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Research report

Distinguishing young people with emerging bipolar disorders from those with unipolar depression

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ABSTRACT

Background: To facilitate early intervention, there is a need to distinguish unipolar versus bipolar illness trajectories in adolescents and young adults with adult-type mood disorders.
Methods: Detailed clinical and neuropsychological evaluation of 308 young persons (aged 12 to 30 years) with moderately severe unipolar and bipolar affective disorders.
Results: Almost 30% (90/308) of young people (mean age = 19.4 ± 4.4 yr) presenting for care with affective disorders met criteria for a bipolar-type syndrome (26% with bipolar *I*). Subjects with bipolar- and unipolar-type syndromes were of similar age (19.8 vs. 19.2 yr) and reported comparable ages of onset (14.5 vs. 14.3 yr). Clinically, those subjects with unipolar and bipolar-type disorders reported similar levels of psychological distress, depressive symptoms, current role impairment, neuropsychological dysfunction and alcohol or other substance misuse. Subjects with unipolar disorders reported more social anxiety ($p < 0.01$). Subjects with bipolar disorders were more likely to report a family history of bipolar (21% vs. 11%; [$\chi^2 = 4.0$, $p < .05$]) or psychotic (19% vs. 9%; [$\chi^2 = 5.5$, $p < .05$]), or substance misuse (35% vs. 23%; [$\chi^2 = 3.9$, $p < .05$]), but not depressive (48% vs. 53%; $\chi^2 = 0.3$, $p = .582$]) disorders.
Conclusions: Young subjects with bipolar disorders were best discriminated by a family history of bipolar, psychotic or substance use disorders. Early in the course of illness, clinical features of depression, or neuropsychological function, do not readily differentiate the two illness trajectories.

1. Introduction

There is international recognition of the degree of premature death and disability attributable to affective disorders—reflecting their early age-of-onset, high population prevalence, chronicity, comorbidity with physical illness and the degree of resultant impairment (Gustavsson et al., 2011; Lopez et al., 2006). The evidence-base for choosing the most relevant treatments for adolescents and young adults with significant mood disorders is sparse (Allen et al., 2007; Hickie, 2011; Hickie and McGorry, 2010; Insel, 2007; McDermott et al., 2010). To advance the design of pharmacological, cognitive or behavioural intervention trials (Hickie, 2011; McGorry et al., 2006, 2009), there is an urgent need to identify various distinctive phenotypes (and, hopefully, related specific therapeutic targets) earlier in the illness course.

Earlier identification of those who are at risk of a bipolar-type illness has been prioritised, since these individuals appear to have a less consistent response to conventional antidepressant therapies, are at risk of developing manic or psychotic episodes and experience the social and neurobiological harm that may result from development of more frequent depressive, manic or hypomanic episodes (Axelson et al., 2011; Berk et al., 2007; Duffy et al., 2010; Perugi et al., 2000; Soreca et al., 2009; Tijssen et al., 2010). A further consideration is whether quite specific neuroprotective strategies should be initiated early in the course of those with bipolar disorders (Berk et al., 2010a, 2010b, 2009; Conus et al., 2010).

Much previous work has determined (cross-sectionally or retrospectively) the illness characteristics of older subjects with well-established bipolar disorders. Proposed identifying factors have included: specific clinical features (e.g., early age of onset, childhood anxiety, brief hypomanic episodes, psychomotor retardation, sleep–wake cycle disruption, severe concurrent anxiety, psychotic features, comorbid substance misuse); family history (bipolar disorder, suicide or severe depression); neuropsychological features; or, adverse or no response to specific antidepressant treatments (see reviews (Mitchell et al., 2008, 2009; Mitchell and Malhi, 2004)). Such discriminating factors are more evident when bipolar subjects are limited to those with bipolar *I* (i.e., clear manic episode) disorders. Where studies have also included subjects with bipolar *II* or spectrum disorders (Angst et al.,

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2011; Parker et al., 2011; Parker and Fletcher, 2009), distinctive clinical features have been less evident.

To date, the search for specific factors that clearly differentiate adult-type bipolar disorders from other unipolar phenotypes, *early in the illness course* (and preferably before the first manic episode), has yielded limited results (Berk et al., 2007; Conus et al., 2010; Duffy, 2010; Duffy et al., 2007, 2010, 2011). Drawing on experiences with early psychosis, the field has attempted to characterise a 'prodromal' period (Berk et al., 2007; Conus et al., 2010), and import 'clinical staging' from general medicine (McGorry et al., 2006, 2007). As well, key high-risk cohort studies have been established (Duffy, 2010; Duffy et al., 2007, 2010, 2011; Nurnberger et al., 2011; Tijssen et al., 2010). However, this body of work tends to indicate that most of these syndromes share many clinical as well as genetic, neuropsychological and neurobiological features (Fornito et al., 2007; Hermens et al., 2010, 2011; Kaur et al., in press; Kaur et al., 2011; Mitchell et al., 2011; Murray et al., 2004; Olley et al., 2005).

Recent analysis of epidemiological evidence from 10,123 US adolescents has indicated that adolescence, rather than early or later adulthood, is the peak period of onset of mania and hypomania; that is, it should be the period at which bipolar disorder (or unipolar mania) could be first diagnosed and effectively treated (Merikangas et al., 2012). Of those aged 13–18 yr, 2.5% met criteria for lifetime bipolar *I* or *II* disorder, and 1.7% for mania only, with a further 7.6% of subjects having major depression only (i.e., about 35% of affective disorder cases having manic or hypomanic features). The same study reported almost a two-fold increase in rates of mania from ages 13–14 to 17–18 yr. Further, mania with depression (i.e., classical bipolar disorder) was associated with a greater number of all indicators of clinical severity and role impairment (and was more likely to be treated), compared with unipolar depression.

There is increasing concern that a diagnosis of bipolar disorder is often delayed and, therefore, appropriate primary and secondary preventive treatments are not delivered early in the course of illness (Berk et al., 2011, 2010a; Highet et al., 2004; Howes and Falkenberg, 2011; Mitchell et al., 2011). This is despite recent evidence that (hypo)manic symptoms are evident in early adolescence (Merikangas et al., 2012) and may become persistent and represent a risk state that may progress to full-blown, clinically relevant bipolar disorder (Axelson et al., 2011; Tijssen et al., 2010). While true bipolar disorder in adolescence is associated with a 1 in 5 suicide attempt rate and nearly two months per year of role impairment, manic episodes alone also result in considerable role impairment (Merikangas et al., 2012).

The lack of clear phenotypic (or neurobiological) predictors of those at risk of developing adult-type bipolar disorders is a major impediment to the design and implementation of specific early intervention studies. To advance this work, there is an ongoing need to examine relevant phenotypic features, neuropsychological function, patterns of comorbidity, family history, childhood risk factors and other neurobiological features in cohorts of adolescents or young adults presenting for care early in the course of more severe mood disorders.

However, it is essential that the predictive capacity of such features be evaluated specifically in subjects who may be suitable for early intervention (i.e., those who are at early clinical stages of relevant affective disorders and are presenting for care or via other high-risk strategies) studies (Hickie et al., in press; McGorry et al., 2009; Scott et al., 2012). As part of that wider research program, we investigate here the extent to which young individuals presenting with more severe unipolar versus bipolar-type disorders differ in terms of demographic factors, depressive and anxiety symptoms, disability, patterns of comorbidity, neuropsychological function or family history characteristics.

2. Methods

Three hundred and eight outpatients aged 12 to 30 years were recruited from our wider network of services for the assessment of mental health problems in young people (Scott et al., 2012). Subjects for this report were included on the basis of: (i) having a primary diagnosis of an affective disorder (as determined by an experienced clinical psychiatrist—principally EMS or IBH); *and* (ii) their participation in more detailed neuropsychological, neuroimaging and longitudinal follow-up studies. All patients were receiving clinician-based case management and relevant psychosocial interventions at the time of detailed clinical and neuropsychological assessment.

Exclusion criteria for all participants were medical instability (as determined by a psychiatrist), history of neurological disease (e.g., tumour, head trauma, epilepsy), medical illness known to impact cognitive and brain function (e.g., cancer, ECT in last 3 months), intellectual and/or developmental disability (a predicted IQ score <70) and insufficient English for testing or psychiatric assessment. The study was approved by the University of Sydney Human Research Ethics Committee and all participants gave written informed consent.

2.1. Clinical assessment

An independent psychiatrist or trained research psychologist/neuropsychologist conducted a structured clinical interview (see below) to assign a DSM-IV (APA, 2000) diagnosis, as well as to characterise the broader nature, history and clinical course of any mental health problems. As a measure for the onset of illness, the age that each patient first engaged a health service for their mental health problem was recorded. In addition to the Hamilton Depression rating Scale (HDRS), the interviewer completed the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) to quantify general psychiatric symptoms (specifically close to the time of neuropsychological assessment rather than on entry to the services). The clinician also completed the social and occupational functioning assessment scale (SOFAS) (Goldman et al., 1992), where a patient's functioning is rated from 0 to 100, with lower scores suggesting more severe impairment.

Subjects completed self-report measures which included role impairment items from the Brief Disability Questionnaire ('days out of role in the last 4 weeks', BDQ; (Von Korff et al., 1996) as well as the complete versions of the Depression Anxiety and Stress Scales (DASS) (Lovibond and Lovibond, 1995); the Kessler-10 (K-10) (Kessler et al., 2002) which is a brief instrument designed to detect severity of general psychological distress (Andrews and Slade, 2001); and the Social Interaction Anxiety Scale (SIAS) (Mattick and Clarke, 1998) which assesses fears of general social interaction.

2.2. Determination of unipolar versus bipolar syndrome status

All subjects were assessed by a senior clinician (psychiatrist or clinical psychologist) and, on at least one separate occasion by a research psychologist/neuropsychologist using our 'BMRI Structured Interview for Neurobiological Studies'. Both of these procedures focus on reviewing critical illness course variables. They include rating the likelihood that the young persons had ever had a manic or hypomanic episode, or had an illness course consistent with a bipolar spectrum disorder. As a significant proportion were receiving ongoing treatment at our service (or participating in longitudinal research), the opportunity to identify these bipolar-type characteristics longitudinally (i.e., over the episode of illness or subsequently), was maximised. After completion of this detailed diagnostic process, subjects were assigned by consensus