Journal of Affective Disorders 147 (2013) 441–445

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Brief report

Neurocognitive functioning in the prodrome of mania—an exploratory study

Aswin Ratheesh [a,*], Ashleigh Lin [b], Barnaby Nelson [c], Stephen J. Wood [b], Warrick Brewer [c], Jennifer Betts [c], Michael Berk [c,d,e], Patrick McGorry [a,c], Alison R. Yung [a,c], Andreas Bechdolf [c,f]

[a] Orygen Youth Health, Melbourne, Australia
[b] School of Psychology, University of Birmingham, UK
[c] Orygen Youth Health Research Centre, Centre for Youth Mental Health, University of Melbourne, Australia
[d] Deakin University, Geelong, Australia
[e] Mental Health Research Institute, Parkville, Australia
[f] Department of Psychiatry and Psychotherapy, University of Cologne, Germany

ARTICLE INFO

Article history:
Received 6 July 2012
Received in revised form
16 September 2012
Accepted 16 September 2012
Available online 8 November 2012

Keywords:
Bipolar
At-risk
Prodrome
Mania
Cognition
Psychosis

ABSTRACT

Background: Cognitive deficits have been well documented in individuals with bipolar disorder (BD) after the first episode of mania. However, little is known about the presence of such deficits prior to the initial manic episode.
Methods: Participants were recruited from a cohort of 416 young people who were at ultra-high risk (UHR) for psychosis and were followed up between 4 and 13 years later. The current report is of 16 participants who developed BD over a mean follow-up period of 8.2 years (UHR-BD). Baseline demographic, clinical and neurocognitive assessment scores were compared with those of 46 age and gender matched UHR subjects who did not transition to psychosis or BD over the follow-up period (UHR-NT) and 66 healthy comparison subjects.
Results: UHR-BD subjects had lower global functioning at baseline compared with UHR-NT subjects. There were no significant differences between UHR-BD and UHR-NT subjects on baseline demographic and neurocognitive characteristics. UHR-BD subjects had lower test performance than HC on picture completion, Trail-Making Tests and measures of global intelligence.
Limitations: Small sample size, limited and variable neurocognitive tests utilised and the confounding effects of psychotic symptoms might have impacted on the ability to detect meaningful clinical and neurocognitive differences.
Conclusions: In this exploratory study, neurocognition in young people who later develop BD is similar to those of subjects who are at a high risk for psychotic disorders, but there may be certain neurocognitive markers that distinguish this group from unaffected and healthy young people.

1. Introduction

Early intervention for bipolar disorder (BD) may hold promise for delaying or preventing disability associated with the illness (Berk et al., 2010). Cognitive dysfunction is of significant interest because of the relationship between cognition and functional disability in adults with BD (Kumar, 2010; Wingo et al., 2009). Cognitive dysfunction has been studied extensively during the symptomatic and euthymic stages of the illness (Lewandowski et al., 2011; Wingo et al., 2009), but the course of these deficits in early illness or the "at-risk" period are less understood (Lewandowski et al., 2011).

Genetic studies in asymptomatic first-degree relatives of BD probands have suggested neurocognitive differences compared with healthy controls. A review (Balanza-Martinez et al., 2008) of genetic studies examining cognitive deficits among twins, first-degree relatives and extended family members of probands with BD identified verbal learning and memory, and working memory as the most common deficits, suggesting potential endophenotypic markers of BD. However, the studies directly measured cognitive functioning in young participants who later developed BD show conflicting results. Three studies have investigated neurocognition in young, asymptomatic conscripts to the armed forces and identified BD from linkage to hospital data (Reichenberg et al., 2002;

* Corresponding author. Tel.: +61 3 9342 2800.
E-mail address: Aswin.Ratheesh@mh.org.au (A. Ratheesh).

0165-0327/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jad.2012.09.017

Tiihonen et al., 2005; Zammit et al., 2004). Two of these studies suggested that those who developed BD did not differ from healthy controls on any function (Reichenberg et al., 2002) (Zammit et al., 2004), while the third reported that lower visuospatial functions and higher arithmetic functions at age 20 were associated with greater odds for later BD (Tiihonen et al., 2005). Subjects in the Dunedin Longitudinal Cohort Study who developed BD by age 26 showed no significant differences in IQ measured between ages 3 and 11 compared with controls (Cannon et al., 2002). Alternatively, another prospective study associated BD with lower IQ and set-shifting in early adolescence (Meyer et al., 2004). In addition to the difficulty in drawing conclusions from inconsistent findings, these studies have been of unselected participants who may differ clinically from help-seeking young people.

Research on the clinical and neurobiological markers of progression to BD in help-seeking individuals at-risk for the illness is limited (Bechdolf et al., 2012), but could be important for early intervention strategies. One study examined adolescents at high risk for developing schizophrenia and reported on the baseline characteristics of the subgroup who developed BD (Olvet et al., 2010). These subjects did not differ on IQ or global neurocognition from subjects who did not transition to either schizophrenia or BD. However, it may be that only specific abilities are reduced in the BD prodrome, which are not reflected in global or IQ scores.

In the current study, we examined the baseline neurocognitive ability of young people who were identified as being at ultra-high risk (UHR) for psychosis, but developed BD over a mean follow-up period of 8.2 years.

2. Method

2.1. Participants

Participants were recruited as part of a follow-up study of young people identified as UHR at the PACE Clinic in Melbourne, Australia, between 1993 and 2006 ($N=416$). At identification (baseline), all participants were aged 15–30 years, had not experienced a previous psychotic episode and met UHR criteria, rated on the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005). These are (1) attenuated psychotic symptoms (APS), (2) brief limited intermittent psychotic symptoms (BLIPS), and/or (3) trait vulnerability for psychotic illness (schizotypal personality disorder or a history of psychosis in a first-degree relative) and deterioration in functioning or chronic low functioning (Yung et al., 2003).

Here we report on 16 individuals who were diagnosed with a bipolar illness (I, II or NOS; UHR-BD) over the follow-up period (Mean=8.19, SD=2.97; range= 4.0–12.9 median= 7.8). They were compared to 46 age and gender matched UHR subjects who did not transition to bipolar or psychotic disorders (UHR-NT) over follow-up (Mean=7.99, SD=3.21; range= 3.2–13.4 median=8.4) and 66 healthy control subjects assessed at a similar time.

The local Research and Ethics Committee approved the study. Written informed consent was obtained from all subjects.

2.2. Measures

At baseline, UHR subjects were recruited into various studies with different protocols and assessment batteries (depending on the year they were recruited). Therefore, there is variability in the number of subjects who completed each measure or task. Because this study is exploratory, we have presented available data, and indicated the sample size for each measure.

2.3. Clinical measures

Diagnosis of bipolar illness was established using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1997). UHR status and transition to psychosis were assessed using the CAARMS (Yung et al., 2005). Baseline symptomatology was measured using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), Brief Psychiatric Ratings Scale (BPRS, psychotic subscale) (Overall and Gorham, 1962), Young Mania Rating Scale (YMRS) (Young et al., 1978) and Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960). Global functioning was measured with the Global Assessment of Functioning scale (GAF) (American Psychiatric Association, 2000).

2.4. Neurocognitive measures

Participants were administered various subtests from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981) or the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999). The subtests administered can be viewed in Table 2. IQ was estimated in the following ways: (a) Ward's (Ward, 1990) 7-subtest estimate of verbal, performance and full-scale IQ from the WAIS-R; (b) Kaufman's (Kaufman et al., 1991) 4-subtest estimate of full-scale IQ from the WAIS-R; (c) Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) estimates.

Logical memory I, verbal paired associates I and visual reproduction I from the Wechsler Memory Scale-R (WMS-R) (Wechsler, 1987) provided indices of visual and verbal new learning and memory. The Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1941), modified to three trials, assessed new verbal list learning. Total time on the Trail Making Test (TMT) A and B (Adjutant General's Office, 1944) was used to assess visuomotor speed and attention. Total words on the Controlled Oral Word Association Test (COWAT) (Benton and Hamsher, 1983) indexed verbal fluency.

2.5. Statistical analysis

Demographic data for the UHR-BD, UHR-NT and HC participants were compared using chi-squares, independent samples *t*-tests and ANOVA. The baseline neurocognitive performance of groups was compared using ANCOVA. Raw scores were used and age was entered as a covariate. Post-hoc tests comparing the different groups were performed using Bonferroni tests.

3. Results

3.1. Demographics and clinical characteristics

There were no significant group differences on age, gender, length of follow-up, BPRS, SANS, HAM-D and YMRS scores (see Table 1). Baseline GAF scores were significantly higher in the UHR-NT group than the UHR-BP group ($p=0.01$).

3.2. Baseline neurocognitive test performance

Group comparisons are presented in Table 2. There were significant group differences on verbal IQ, performance IQ and full-scale IQ; picture completion, block design, information and digit symbol coding from the WAIS-R; logical memory; and TMT A and B. Post hoc comparisons showed no significant differences between UHR-BD and UHR-NT on any measure. UHR-BD had significantly lower scores than healthy controls on IQ (Verbal IQ-mean difference [MD]= −12.88, standard error [SE]=4.47, $p=0.014$; performance IQ-MD= −11.82, SE=4.39, $p=0.025$; full-scale IQ-MD= −12.49,