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What clinical features precede the onset of bipolar disorder?

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ABSTRACT

Despite a growing number of reports, there is still limited knowledge of the clinical features that precede the onset of bipolar disorder (BD). To explore this, we investigated baseline data from a prospectively evaluated longitudinal cohort of subjects aged 12–30 years to compare: first, lifetime rates of clinical features between a) subjects at increased genetic risk for developing BD ('AR'), b) participants from families without mental illness ('controls'), and c) those with established BD; and, second, prior clinical features that predict the later onset of affective disorders in these same three groups. This is the first study to report such comparisons between these three groups (though certainly not the first to compare AR and control samples). 118 AR participants with a parent or sibling with BD (including 102 with a BD parent), 110 controls, and 44 BD subjects were assessed using semi-structured interviews. AR subjects had significantly increased lifetime risks for depressive, anxiety and behavioural disorders compared to controls. Unlike prior reports, preceding anxiety and behavioural disorders were not found to increase risk for later onset of affective disorders in the AR sample, perhaps due to limited sample size. However, preceding behavioural disorders did predict later onset of affective disorders in the BD sample. The findings that i) AR subjects had higher rates of depressive, anxiety and behavioural disorders compared to controls, and ii) prior behavioural disorders increased the risk to later development of affective disorders in the BD group, suggest the possibility of therapeutic targeting for these disorders in those at high genetic risk for BD.

1. Introduction

There is a growing interest in identifying the earliest stages of bipolar disorder (BD) (Berk et al., 2014; Scott et al., 2013) so as to ultimately enable the capacity for developing early intervention programs for this condition (Mitchell et al., 2013). As BD is a strongly genetic disorder (McGuffin et al., 2003; Mortensen et al., 2003) which usually presents in late adolescence or the early twenties (Merikangas et al., 2007), prospective longitudinal studies of cohorts at high genetic risk provide the potential means for identifying early features of this condition, in terms of both baseline differences compared to controls and, moreover, those features that are predictive of the later development of mania or hypomania.

There has been a growing but still relatively small number of reports of such high-risk BD studies, both cross-sectional and longitudinal. A recent major example which epitomises the expected rates of "conversion" to BD in such cohorts came from the Dutch high risk bipolar cohort (Mesman et al., 2013). That paper reported 13% of the offspring of parents with bipolar I or II disorders developing some form of BD spectrum by the 12-year follow-up.

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The striking finding – from both the longitudinal reports and cross-sectional studies comparing high risk groups to controls – is the high rate and broad range of psychopathology reported in this population. The prospective Dutch study (Mesman et al., 2013) reported that by 12 years, 72% had developed at least one lifetime DSM-IV disorder. Fifty-four percent had experienced some mood disorder (mainly depression), 27% an anxiety disorder, 25% a substance use disorder (SUD), and 8% a disruptive behavioural disorder. Similarly, cross-sectional comparisons of populations of high-risk young people have also reported a greater prevalence of lifetime non-affective psychiatric diagnoses such as anxiety, disruptive behavioural disorders and SUDs when compared to control and major depressive disorder samples (Birmaher et al., 2009; Duffy et al., 2014; Hillegers et al., 2005; Leopold et al., 2014; Nurnberger et al., 2011; Shaw et al., 2005; Vandeleur et al., 2012; Wals et al., 2001; Whalley et al., 2011).

Another issue arising from recent studies is whether the risk to developing later depression or BD in these high risk families is increased by the prior occurrence of non-affective conditions. Two groups have reported that the prior onset of anxiety disorders, behavioural disorders and SUDs increase the risk for developing later affective disorders (Duffy et al., 2007, 2010, 2014; Nurnberger et al., 2011).

Most studies of BD high-risk subjects have compared findings against control subjects with no family history of severe mental illness. However, also comparing those at high-risk to those with established BD may provide complementary information on both the prior developmental trajectory and comorbid characteristics of the condition. To date, there has only been one such study (Goldstein et al., 2010) which compared rates of lifetime comorbid disorders in high-risk offspring without BD against high-risk offspring with BD. It demonstrated that those with BD have higher lifetime rates of anxiety disorders, oppositional defiant disorder or conduct disorder, and ADHD compared to those without BD.

This current study is novel in comparing rates and ages of onset of a range of psychiatric disorders between three groups: i) those genetically at-risk for developing BD who have not yet developed this condition (i.e. those with a first-degree relative with the disorder) – the 'AR' group; ii) those with no family of significant psychiatric history – 'controls'; and iii) those with established BD (with or without a family history of BD) – the 'BD' group. All subjects were within the age range of 12–30 years. As detailed above, there have been a number of prior studies which have compared AR and control samples.

The focus of this study was on clarifying the clinical features that precede the onset of bipolar disorder. We hypothesised that: i) AR subjects would have higher lifetime rates of depressive, anxiety and behavioural disorders compared to controls; and ii) within the AR and BD cohorts, onset of anxiety and behavioural disorders would precede the onset of their first major mood episode.

2. Method

The study was conducted with the approval of the University of New South Wales Human Research Ethics Committee (HREC Protocol 09/104) and the South Eastern Sydney Illawarra Health Service HREC (Protocol 09/097) in Sydney, Australia. Written informed consent from all participants was obtained and additional parental consent was obtained for participants under the age of 16. Recruited participants are involved in an ongoing longitudinal study with annual follow-up evaluations. The clinical protocol for those aged between 12 and 21 years of age was identical to that for a NIMH-funded collaborative prospective study of an at-risk cohort (Nurnberger et al., 2011), but there was no overlap between the sample described in this paper, and that of Nurnberger et al. (2011).

2.1. Ascertainment and assessments

AR and BD participants were recruited from: families who had previously participated in a BD pedigree molecular genetics study or a specialised BD research clinic; clinicians; mental health consumer organisations; publicity through print and electronic media; and noticeboards in universities and local communities. (The majority of AR and BD subjects were recruited via print and electronic media publicity). Control subjects were recruited from print and electronic media, and noticeboards in universities and local communities.

AR subjects were defined as first degree relatives – children or siblings – of a proband with a confirmed DSM-IV-TR diagnosis of BD I or II. As confidence in the validity of the proband BD diagnosis was critical to this study, only those AR subjects with confirmed proband consensus best-estimate BD diagnoses based on the Diagnostic Interview for Genetic Studies (DIGS v. 4, Nurnberger et al., 1994), the Family Interview for Genetic Studies (FIGS, (Maxwell, 1992)) and medical records (where available) were included.

Controls were defined as those without a parent or sibling with BD I or II, recurrent major depression (MDD), schizoaffective disorder, schizophrenia, recurrent substance abuse or any past psychiatric hospitalisation; and those who did not have a second degree relative who had a past mood disorder hospitalisation or history of psychosis.

AR and control participants with a lifetime or current presence of psychiatric symptoms (apart from the occurrence of BD) were not excluded from the study; this ecological approach has been used by similar studies of individuals at high genetic risk for BD (Nurnberger et al., 2011).

All potentially interested subjects underwent an initial screening process which involved a brief family history of psychiatric diagnoses and general information about affected relatives. The Family Interview for Genetic Studies (FIGS) (Maxwell, 1992) was administered to all participants at baseline entry to determine any family history of affective disorders. For those aged between 12 and 21 (in all three groups), at least one parent had to be available to complete the FIGS and the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Present and Lifetime Version (K-SADS-BP) (Kaufman et al., 1997; Nurnberger et al., 2011) about their participating child. The K-SADS-BP was administered to both the parent and child; ratings from both the parent and child were then used to determine summary ratings for each symptom. The Diagnostic Interview for Genetic Studies, DIGS v. 4 (Nurnberger et al., 1994), was administered to all participants aged between 22 and 30, and the BD proband (parent or sibling) of all AR participants to confirm proband diagnosis. Similarly, parents of the control participants completed the DIGS to confirm eligibility into the study.

All clinical interviewers possessed at least an honours degree in psychology with some possessing postgraduate degrees in psychology-related fields. Interviewers were extensively trained by a clinical research manager from one of the collaborating US sites, the principal investigator and the study coordinator.

2.2. Diagnostic procedure

Using the Best Estimate Methodology (Leckman et al., 1982), lifetime diagnoses and age of onset were determined by the consensus of two independent raters (psychiatrists) who were blind to the family status of participants. This approach combined information from the DIGS or the K-SADS-BP, the FIGS, and medical records (where available) in order to determine whether the participant met diagnostic criteria for a lifetime DSM-IV-TR diagnosis and its age of onset. For each diagnosis, the independent