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Research paper

Cognitive abilities in first-degree relatives of individuals with bipolar disorder

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ABSTRACT

Background: Although the study of cognition in first degree relatives (FDRs) is not new, findings in this group are still somewhat inconsistent and much of the research examining FDR populations include individuals under the age of 25, who are arguably still at significant risk to go on to develop BD. The present study aimed to establish the value of cognitive performance as a genuine endophenotypic marker of familial risk for bipolar disorder (BD), by examining cognition in FDRs aged 25 years or older.
Methods: The current study compared the cognitive performance of 27 unaffected FDRs to 47 healthy controls (HCs) and 28 BD patients using the MATRICS Consensus Cognitive Battery (MCCB).
Results: Results indicated that FDRs had impaired verbal learning performance, as well as selective impairments on a measure of speed of processing; and a measure of spatial working memory compared to HC.
Limitations: Limitations relate to the potential insensitivity of some of the tests in the MCCB for detecting cognitive deficits that have been previously noted in BD and FDR samples using other batteries.
Conclusions: Findings from this study implicate verbal learning, processing speed and working memory performance as promising candidate endophenotypes of familial risk for BD.

Cognitive deficits are well documented in bipolar disorder (BD), particularly in the domains of sustained attention, verbal learning and executive functioning (Balanza-Martinez et al., 2008; Bora et al., 2009; Clark and Goodwin, 2004; Douglas and Van Rheenen, 2016; Martinez-Aran et al., 2000; Robinson and Ferrier, 2006; Russo et al., In press; Van Rheenen et al., 2017; Van Rheenen et al., 2016; Van Rheenen and Rossell, 2014a). These deficits are evident during symptomatic episodes, but converging evidence suggests that patients continue to experience persistent cognitive impairment, albeit to a lesser degree, across a range of tasks during symptom remission (Antila et al., 2007b; Arts et al., 2008; Bearden et al., 2010; Bora et al., 2009; Kurtz and Gerraty, 2009; Mann-Wrobel et al., 2011; Martinez-Aran et al., 2004; Robinson et al., 2006; Thompson et al., 2005; Torres et al., 2007). The enduring nature of these deficits suggests that they represent trait rather than state abnormalities of the disorder.

Cognitive impairments observed in unaffected first-degree relatives (FDRs) may serve as endophenotypic markers for BD, particularly if FDRs exhibit an intermediate pattern of performance when compared to BD patients and healthy controls (HC). Investigating cognitive function in healthy individuals with high familial risk of BD, such as unaffected FDRs, can avoid many of the confounds of BD studies, such as medication use, the presence of mood symptoms (either clinical or subclinical), and the possibility that patients have endured lasting neuroanatomical changes as a result of the illness (Antila et al., 2007b; Hellvin et al., 2012). As such, research attention focussed on FDRs offer a unique means by which to explore the heritability of cognitive impairments in BD.

Although the study of cognition in relatives of individuals with BD is not new, findings in this group are still somewhat inconsistent (Balanza-Martinez et al., 2008; Cardenas et al., 2016; Hasler et al., 2006). For example, current work suggests that endophenotypic markers of genetic vulnerability for BD may be represented by deficits in verbal memory (Arts et al., 2008; Balanza-Martinez et al., 2008; Cardenas et al., 2016; Kieseppä et al., 2005; Kulkarni et al., 2010; McIntosh et al., 2005) and selective deficits in aspects of executive function and sustained attention (Arts et al., 2008; Bauer et al., 2016; Bora et al., 2008; Clark et al., 2005b; Ferrier et al., 2004a; Glahn et al., 2004; Nehra et al., 2006; Trivedi et al., 2008; Zalla et al., 2004), since FDRs have shown

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impairments on these domains relative to HCs. Speed of processing and verbal working memory deficits also seem to be related to genetic risk for BD, yet results on these domains are mixed, with some studies evidencing deficits in FDRs and others not (Antila et al., 2007b; Cardenas et al., 2016; Daban et al., 2012; Nehra et al., 2006; Pierson et al., 2000).

Discrepant findings in the literature suggest that the cognitive profile of relatives of BD patients is still unclear and requires replication in well-defined samples; this includes samples in which the modal age of BD onset has been taken into account. Our review of the literature indicates that much of the research examining FDR populations include individuals between the ages of 18–25. As BD typically develops during late adolescence and early adulthood, these individuals are arguably still at significant risk to go on to develop BD (Baldessarini et al., 2012). Thus, assessment of FDRs in this age-bracket blurs understandings of the extent to which cognitive deficits represent true familial risk as opposed to premorbid processes occurring prior to illness onset. The current study aimed to overcome this limitation by comparing the cognitive performance of unaffected FDRs aged 25 years or older, to HCs and BD patients across a battery of cognitive tasks. Hence, we aimed to establish the value of cognitive performance as a genuine endophenotypic marker of *familial* risk for BD. On the basis of previous literature we predicted that unaffected FDRs of individuals with BD would show selective cognitive dysfunction on measures of verbal memory, executive function, and speed of processing when compared to HCs, and that the magnitude of dysfunction would be intermediate to that of BD patients and HCs.

1. Method

This study was approved by the relevant Human Ethics Review Boards and abided by the Declaration of Helsinki. Written informed consent was obtained from each participant before the study commenced.

1.1. Participants

The FDR sample comprised 27 individuals over the age of 25, with a first-degree biological sibling or parent with a diagnosis of BD (I or II) and no current or past history of psychiatric disorder. The clinical sample comprised 28 patients with a DSM-IV-TR diagnosis of BD-I. These BD participants were drawn from a pre-existing database and as such, the neurocognitive performance of parts of this sample has previously been reported (Van Rheenen et al., 2017, 2016, 2014; Van Rheenen and Rossell, 2014a). FDRs were unrelated to individuals in the BD sample in this study to circumvent the effect of shared environmental influences on cognitive performance. A sample of 47 HC participants was recruited for comparison purposes. The Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) was used to screen all participants for psychiatric disorder. Current mood symptomology was assessed using the Young Mania Rating Scale (YMRS) (Young et al., 1978) and the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979).

Exclusion criteria included: i) difficulties with spoken English, ii) a history of traumatic brain injury, iii) hearing or visual impairments, iv) neurological or degenerative illness, v) alcohol or substance abuse/dependence in the past 3 months, vi) pregnancy, vii) an estimated IQ of less than 75 on the Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001), viii) a history of psychotropic medication use such as antidepressants, antipsychotics, benzodiazepines and mood stabilizers (FDRs and HCs), xi) a family history of mood or psychiatric disorder (HCs only) or x) within the age range of 18–65 (HC or BD) or 25–65 years (FDRs). Participants were recruited using general advertisements as well as online websites and social media. Participants were reimbursed for their participation.

1.2. Materials

The MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein and Green, 2006) was used as a measure of cognitive functioning, assessing the domains of attention/vigilance (Continuous Performance Test- identical pairs[CPT-IP]), speed of processing (Tail Making Test –A[TMT-A], Brief Assessment of Cognition in Schizophrenia - Symbol Coding [BACS-SC], Animal Naming), working memory (Wechsler Memory Scale – Spatial Span[WMS-R], Letter-Number Sequencing [LNS]), visual learning (Brief Visual Memory Test-Revised [BVMT-R]) verbal learning (Hopkins Verbal Learning Test Revised [HVLT-R]), reasoning/problem solving (Neuropsychological Assessment Battery [NAB]-Mazes) and social cognition (Mayer-Salovey-Caruso Emotional Intelligence Test [MSCEIT]). The MCCB has been used in BD previously (Burdick et al., 2011a; Van Rheenen and Rossell, 2014a) and shows good test-retest reliability. Supplementary Table 1 provides a summary of the MCCB domain measures and subtests.

1.3. Statistical analysis

Chi square analyses and analysis of variance (ANOVA) with follow-up Least Significant Difference (LSD) *t*-tests were used to compare group differences on key demographic and clinical characteristics. Raw scores on the neuropsychological tests were transformed to standard equivalents (*z*-scores with a mean = 0 and SD = 1) based on the means and standard deviations of the HC group. The TMT-A had a different metric to the other tests and was reversed to be consistent with the other measures, so that higher test scores represented better performance. On domains that comprised more than one test measure (i.e., speed of processing and working memory), a composite score was created from the summed *z* scores; this was then re-standardised. Standardised domain and subtest scores were entered into two separate multivariate analyses of covariance analyses (MANCOVA), with post-hoc LSD correction to assess group differences; age and gender were added into the analyses as covariates *a-priori* given that they are known to be associated with cognitive performance (Lezak et al., 2004; Strauss et al., 2006; Tombaugh et al., 1999). The domains of the MCCB were entered as fixed factors.

Exploratory bivariate correlations were conducted to examine the association of scores of the symptom rating scales (YMRS and MADRS) with cognitive test performance in the BD and FDR group separately. Conservative $\alpha = .01$ was used for all correlational and post-hoc tests to account for multiple testing.

2. Results

2.1. Demographics

Table 1 displays the demographic and clinical descriptives for the sample. As expected, the BD group differed significantly from HCs and FDRs on both the MADRS and YMRS. No significant differences were found between groups on age, premorbid IQ or gender distribution.

2.2. Cognitive performance

There was a significant omnibus group effect for cognitive performance (Pillai's Trace = .34, $F(14, 178) = 2.64$, $p = .002$, $\eta^2 = .17$), with BD patients showing the greatest impairment overall ($M = 31.15$, SD = 7.14), and FDRs ($M = 31.45$, SD = 5.39) performing less accurately than HCs ($M = 32.98$, SD = 5.92). Inspection of each domain showed no group differences for speed of processing ($F(2, 94) = .79$, $p = .460$), attention/vigilance ($F(2, 94) = .17$, $p = .840$), or social cognition ($F(2, 94) = .77$, $p = .470$). Significant group differences were evident for verbal learning ($F(2, 94) = 4.29$, $p = .016$), visual learning ($F(2, 94) = 3.99$, $p = .02$), working memory ($F(2, 94) = 5.76$, $p = .004$) and reasoning/problem solving ($F(2, 94) = 4.22$, $p = .018$).