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Pre-onset risk characteristics for mania among young people at clinical high risk for psychosis

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ABSTRACT

Introduction: Psychosis and mania share conceptual, genetic and clinical features, which suggest the possibility that they have common antecedents. Participants identified to be at-risk for psychosis might also be at-risk for mania. We aimed to identify the rate and predictors of transition to mania in a cohort of youth with clinical or familial risk for psychosis.

Methods: Among a cohort of 416 young people with an at-risk mental state for psychosis defined using the Ultra-High-Risk (UHR) criteria, 74.7% were followed up between 5 and 13 years from their baseline assessment. We undertook a matched case-control examination of those who developed mania over the follow-up period compared to those who did not develop mania or psychosis. Transition to mania was determined using either a structured clinical interview, or diagnoses from a state-wide public mental health contact registry. Clinical characteristics and risk factors were examined at baseline using information from structured interviews, clinical file notes, rating scales and unstructured assessments.

Results: Eighteen participants developed mania (UHR-Manic transition or UHR-M, 4.3%). In comparison with participants matched on age, gender and baseline-study who developed neither mania nor psychosis, more UHR-M participants had subthreshold manic symptoms or were prescribed antidepressants at baseline. They also had lower global functioning.

Discussion: In addition to the UHR criteria, features such as subthreshold manic symptoms and antidepressant use may help identify at-risk groups that predict the onset of mania in addition to transition to psychosis. Presence of manic symptoms may also indicate syndrome specificity early in the prodromal phase.

1. Introduction

Prediction of the onset of mania may assist in prevention efforts and help to decrease the disability associated with this disorder (Bechdolf et al., 2012). Early or preventive interventions (Berk et al., 2007b) may also help prevent the possible decline in neurocognition (Lewandowski et al., 2011) or the risk of recurrence (Gignac et al., 2015) associated with onset of one or more manic episodes. Hence, methods to define clinical at-risk stages for bipolar disorder (BD) before the onset of frank manic episodes are important. Several findings point to a relationship between psychotic symptoms and risk of development of BD. These include the genetic overlap between schizophrenia and BD (Smoller, 2013), common therapeutic agents and the common structural and functional brain changes, cognition and peripheral markers (Clementz et al., 2016) seen across the two disorders. Psychosis-at-risk samples may, thus, represent one of the common at-risk stages for BD, or more specifically, mania.

Previous studies in at-risk cohorts for psychosis (Olvet et al., 2010) have been limited by the lack of information on characteristics such as sub-threshold mood symptoms, which may represent a useful risk

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identification approach prior to the onset of mania (Berk et al., 2007a). A meta-analysis of transition from at-risk cohorts (Fusar-Poli et al., 2013) identified that 6% developed BD, but no specific predictors of transition to BD were identified. Those who developed a broader group of affective psychoses had a lower mean age at baseline and were less likely to be identified using 'basic symptoms'. Further characterisation of pre-manic states may help identify a sub-group of participants within psychosis-at-risk clinical services. Additionally, such characteristics may add to the understanding of clinical prodromal characteristics for manic episodes. Several such characteristics have been identified to be predictive of later mania in longitudinal studies including the presence of a family history of bipolar disorder (Duffy et al., 2009), substance use disorders (Henquet et al., 2006), antidepressant use (Strober and Carlson, 1982), subthreshold manic symptoms (Fiedorowicz et al., 2011), anxiety symptoms (Gilman et al., 2012)and severity of depression (Holma et al., 2008). An association between these factors and later mania in psychosis-risk samples may help enrich such samples for prediction of onset of mania.

Thus, the aims of this study were: (i) to determine the proportion who transitioned to mania; and (ii) identify the clinical risk factors associated with the onset of mania, among help-seeking youth aged 15–30 years who were identified as ultra-high-risk (UHR) for psychosis. As the study was exploratory, no a-priori hypotheses were posited.

2. Method

We conducted a matched case-control examination of baseline clinical and research data within a large prospective cohort of help-seeking young people at ultra-high risk (UHR) of developing psychosis (Yung et al., 2012; Yung et al., 2004) and who were selected based on their inclusion in five research studies at baseline.

2.1. Participants

All participants were part of a cohort of 416 young people aged 15 to 30 years, were help-seeking and met criteria for being at UHR for psychotic disorder. The participants were recruited from a specialist clinic – the Personal Assessment and Crisis Evaluation (PACE) clinic – in a publicly funded youth mental health service in Melbourne, Australia. The referral characteristics of the PACE clinic (Yung et al., 2007), and the UHR features for psychosis (Yung et al., 2012), have been previously described. Briefly, all participants had one or more of the following criteria: (i) attenuated psychotic symptoms; (ii) brief limited intermittent psychotic symptoms; and/or (iii) trait vulnerability for psychotic illness (schizotypal personality disorder or history of psychosis in a first-degree relative) along with deterioration in functioning or chronic low functioning. The exclusion criteria for entry to PACE clinic included a previous psychotic episode, an organic cause for presentation, and past total antipsychotic exposure equivalent to a haloperidol dosage of more than 15 mg. A detailed description of the cohort has been previously published (Lin et al., 2015; Nelson et al., 2013). In addition, participants with full threshold BD I or II at baseline were excluded from the examination of incident mania in this study. Participants included in this study were recruited for five baseline studies focusing on: (i) prediction of onset of psychosis (Yung et al., 2003); (ii) stress-vulnerability (Thompson et al., 2007); (iii) randomized intervention of risperidone vs placebo (McGorry et al., 2002); (iv) open label intervention using lithium (Berger et al., 2012); and (v) longitudinal monitoring (Phillips et al., 2009). The lithium intervention was not aimed at (sub)threshold manic or affective symptoms, but was an open label intervention for attenuated psychotic symptoms related to UHR status (Berger et al., 2012). Thus, these studies represent a sub-proportion of young people referred to the PACE clinic and who consented to research studies at the clinic. Assessments in these studies were conducted by trained research assistants. The studies associated with this project were approved by the Melbourne Health Human Research Ethics Committee, and all participants provided written informed consent.

2.2. Baseline measures and risk variables

The baseline data on subthreshold symptoms, use of substances or antidepressants and family history were extracted by the first author (AR, a consultant psychiatrist) from a number of sources including: (i) the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I/P, First et al., 1997), including additional notes made by baseline assessors; (ii) Family Interview for Genetic Studies (FIGS, Maxwell, 1992); and (iii) patients' clinical files. In case of discrepancies across these sources, these were resolved using clinical judgment of the first author. BD I or II at baseline were excluded as possible diagnoses for all participants in the current study using SCID-I/P.

The clinical risk factors examined at baseline included:

i. *subthreshold manic symptoms*, defined as two or more mania symptoms at threshold/sub-threshold severity (rated 2 or 3 on the SCID-I/P) coded within the Current or Past section of mania or hypomania in SCID-I/P;
ii. *depression* documented in SCID-I/P as major depressive episodes or minor depressive episodes;
iii. *family history* of bipolar disorder, schizophrenia and/or psychotic disorders, and depression among first or second degree relatives. This was examined first in the ratings on the FIGS and if this information was not available, then by examining the assessment proforma in clinical files;
iv. *substance use,* primarily alcohol, cannabis and stimulants, as recorded in the Substance Use Questionnaire (Phillips et al., 2002). This instrument provided details on the ratings of frequency of use in the 'previous month' or 'lifetime before'. This was supplemented by information from clinical records. Cannabis or alcohol use was defined as more than once monthly use, as a categorical variable of 'lifetime use';
v. *symptom severity* measured using the Brief Psychiatric Rating Scale - total score ((BPRS, Overall and Gorham, 1962)), Scale for Assessment of Negative Symptoms ((SANS, Andreasen, 1984)), Hamilton Rating Scale for Depression ((HRSD, Hamilton, 1960)), and the Comprehensive Assessment of At-Risk Mental States ((CAARMS, Yung et al., 2005));
vi. *functioning* as measured by the Global Assessment of Functioning scale ((GAF, Endicott et al., 1976)) and Heinrichs Quality of Life Scale ((QLS, Heinrichs et al., 1984)).
vii. *medication use* as described in clinical files. A participant was considered to have had significant medication exposure if the clinical note indicated prescription of these medications on at least two occasions without documented non-compliance to this medication.

2.3. Follow-up

Among the participants initially assessed between 1993 and 2006, 74.8% (311) were followed up between 5 and 13 years later. The participants included in the study were followed up in two waves; first from October 2007 to May 2009 and the second from August 2012 to December 2013. In each follow-up wave, we contacted the participants and reassessed them using the SCID-I/P via face-to-face (64.4%) or telephone interviews (9.6%). If the participants could not be contacted, the state-wide mental health registry was examined to determine if there had been contact with public mental health services and the diagnoses provided if such contact had occurred. Given the accessibility of public mental health services for significant episodes of mental illness in Victoria, requirements of the local mental health legislation, limits of private practice services in Australia, and the high reliability of clinical diagnoses of BD I disorder diagnoses in general (Regier et al., 2013;

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