop the full-blown disorder. Based on the studies in this thesis, characteristics that could be included in this risk profile are particular environmental risk factors or personality traits, as well as the degree of symptom expression (i.e. persistence) in time. Other studies suggest that lack of social support and comorbidity with other psychiatric disorders or physical illness might turn out to be important as well (Spijker and Nolen, 1998; Spijker et al., 2004). Indeed, the persistence of depression score (PDS) developed by Spijker and colleagues (2006) has already shown reasonable performance in predicting persistence in individuals with major depressive disorder (Spijker et al., 2006).

Second, clarification of factors that might be (at least partly) responsible for the development of full-blown bipolar disorder can provide us with good starting points in determining the best treatment options. For example, the recognition that different biopsychological systems might underlie the difference in symptom expression between patients implies that different patients might be best helped by different pharmacologic treatments. More specifically, while a mood stabilizer might be useful for most patients, an antipsychotic might be indicated when bipolar patients present mainly with (hypo)manic symptoms, and an antidepressant might be more appropriate for patients presenting mainly with depressive symptoms. Indeed, a combination of a mood stabilizer and an antipsychotic has been shown to reduce (hypo)manic symptoms (Sachs et al., 2002; Tohen et al., 2002). However, reports on the efficacy of antidepressants in bipolar depression are inconsistent (Gijsman et al., 2004; Sachs et al., 2007). Aside from pharmacological treatment, it appears that psychosocial intervention therapies might be useful, as it was shown that besides biological factors, envi-

ronmental factors and personality traits could play an important part in the development of bipolar disorder: research has shown that these interventions can represents a useful addition to pharmacological treatment (Miklowitz et al., 2007), especially in the early course of illness (Scott et al., 2006).
To conclude, the findings of this study present us with indications for useful prevention strategies as well as treatment tactics that can be matched with the specific treatment needs of individual patients.

Suggestions for Future Research

The developmental model presented in this thesis is supported theoretically by normal physiology and by pathologic findings in bipolar patients. However, several speculations were made and, aside from replication of these findings, further research needs to be done to confirm the validity of this model, for instance by finding a direct link with underlying biopsychological systems. Obligatory characteristics of these studies are: (1) the use of a young, general population sample to ensure that the characteristics of these individuals are assessed before psychopathology occurs and before, for example, treatment issues influence them; (2) investigation of bipolar disorder on a symptom level, in which a division should be made between (hypo)manic symptom expression and depressive symptom expression as different mechanisms might underlie the different kinds of expression; and (3) a longitudinal design to account for changes over the lifespan. Interesting candidates, as explained in this thesis, might be dopamine and the reward system for (hypo)manic systems and a stress response system for depressive symptoms. However, in explaining the theoretical backgrounds to the model, the emphasis was on these two separate systems for the different mood dimensions, while it seems plausible that a common system might underlie the shared characteristic of mood instability in both dimensions. As yet, it is not clear whether bipolar disorder should be distinguished from unipolar disorder (as categorized in the DSM-IV-TR), or whether it would be more appropriate to distinguish between (hypo)manic episodes with/without depressive episodes and depressive episodes with/without (hypo)manic episodes, respectively. Thus, future research should clarify this issue, for instance by examining to what extent biology, course, symptomatology, risk factors and treatment are comparable in unipolar depression and bipolar depression, and to what extent these characteristics are comparable in (hypo)manic episodes and depressive episodes.

LITERATURE

Akiskal HS, Bourgeois ML, Angst J, Post R, Möller H, Hirschfeld R. (2000) Re-evaluating the prevalence of and diagnostic composition within the broad clinical spectrum of bipolar disorders. *J Affect Disord*, 59 Suppl 1:S5-S30.

Alloy LB, Abramson LY, Urosevic S, Walshaw PD, Nusslock R, Neeren AM. (2005) The psychosocial context of bipolar disorder: environmental, cognitive, and developmental risk factors. *Clin Psychol Rev*, 25(8):1043-1075.

Alloy LB, Abramson LY, Walshaw PD, Cogswell A, Smith JM, Neeren AM, Hughes ME, Iacoviello BM, Gerstein RK, Keyser J, Urosevic S, Nusslock R. (2006a) Behavioral Approach System (BAS) Sensitivity and Bipolar Spectrum Disorders: A retrospective and Concurrent Behavioral High-Risk Design. *Motiv Emot*, 30:143-155.

Alloy LB, Abramson LY, Walshaw PD, Keyser J, Gerstein RK. (2006b) A cognitive vulnerability-stress perspective on bipolar spectrum disorders in a normative adolescent brain, cognitive, and emotional development context. *Dev Psychopathol*, 18(4):1055-1103.

Anand A, Verhoeff P, Seneca N, Zoghbi SS, Seibyl JP, Charney DS, Innis RB. (2000) Brain SPECT imaging of amphetamine-induced dopamine release in euthymic bipolar disorder patients. *Am J Psychiatry*, 157(7):1108-1114.

Ashby FG, Isen AM, Turken AU. (1999) A neuropsychological theory of positive affect and its influence on cognition. *Psychol Rev*, 106(3):529-550.

Askland K, Parsons M. (2006) Toward a biaxial model of "bipolar" affective disorders: spectrum phenotypes as the products of neuroelectrical and neurochemical alterations. *J Affect Disord*, 94(1-3):15-33.

Baldwin DS, Evans DL, Hirschfeld RM, Kasper S. (2002) Can we distinguish anxiety from depression? *Psychopharmacol Bull*, 36 Suppl 2:158-165.

Bardo MT, Donohew RL, Harrington NG. (1996) Psychobiology of novelty seeking and drug seeking behavior. *Behav Brain Res*, 77(1-2):23-43.

Biederman J, Faraone SV, Wozniak J, Mick E, Kwon A, Cayton GA, Clark SV. (2005) Clinical correlates of bipolar disorder in a large, referred sample of children and adolescents. *J Psychiatr Res*, 39(6):611-622.

Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Keller M. (2006) Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry*, 63(2):175-183.

Blumberg HP, Stern E, Martinez D, Ricketts S, de Asis J, White T, Epstein J, McBride PA, Eidelberg D, Kocsis JH, Silbersweig DA. (2000) Increased anterior cingulate and caudate activity in bipolar mania. *Biol Psychiatry*, 48(11):1045-1052.

Brown WA, Sirota AD, Niaura R, Engebretson TO. (1993) Endocrine correlates of sadness and elation. *Psychosom Med*, 55(5):458-467.

Buchanan TW, al'Absi M, Lovallo WR. (1999) Cortisol fluctuates with increases and decreases in negative affect. *Psychoneuroendocrinology*, 24(2):227-241.

Caligiuri MP, Brown GG, Meloy MJ, Eberson S, Niculescu AB, Lohr JB. (2006) Striatopallidal regulation of affect in bipolar disorder. *J Affect Disord*, 91(2-3):235-242.

Cassano GB, Dell'Osso L, Frank E, Miniati M, Fagiolini A, Shear K, Pini S, Maser J. (1999) The bipolar spectrum: a clinical reality in search of diagnostic criteria and an assessment methodology. *J Affect Disord*, 54(3):319-328.

Chambers RA, Taylor JR, Potenza MN. (2003) Developmental neurocircuitry of motivation in adolescence: a critical period of addiction vulnerability. *Am J Psychiatry*, 160(6):1041-1052.

Cuellar AK, Johnson SL, Winters R. (2005) Distinctions between bipolar and unipolar depression. *Clin Psychol Rev*, 25(3):307-339.

D'Souza DC, Abi-Saab WM, Madonick S, Forselius-Bielen K, Doersch A, Braley G, Gueorguieva R, Cooper TB, Krystal JH. (2005) Delta-9-tetrahydrocannabinol effects in schizophrenia: implications for cognition, psychosis, and addiction. *Biol Psychiatry*, 57(6):594-608.

Davidson RJ. (2000) Affective style, psychopathology, and resilience: brain mechanisms and plasticity. *Am Psychol*, 55(11):1196-1214.

Drevets WC, Gautier C, Price JC, Kupfer DJ, Kinahan PE, Grace AA, Price JL, Mathis CA. (2001) Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol Psychiatry*, 49(2):81-96.

Egeland JA, Blumenthal RL, Nee J, Sharpe L, Endicott J. (1987) Reliability and relationship of various ages of onset criteria for major affective disorder. *J Affect Disord*, 12(2):159-165.

Flett GL, Vredenburg K, Krames L. (1997) The continuity of depression in clinical and nonclinical samples. *Psychol Bull*, 121(3):395-416.

Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. (2004) Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry*, 161(9):1537-1547.

Gold JI. (2003) Linking reward expectation to behavior in the basal ganglia. *Trends Neurosci*, 26(1):12-14.

Grace AA. (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience*, 41(1):1-24.

Harkness KL, Bruce AE, Lumley MN. (2006) The role of childhood abuse and neglect in the sensitization to stressful life events in adolescent depression. *J Abnorm Psychol*, 115(4):730-741.

Heim C, Nemeroff CB. (1999) The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. *Biol Psychiatry*, 46(11):1509-1522.

Ketter TA, Wang PW, Becker OV, Nowakowska C, Yang Y. (2004) Psychotic bipolar disorders: dimensionally similar to or categorically different from schizophrenia? *J Psychiatr Res*, 38(1):47-61.

Knutson B, Adams CM, Fong GW, Hommer D. (2001) Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *J Neurosci*, 21(16):RC159.

Kupka RW, Altshuler LL, Nolen WA, Suppes T, Luckenbaugh DA, Leverich GS, Frye MA, Keck PE, Jr., McElroy SL, Grunze H, Post RM. (2007) Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder. *Bipolar Disord*, 9(5):531-535.

Ladd CO, Owens MJ, Nemeroff CB. (1996) Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. *Endocrinology*, 137(4):1212-1218.

Leibenluft E, Charney DS, Pine DS. (2003) Researching the pathophysiology of pediatric bipolar disorder. *Biol Psychiatry*, 53(11):1009-1020.

Leverich GS, McElroy SL, Suppes T, Keck PE, Jr., Denicoff KD, Nolen WA, Altshuler LL, Rush AJ, Kupka R, Frye MA, Autio KA, Post RM. (2002) Early physical and sexual abuse associated with an adverse course of bipolar illness. *Biol Psychiatry*, 51(4):288-297.

Lewinsohn PM, Solomon A, Seeley JR, Zeiss A. (2000) Clinical implications of "subthreshold" depressive symptoms. *J Abnorm Psychol*, 109(2):345-351.

Maldonado R, Rodriguez de Fonseca F. (2002) Cannabinoid addiction: behavioral models and neural correlates. *J Neurosci*, 22(9):3326-3331.

McGuffin P, Rijsdijk F, Andrew M, Sham P, Katz R, Cardno A. (2003) The heritability of bipolar affective disorder and the genetic relationship to unipolar depression. *Arch Gen Psychiatry*, 60(5):497-502.

Miklowitz DJ, Otto MW, Frank E, Reilly-Harrington NA, Wisniewski SR, Kogan JN, Nierenberg AA, Calabrese JR, Marangell LB, Gyulai L, Araga M, Gonzalez JM, Shirley ER, Thase ME, Sachs GS. (2007) Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. *Arch Gen Psychiatry*, 64(4):419-426.

Munafo MR, Yalcin B, Willis-Owen SA, Flint J. (2008) Association of the dopamine D4 receptor (DRD4) gene and approach-related personality traits: meta-analysis and new data. *Biol Psychiatry*, 63(2):197-206.

Murray RM, Sham P, Van Os J, Zanelli J, Cannon M, McDonald C. (2004) A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophr Res*, 71(2-3):405-416.

O'Connell RA, Van Heertum RL, Luck D, Yudd AP, Cueva JE, Billick SB, Cordon DJ, Gersh RJ, Masdeu JC. (1995) Single-photon emission computed tomography of the brain in acute mania and schizophrenia. *J Neuroimaging*, 5(2):101-104.

Overbeek T, Schruers K, Vermetten E, Griez E. (2002) Comorbidity of obsessive-compulsive disorder and depression: prevalence, symptom severity, and treatment effect. *J Clin Psychiatry*, 63(12):1106-1112.

Overbeek T, Schruers K, Van Leeuwen ID, Klaassen T, Griez E. (2005) Experimental affective symptoms in panic disorder patients. *Can J Psychiatry*, 50(3):175-178.

Peeters F, Nicolson NA, Berkhof J, Delespaul P, deVries M. (2003) Effects of daily events on mood states in major depressive disorder. *J Abnorm Psychol*, 112(2):203-211.

Peeters F, Nicolson NA, Berkhof J. (2004) Levels and variability of daily life cortisol secretion in major depression. *Psychiatry Res*, 126(1):1-13.

Petersen AC, Compas BE, Brooks-Gunn J, Stemmler M, Ey S, Grant KE. (1993) Depression in adolescence. *Am Psychol*, 48(2):155-168.

Phan KL, Wager T, Taylor SF, Liberzon I. (2002) Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage*, 16(2):331-348.

Plotsky PM, Meaney MJ. (1993) Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Brain Res Mol Brain Res*, 18(3):195-200.

Post RM. (1992) Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. *Am J Psychiatry*, 149(8):999-1010.

Regeer E, Krabbendam L, De Graaf R, Ten Have M, Nolen W, Van Os J. (in press) Berkson's bias and the mood dimensions of bipolar disorder. *Int J Methods Psychiatr Res*.

Rybakowski JK, Twardowska K. (1999) The dexamethasone/corticotropin-releasing hormone test in depression in bipolar and unipolar affective illness. *J Psychiatr Res*, 33(5):363-370.

Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. (2002) Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. *Am J Psychiatry*, 159(7):1146-1154.

Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ, Ketter TA, Patel J, Hauser P, Rapport D, Martinez JM, Allen MH, Miklowitz DJ, Otto MW, Dennehy EB, Thase ME. (2007) Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med*, 356(17):1711-1722.

Schultz W. (2002) Getting formal with dopamine and reward. *Neuron*, 36(2):241-263.

Scott J, Paykel E, Morriss R, Bentall R, Kinderman P, Johnson T, Abbott R, Hayhurst H. (2006) Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. *Br J Psychiatry*, 188:313-320.

Spear LP. (2000) The adolescent brain and age-related behavioral manifestations. *Neurosci Biobehav Rev*, 24(4):417-463.

Spijker J, Nolen WA. (1998) Voorspellende factoren voor chroniciteit van een depressie. Een literatuuronderzoek. *Tijdschr Psychiatrie*, 40:696-708.

Spijker J, De Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA. (2004) Determinants of persistence of major depressive episodes in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). *J Affect Disord*, 81(3):231-240.

Spijker J, de Graaf R, Ormel J, Nolen WA, Grobbee DE, Burger H. (2006) The persistence of depression score. *Acta Psychiatr Scand*, 114(6):411-416.

Suppes T, Mintz J, McElroy SL, Altshuler LL, Kupka RW, Frye MA, Keck PE, Jr., Nolen WA, Leverich GS, Grunze H, Rush AJ, Post RM. (2005) Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the Stanley Foundation Bipolar Treatment Network: a sex-specific phenomenon. *Arch Gen Psychiatry*, 62(10):1089-1096.

Tohen M, Chengappa KN, Suppes T, Zarate CA, Jr., Calabrese JR, Bowden CL, Sachs GS, Kupfer DJ, Baker RW, Risser RC, Keeter EL, Feldman PD, Tollefson GD, Breier A. (2002) Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. *Arch Gen Psychiatry*, 59(1):62-69.

Tsapakis EM, Guillin O, Murray RM. (2003) Does dopamine sensitization underlie the association between schizophrenia and drug abuse? *Curr Opin Psychiatry*, 16(Suppl 2):S45-S52.

Tyrka AR, Mello AF, Mello MF, Gagne GG, Grover KE, Anderson GM, Price LH, Carpenter LL. (2006) Temperament and hypothalamic-pituitary-adrenal axis function in healthy adults. *Psychoneuroendocrinology*, 31(9):1036-1045.

Van Eck M, Nicolson NA, Berkhof J. (1998) Effects of stressful daily events on mood states: relationship to global perceived stress. *J Pers Soc Psychol*, 75(6):1572-1585.

Van Laar M, Van Dorsselaer S, Monshouwer K, De Graaf R. (2007) Does cannabis use predict the first incidence of mood and anxiety disorders in the adult population? *Addiction*, 102(8):1251-1260.

Van Praag HM. (2004a) The debit balance of present day stress research. *World J Biol Psychiatry*, 5:154-159.

Van Praag HM. (2004b) Can stress cause depression? *Prog Neuropsychopharmacol Biol Psychiatry*, 28(5):891-907.

Watson S, Gallagher P, Ritchie JC, Ferrier IN, Young AH. (2004) Hypothalamic-pituitary-adrenal axis function in patients with bipolar disorder. *Br J Psychiatry*, 184:496-502.

Wenger T, Moldrich G, Furst S. (2003) Neuromorphological background of cannabis addiction. *Brain Res Bull*, 61(2):125-128.

Wichers M, Myin-Germeys I, Jacobs N, Peeters F, Kenis G, Derom C, Vlietinck R, Delespaul P, Van Os J. (2007) Genetic risk of depression and stress-induced negative affect in daily life. *Br J Psychiatry*, 191:218-223.

Wichers MC, Schrijvers D, Geschwind N, Jacobs N, Germeys I, Thiery E, Derom C, Sabbe B, Mengelers R, Delespaul P, Van Os J. (submitted) Mechanisms of gene-environment interactions in depression: Evidence that genes potentiate multiple sources of adversity. *Arch Gen Psychiatry*.

Wittchen HU, Mühlig S, Pezawas L. (2003) Natural course and burden of bipolar disorders. *Int J Neuropsychopharmacol*, 6(2):145-154.

Young SN, Smith SE, Pihl RO, Ervin FR. (1985) Tryptophan depletion causes a rapid lowering of mood in normal males. *Psychopharmacology (Berl)*, 87(2):173-177.

Zahn TP, Nurnberger JI, Jr., Berrettini WH, Robinson TN, Jr. (1991) Concordance between anxiety and autonomic nervous system activity in subjects at genetic risk for affective disorder. *Psychiatry Res*, 36(1):99-110.

Chapter 6

Summary

Due to a lack of prospective longitudinal data, hardly anything is known about the natural course of bipolar disorder. However, this information is important as it might provide us with diagnostic guidelines and indicate useful intervention strategies.
In this thesis – 'Tracing Bipolar Disorder to its Developmental Origin in the General Population' – the development and the longitudinal course of bipolar disorder is described in a large representative cohort of adolescents from the general population.

In **Chapter 1**, the phenomenology of bipolar disorder is described and points of interest in epidemiologic research mentioned. The continuum theory as an alternative to the present approach to bipolar disorder is introduced and the advantages of this approach are described. Furthermore, the age at which bipolar disorder commences is discussed, as is the association between bipolar disorder and childhood disorders, in particular ADHD. It is suggested that bipolar disorder might be a developmental disorder. Several risk factors of bipolar disorder are mentioned, and it is suggested that an interaction between genetic risk factors and environmental risk factors might influence the course of bipolar disorder. The best research design for studies on bipolar disorder is discussed. Finally, the objectives and an outline of the thesis are provided.

Chapter 2 describes a study in which prevalence and incidence rates of continuous (hypo)manic phenotypes were determined by use of the EDSP study (a prospective cohort study). In total, 1395 adolescents in the 14-17 age range were followed up for a maximum period of 10 years. The results seem to support a continuous distribution of bipolar disorder and show that both prevalence and incidence rates are considerably higher than previously assumed (the last finding is linked to the small number of adolescents who are in care for bipolar disorder). Furthermore, it was shown that bipolar disorder usually commences before the age of 22 and that such childhood disorders as ADHD regularly precede the development of bipolar disorder. It is concluded that bipolar disorder is the poor outcome of the relatively common expression of (hypo)manic symptoms and that the beginning of this disorder can be traced back to adolescence and childhood disorders.

In **Chapter 3**, the EDSP study is used to investigate two hypotheses. First, it is investigated whether there is an association between the number of (hypo)manic and/or depressive symptoms and the development of DSM-IV bipolar disorder or the use of mental health care. Second, it is investigated whether there is an association with the level of persistence of (hypo)manic and/or depressive symptoms. In total, 2029 adolescents and young adults aged 14-24 years were followed up for a period of approximately 8.3 years. A dose-response relationship was found for both the number of symptoms and the level of persistence as regards the risk of developing a DSM-IV bipolar disorder or the use of mental health care. Even more interesting, however, is that the combination of a high number of symptoms with a high level of persistence (i.e. many symptoms over a long period of time) gave the highest risk of a DSM-IV bipolar disorder or use of mental health care. The results support the continuum theory of bipolar disorder and emphasize the importance of the longitudinal follow-up of adolescents with affective symptoms.

Chapter 4 describes a longitudinal study (the EDSP study) in which it was investigated for both (hypo)manic symptoms and bipolar symptoms (i.e. depressive symptoms occurring in the context of (hypo)mania) whether risk factors can increase the risk of experiencing these symptoms for the first time (onset) and increase the risk that transitory symptom expressions become persistent (persistence). The risk factors investigated are a positive family history of mood disorders, negative life events (early trauma/loss of parent), substance use (alcohol/cannabis), ADHD and temperamental/personality traits. The results indicate that
cannabis use and novelty seeking increase the risk of onset of (hypo)manic symptoms, whereas early trauma, novelty seeking and harm avoidance are associated with increased onset of bipolar symptoms. Novelty seeking decreases the risk of persistence of (hypo)manic symptoms while reward dependence increases the risk of persistence of bipolar symptoms.
It is concluded that mood abnormalities in the context of bipolar disorder may arise stepwise, and that different biological and psychological mechanisms might underlie (hypo)manic and depressive dimensions of bipolar disorder.

Chapter 5 presents an overview of the most important findings of the previous chapters. An interactive developmental model is introduced in which these findings can be integrated. A profound discussion of possible biopsychological

mechanisms that might explain the different characteristics of this model is provided. Finally, clinical implications of the findings and suggestions for future research are given.

Samenvatting

Als gevolg van een gebrek aan prospectief-longitudinaal onderzoek is er nauwelijks informatie over het natuurlijk beloop van bipolaire stoornis. Desondanks is deze informatie van het grootste belang aangezien het ons kan voorzien van richtlijnen voor diagnostiek evenals nuttige interventie strategieën. In dit proefschrift, getiteld "Tracing Bipolar Disorder to its Developmental Origin in the General Population" wordt de ontwikkeling en het longitudinaal beloop van de bipolaire stoornis beschreven in een groot representatief cohort van adolescenten uit de algemene populatie.

In **hoofdstuk 1** wordt de fenomenologie van bipolaire stoornis beschreven en worden aandachtspunten voor epidemiologisch onderzoek genoemd. De continuüm opvatting wordt geïntroduceerd als alternatief op de huidige benadering van bipolaire stoornis, en de verschillende voordelen van deze benadering worden beschreven. Verder wordt ingegaan op het tijdstip van ontstaan van bipolaire stoornis en de associatie tussen bipolaire stoornis en stoornissen van de kindertijd zoals ADHD. Er wordt gesuggereerd dat bipolaire stoornis mogelijk een ontwikkelingsstoornis is. Een aantal risicofactoren voor bipolaire stoornis wordt genoemd, en er wordt geopperd dat de interactie van genetische risicofactoren met omgevingsfactoren het beloop van bipolaire stoornis kan beïnvloeden. De beste onderzoeksopzet voor onderzoek van bipolaire stoornis wordt besproken. Tot slot worden de doelstellingen weergegeven alsmede een uiteenzetting van het proefschrift.

Hoofdstuk 2 beschrijft een studie waarin de prevalentie en incidentie van continue (hypo)mane fenotypes bepaald worden. Hierbij is gebruik gemaakt van de EDSP-studie, een prospectief cohort onderzoek. In totaal werden 1395 adolescenten tussen de 14 en 17 jaar gedurende een periode van maximaal 10 jaar gevolgd. De resultaten lijken een continue verdeling van bipolaire stoornis te ondersteunen en tonen aan dat zowel prevalentie als incidentie cijfers van deze stoornis beduidend hoger zijn dan voorheen gedacht, waarbij het laatste in verband werd gebracht met het kleine aantal adolescenten dat in zorg is voor bipolaire stoornis. Tevens werd gezien dat de stoornis meestal reeds voor het 22e levensjaar begint en dat stoornissen van de kindertijd zoals ADHD regelmatig voorafgaan aan het ontstaan van bipolaire stoornis. Er wordt geconcludeerd dat

bipolaire stoornis de klinische manifestatie van relatief frequent voorkomende (hypo)mane symptomen is en dat het begin van deze stoornis herleid kan worden naar de adolescentie en stoornissen die reeds in de kindertijd ontstaan zijn.

In **hoofdstuk 3** worden met behulp van de EDSP-studie twee hypothesen onderzocht. Allereerst wordt gekeken of er een associatie is tussen het aantal (hypo)mane en/of depressieve symptomen en (1) het ontstaan van een DSM-IV bipolaire stoornis of (2) het krijgen van psychische hulp. Ten tweede wordt onderzocht of er een associatie is met de mate van persistentie van (hypo)mane en/of depressieve symptomen. In totaal werden 2029 adolescenten en jong volwassen tussen de 14 en 24 jaar gedurende ongeveer 8,3 jaar vervolgd. Er werd een dosis-respons relatie gevonden voor zowel aantal symptomen als mate van persistentie wat betreft het vergroten van het risico op een DSM-IV bipolaire stoornis en het krijgen van psychische hulp. Nog interessanter is echter, dat de combinatie van een hoog aantal symptomen met een hoge mate van persistentie (i.c. veel symptomen gedurende langere tijd) het grootste risico op een stoornis of psychische hulp gaf. De resultaten ondersteunen de continuüm theorie voor bipolaire stoornis en benadrukken het belang van longitudinale vervolging van adolescenten met affectieve symptomen.

Hoofdstuk 4 beschrijft een longitudinale studie (de EDSP-studie) waarin voor zowel (hypo)mane symptomen als bipolaire symptomen (i.c. depressieve symptomen in het kader van (hypo)mane symptomen) bepaald wordt of risicofactoren (i) het risico op het ontstaan van symptomen kan verhogen en (ii) het risico op het persistent worden van de (doorgaans tijdelijke) symptomen kan verhogen. De risicofactoren die worden onderzocht zijn een positieve familiegeschiedenis voor stemmingsstoornissen, negatieve life events (trauma/verlies van ouder), middelengebruik (alcohol/cannabis), ADHD en temperament/persoonlijkheidsfactoren. De resultaten tonen aan dat cannabis gebruik en "novelty seeking" het risico op het ontstaan van (hypo)mane symptomen verhogen, terwijl trauma, "novelty seeking" en "harm avoidance" geassocieerd zijn met een toegenomen ontstaan van bipolaire symptomen. Novelty seeking verlaagt het risico op persistentie van (hypo)mane symptomen terwijl "reward dependence" het risico op persistentie van bipolaire symptomen doet toenemen. Geconcludeerd wordt dat afwijkingen in de stemming in de context van bipolaire stoornis mogelijk stapsgewijs ontstaan en dat verschillende biologische en

psychologische mechanismen ten grondslag zouden kunnen liggen van de (hypo)mane en depressieve dimensie van bipolaire stoornis.

Hoofdstuk 5 biedt een overzicht van de belangrijkste bevindingen van de voorgaande hoofdstukken. Een interactief ontwikkelingsmodel wordt geïntroduceerd waarin deze bevindingen geïntegreerd kunnen worden. Een diepgaandere discussie van mogelijke biopsychologische mechanismen vindt plaats die de verschillende kenmerken van het model kunnen verklaren. Tot slot worden klinische implicaties van de bevindingen gegeven en aanbevelingen voor toekomstig onderzoek gedaan.

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Curriculum Vitae

Marijntje Tijssen werd geboren op 6 mei 1983 in Melick. Nadat zij succesvol het Gymnasium afsloot aan het Bisschoppelijk College Schöndeln, begon ze in 2001 aan de opleiding Geneeskunde aan de Universiteit Maastricht. Gedurende deze opleiding heeft ze op verschillende stageplaatsen ervaring opgedaan in de psychiatrie, waaronder onder meer een stage in de kinderpsychiatrie op de Child and Family Therapy Unit van het Royal Children's Hospital te Brisbane, Australië en een sociale psychiatrie stage bij een 'Assertive Community Treatment' team van Psycope Maastricht. Tijdens het laatste jaar van haar opleiding Geneeskunde (2006-2007) volgde ze een wetenschapsstage op het gebied van de bipolaire stoornis bij de sectie Sociale Psychiatrie en Psychiatrische Epidemiologie van de Capaciteitsgroep Psychiatrie en Neuropsychologie. Voor deze stage, die plaatsvond in samenwerking met het Max-Planck Instituut voor Psychiatrie te München, Duitsland, ontving zij in 2007 de Studentenprijs van de Stichting Wetenschapsbeoefening Universiteit Maastricht 2007. Na afronding van haar studie werd deze stage middels een Kootstra Fellowship van de Universiteit Maastricht, faculteit Geneeskunde voortgezet als promotietraject. Per 1 april 2008 is ze in opleiding tot psychiater bij de Universitaire Opleiding Psychiatrie Zuid Limburg.

List of publications

SUBMITTED PAPERS

Tijssen MJA, Van Os J, Wittchen HU, Lieb R, Beesdo K, Mengelers R, Krabbendam L, Wichers MC. Evidence that bipolar disorder is the poor outcome fraction of a common developmental phenotype: an 8-year cohort study in young people. Submitted.

Tijssen MJA, Van Os J, Wittchen HU, Lieb R, Beesdo K, Mengelers R, Wichers MC. Prediction of transition from common adolescent bipolar experiences to bipolar disorder. Submitted.

Tijssen MJA, Van Os J, Wittchen HU, Lieb R, Beesdo K, Wichers MC.
Risk factors predicting onset and persistence of subthreshold expression of bipolar psychopathology among youth from the community. Submitted.