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Research paper

Neurocognitive functioning in individuals with bipolar disorder and their healthy siblings: A preliminary study

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ABSTRACT

Background: Cognitive deficits have been consistently reported in individuals with bipolar disorder (BD). The cognitive profile of siblings of individuals with BD is, however, less clearly established possibly due to the heterogeneity of neuropsychological measures used in previous studies. The aim of this exploratory study was to assess the cognitive function of siblings of individuals with BD and compare it with that of their first-degree relatives suffering with BD, and healthy controls (HC) using the Cambridge Neuropsychological Test Automated Battery (CANTAB) – a comprehensive and validated computerized cognitive battery.

Methods: We recruited 23 HC (33.52 ± 10.29 years, 8 males), 27 individuals with BD (34.26 ± 10.19 years, 9 males, 25 BDI, 1BDII and 1 BD-NOS), and 15 of their biologically related siblings (37.47 ± 13.15 years, 4 males). Siblings had no current or lifetime history of mental disorders. Participants performed the CANTAB and completed questionnaires assessing mood and global functioning. Multivariate analyses compared CANTAB measures across the three participant groups.

Results: Individuals with BD and their siblings were less accurate in a task of sustained attention (Rapid Visual Processing) when compared to HC. Further, individuals with BD displayed pronounced deficits in affective processing (Affective Go/No-Go) compared to HC. There were no cognitive differences between siblings and individuals with BD. After correcting for current depressive symptoms, these results did not reach statistical significance.

Conclusions: Subthreshold depressive symptoms may be associated with reduced sustained attention in healthy siblings of BD patients. This preliminary result needs to be corroborated by large-scale, longitudinal studies assessing the relationship between cognition and mood in vulnerable individuals.

1. Introduction

Bipolar disorder (BD) is a serious illness characterized by mood fluctuations, brain abnormalities, poor emotional regulation and affective processing, and cognitive deficits that, in the majority of cases, persist across mood phases (Bora et al., 2009). Despite the substantial genetic component of BD and heritability estimates ranging from 70% to 80% (Akiskal, 1996; Chang et al., 2003; DelBello and Geller, 2001; Duffy et al., 2013; Rasic et al., 2013) little is known about the protective and precipitating factors of BD. Current research is, therefore, focusing on early markers of BD in populations at high risk for BD such as siblings of individuals with BD to identify new venues for treatment.

Cognitive deficits are promising vulnerability markers of BD. Prior meta-analyses (Bora et al., 2009; Sweeney et al., 2000) and studies in the field showed that the primary affected domains in BD and, to a lesser extent, their relatives (Bora et al., 2009), are learning and memory, working memory, attention, inhibition and cognitive control (Arts et al., 2008; Bauer et al., 2015b; Gotlib et al., 2005). Affective biases favoring negative material (Gotlib et al., 2005; Peckham et al., 2015) and poor facial affective recognition (Getz et al., 2003; Manelis et al., 2015) are also commonly observed features of BD and their offspring (Bauer et al., 2015a; Brotman et al., 2008).

Surprisingly, there is little data on cognitive functioning and

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processing of affective stimuli (other than facial expressions) in siblings of individuals with BD patients. Previous studies of unaffected siblings found that they scored lower on tests of verbal learning, attention and planning than healthy individuals (Keri et al., 2001; Kulkarni et al., 2010; Nehra et al., 2014; Trivedi et al., 2008). Further, across these studies, siblings display deficits in distinct cognitive domains and their performance usually falls in between that of healthy individuals and BD patients. In agreement with these behavioral findings, functional neuroimaging studies have detected altered patterns of neural activity in prefrontal, cingulate and limbic regions known to be activated during complex cognitive tasks involving response inhibition, cognitive control and affective processing in BD and their relatives (Houenou et al., 2011; Malhi et al., 2005; Morris et al., 2012; Pavuluri et al., 2008; Wessa et al., 2007). Thus, there appears to be strong evidence for a distinct neural and cognitive profile in siblings of individuals with BD. However, previous studies did not use standardized and validated cognitive batteries (Bora et al., 2009) and in the majority of cases, siblings and individuals with BD did not belong to the same family. Further in some studies the sample included individuals of various degrees of closeness to BD patients (Balanzá-Martínez et al., 2008; Trivedi et al., 2008). These findings may be biased by environmental and genetic variance across individuals (Clark et al., 2005). There is therefore a need for additional studies 1. examining a wide range of cognitive abilities in siblings of individuals with BD; 2. using standardized cognitive batteries enabling generalization and comparisons across studies; and 3. comparing cognitive function in BD patients and their healthy biological siblings.

To address these issues, we compared the cognitive performance of individuals with BD, their biological siblings, and healthy controls by using a validated computerized cognitive battery, the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Kim et al., 2014). Given the limited amount of findings related to cognitive performance in siblings we approached our analyses in an exploratory manner.

2. Methods and materials

2.1. Subjects

We recruited 23 healthy controls (HC; 33.52 ± 10.29, 8 males), 15 siblings of bipolar patients (37.47 ± 13.15, 4 males) and 27 individuals with BD (34.26 ± 10.19, 9 males, 25 BDI, 1BDII and 1 BD-NOS). Participants were recruited at the University of Texas Health Science Center at Houston. The local institutional review board approved the study protocol and informed consent was obtained from all the participants. Participants included in this study had no current medical disorder including neurological disorders and traumatic brain injury. Siblings had no current or lifetime of history of mental illness and were enrolled provided they had at least one relative who met criteria for BD as determined via a detailed family history assessment. Common comorbidities were generalized anxiety disorder (n=7), panic disorder (n=7), posttraumatic stress disorder (n=3), social phobia (n=3), agoraphobia (n=3), alcohol abuse (n=3), anxiety disorder (n=1), binge eating disorder (n=3), bulimia (n=4), and seasonal affective disorder (n=11). Participants with history of substance abuse in the six months prior to enrollment, schizophrenia, developmental disorders, eating disorders, and intellectual disability were excluded. The majority of the individuals with BD were medicated (Table 1). HC with a history of any Axis I disorder in first-degree relatives and having taken a prescribed psychotropic medication at any point in their lives were excluded. Female participants of reproductive age underwent a urine pregnancy test. All participants underwent a urine drug screen to exclude illegal drug use.

Table 1
Demographic and Clinical Characteristic of the Sample (mean ± standard deviation).

	HC mean (SD)	Siblings mean (SD)	BD mean (SD)	F/chi-square	p-Value
Age (years)	33.52 (10.29)	37.47 (13.15)	34.26 (10.19)	.591	.557
Female/total	15/23	11/15	18/27	3.844	.428
Bipolar type	–	–	BD-I 25/27 BD-II 1/27 BD-NOS 1/27		
Education (years)	15 (1.68)	14.73 (1.98)	13.81 (2.55)	1.83	.169
WASI	99.83 (12.81)	96.87 (15.77)	97.73 (11.86)	.267	.767
YMRS	.09 (0.29)	.93 (1.53)**	5 (5.91)**	11.096	< **.001**#, ##
GAF	90.39 (4.72)	88.13 (4.36)	63.19 (11.34)**	82.968	< **.001**#
MADRS	.22 (0.6)	1.4 (3.58)**	10.63 (9.25)**	20.214	< **.001**#, ##
Age of onset	–	–	23.41 (8.59)		
Illness duration	–	–	10.85 (8.07)		
Number of episodes			0–3 episodes-3 4–9 episodes-5 > 10 episodes-19		
Currently or previously taken any psychotropic medicine (N/total)	–	2	24/27 (Lithium-6, Antidepressants-9, Anticonvulsants-8, Stimulants-1)		
Current mood	–	–	Euthymic-9 Depressed-11 Manic-4 Hypomanic-1 Mixed-2		
Comorbidities	–	–	GAD- 7 PD- 7 PTSD-3 Social phobia-3 Agoraphobia-3 Alcohol abuse-3 Anxiety disorder-1 Binge eating disorder-3 Bulimia-4 SAD- 11		

Abbreviations: BD: Bipolar Disorder; GAF: Global Assessment of Functioning; GAD: Generalized Anxiety Disorder; HC: Healthy Controls; MADRS: Montgomery–Åsberg Depression Rating Scale, PD: Panic Disorder; PTSD: Posttraumatic Stress Disorder; SAD: Seasonal Affective Disorder; YMRS: Young Mania Rating Scale, WASI: Wechsler Abbreviated Scale of Intelligence.

*p < .05.

** p < .01.

Comparisons: BD vs. HC.

Comparisons: BD vs. siblings.

2.2. Clinical assessment

Psychiatric diagnosis of individuals with BD and their siblings was based on the Structured Clinical Interview for the Diagnostic