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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.

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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 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.

Methods and materials

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 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.

Clinical assessment

Psychiatric diagnosis of individuals with BD and their siblings was based on the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders Axis I (SCID I) (First et al., 2012), and confirmed subsequently in a clinical evaluation with a research psychiatrist. All interviews were administered to participants by trained evaluators, and were later reviewed by a board-certified psychiatrist. The individuals' current affective state was assessed with the Young Mania Rating Scale (YMRS; (Young et al., 1978)) and the Montgomery-Åsberg Depression Rating Scale (MADRS; (Montgomery and Asberg, 1979)). Both instruments have satisfactory psychometric properties (Carmody et al., 2006; Fristad et al., 1995).

Cognitive assessment

The Wechsler Abbreviated Scale of Intelligence (WASI; (Corporation, 1999)) was used to estimate the participant's full-scale intelligence quotient (IQ). Participants were administered the computerized Cambridge Neurocognitive Test Automated Battery (CANTAB - <http://www.cantab.com>). This cognitive battery has well-established sensitivity to cognitive impairment in psychiatric disorders (Barnett et al., 2010; Sweeney et al., 2000). Participants completed tests evaluating processing speed and attention (Match to Sample Visual Search – MTS, Rapid Visual Processing – RVP), working memory (Spatial Span – SSP), inhibition and affective control (Affective Go/No-Go-AGN), decision-making (Cambridge Gambling

Task – CGT), and spatial memory (Spatial Recognition Memory – SRM). Outcome measures of interest across tasks included reaction times (ms) and accuracy (commission errors). Notably, the AGN task consists of blocks of alternating positive and negative stimuli (shift) and blocks with both positive or negative stimuli (non-shift). Each block starts randomly with positive or negative stimuli (e.g. shift positive). Table 1S provides a comprehensive description of the CANTAB tasks included in this study.

Statistical analysis

Statistical analyses were performed using IBM SPSS statistics (Version 21.0). Normality assumptions were examined. Where appropriate, outliers were winsorised and log, square root or reciprocal transformations applied to achieve normality, if appropriate. One-way ANOVAs and χ^2 analyses were used to compare demographic and clinical differences between groups. Multiple ANOVAs were conducted to compare variables within each cognitive task (see outcome measures for each CANTAB task in Table 2S). For the AGN task, we conducted three separate MANOVAs comparing mean latency and commission errors across the shift and non-shift conditions, and latencies and commission errors for each condition, individually. Outcome measures of the RVP task included response latency and number of correct hits. To evaluate the potential effects of current mood on cognitive performance (Basso et al., 2002; del Mar Bonnín et al., 2014) we compared the findings of our analyses before and after covarying for MADRS and YMRS scores. Given the exploratory nature of our analyses, a critical statistical threshold of $p=0.05$ was applied but we reported both uncorrected and Bonferroni-corrected p-values of relevant tests. Retrospective statistical power analyses were computed using G*Power (Faul et al., 2007).

Results

Group characteristics

Demographics and clinical features of the participants included in this study are reported in Table 1. The three groups were comparable in terms of age, gender, intellectual quotient (IQ), and education. There were, however, significant differences between the three groups on the YMRS [$F(2, 64)=11.096$, $p<.001$, partial $\eta^2 = .264$], the MADRS [$F(2, 64)=20.214$, $p<.001$, partial $\eta^2 = .395$] and the GAF [$F(2, 64)=89.968$, $p<.001$, partial $\eta^2 = .728$]. As expected, individuals with BD had higher YMRS and MADRS scores, and lower GAF score compared to their siblings and HC ($p<.01$).

Cognitive functioning

Statistical analyses showed group differences in sustained attention (RVP) ($F(2,61)=3.361$, $p=.041$), specifically related to the number of hits [$F(2, 61)=3.355$, $p=.044$, partial $\eta^2 = .099$]. When compared to HC, siblings of BD patients and patients with BD were less accurate than HC (BD vs HC: uncorrected $p=.045$; BD siblings vs HC: uncorrected $p=.022$). After correcting for multiple comparison the difference in number of hits between BD and HC was no longer significant (corrected $p=.136$), while that between BD siblings vs HC approached significance (corrected $p=.066$) - Table 1 and Figure 1).

Differences in group performance were also found in the latencies to negative and positive stimuli of the “shift” condition of the AGN task ($F(6,118)=2.64$, $p=.019$, partial $\eta^2=.118$). Univariate analyses showed differences in latencies in the “shift positive” condition [$F(2, 60)=4.180$, $p=.020$, partial $\eta^2=.122$], with participants with BD displaying slower response times than HC (BD vs HC: $p=.005$ (uncorrected); $p=.016$ (corrected)). Notably, the “shift positive” condition of the AGN task contains a combination of positive and negative words and starts with a positive stimulus.

After covarying for YMRS scores, uncorrected p-values of AGN latencies in the “shift positive” condition and the number of RVP hits were still statistically significant (AGN latencies in the positive shift condition: [$F(2, 59)=5.098$, $p=.009$, partial $\eta^2=.147$]; RVP hits: [$F(2, 60)=4.535$, $p=.015$, partial $\eta^2=.131$]). These findings were, however, no longer significant when covarying for MADRS scores (AGN latencies in the positive shift condition: [$F(2, 59)=2.819$, $p=.068$, partial $\eta^2=.087$]; RVP hits: [$F(2, 60)=2.631$, $p=.080$, partial $\eta^2=.081$]). No other statistical differences in cognitive functioning were observed across groups (Table 2 and Table 2S).

Discussion

Based on previous evidence of cognitive deficits in both adults with BD and their offspring, this exploratory study compared the cognitive functioning of in adults with BD, their unaffected biological siblings, and HC using the CANTAB battery, a computerized cognitive battery widely used in research on mood disorders. In line with previous findings, patients with BD displayed slowed response times in an affective processing task (AGN). Further, there was a trend toward significance for accuracy in the RVP task suggesting that in siblings of BD patients were slightly less accurate than HC. However, when controlled for the severity of depressive symptoms (MADRS scores), the AGN and RVP findings no longer reached statistical significance. The most compelling finding of our study is that depressive symptoms, at both the threshold and subthreshold diagnostic levels, may contribute to deficits in affective processing and sustained attention in euthymic BD patients and their healthy siblings.

The neurocognitive profile observed in our group of siblings is consistent with a previous meta-analysis showing that siblings of BD patients maintain intact functioning in the domains of visual memory and psychomotor speed (Balanzá-Martínez et al., 2008). Evidence for the presence of attentional deficits in siblings of BD patients remains, however, controversial. Two studies reported deficits in selective and sustained attention in first-degree relatives of individuals with BD with no history of psychiatric history compared to healthy volunteers (Sobczak et al., 2003; Trivedi et al., 2008). By contrast, two studies comparing siblings and healthy controls did not detect differences in attentional functioning (Balanzá-Martínez et al., 2008; Clark et al., 2005). These inconsistent findings may be partly due to the fact that previous studies compared relatives of different degrees of closeness to BD patients and/or that in some studies healthy controls were compared to siblings with BD (Kulkarni et al., 2010; Trivedi et al., 2008) but did not include a sample of BD patients. It is noteworthy that, in this study, we selected siblings of BD patients and compared these to their biological relatives. Further, as shown in our study, the presence of subthreshold or

even mild mood symptoms may be associated with specific cognitive deficits in siblings of BD patients. The relationship between mood symptoms, more specifically of depressive nature, and the cognitive deficits observed in euthymic BD has been shown in a number of studies (Bonnin et al., 2012; Ferrier et al., 1999; Romero et al., 2016; Torrent et al., 2012). In acutely ill BD patients, higher MADRS scores were found to be associated with slower processing speed, reduced attention, and poor memory (Volkert et al., 2015). By contrast, higher YMRS scores were only linked to reduced immediate verbal recall. Another study by Clark et al. found deficits in verbal memory, learning and attention shifting in a population with BD (Clark et al., 2002). These deficits were, however, no longer significant when the authors corrected their results for manic and depressive symptoms. Distinguishing between cognitive deficits associated with the individuals' current mood state and those induced by BD may therefore pose a challenge. To address this issue, future studies could, for instance, implement a longitudinal design to monitor both cognitive functioning and mood during the course of BD.

Another important issue is related to the homogenous definition of “euthymia” across studies. For instance, Nehra et al.'s sibling study included euthymic BD participants with an HDRS score below 8, and a YMRS score below 6 (Nehra et al., 2014), while in another study euthymic BD patients had an HDRS score 6 and an YMRS score 4 (Houshmand et al., 2010). By contrast, our study included BD patients in different mood phases and the severity of their manic/depressive scores was overall higher than those reported in previous studies. This issue is once again particularly relevant when assessing the impact of mood on cognition (Ferrier et al., 1999; Trivedi et al., 2008). The current study design was therefore powerful in limiting confounding biases related to varying genetic loadings, but a stricter definition of euthymia would have facilitated the interpretation of our findings.

Prior to covarying for depressive mood, our analyses showed that BD patients displayed deficits in affective processing and sustained attention. The concept of cognitive bias toward affective stimuli is well established in the BD literature (Gotlib et al., 2005). It is still unclear whether this is due to a problem in disengaging attention from affective stimuli or rather due to psychomotor retardation. Notably, in the AGN task BD patients were slow in task conditions starting with a positive stimulus and alternating between negative and positive stimuli. This pattern of responses is in line with the concept of “affective bias”, a well-established feature of mood disorders including BD (Bauer et al., 2015a; Gotlib et al., 2005). In particular, the term “negative affective bias” is defined by the inability to disengage from processing negative stimuli even after they disappear. This “inability” impairs the processing of subsequent stimuli and could explain the reduced speed in processing positive and neutral stimuli observed in the current study (Singhal et al., 2012). Although our data is consistent with previous findings, our results must be interpreted with caution due to the potential link between depressive symptoms and negative affective bias, which could affect the generalizability of these findings.

Notably, individuals with BD did not present with more severe deficits in the CGT task, a measure of executive functioning, impulsivity and risk taking. The presence of reduced planning abilities in BD has been previously reported (Murphy and Sahakian, 2001; Quraishi and Frangou, 2002) and, based on previous findings in euthymic BD, one could

have expected to observed pronounced executive deficits and impulsivity traits in individuals with BD compared with HC (Najt et al., 2007; Robinson et al., 2006; Swann et al., 2009). Further, evidence suggests that this deficit is independent from current mood state (Robinson et al., 2006). Potential explanations for this result could be that our individuals with BD were medicated (Sanches et al., 2014). Additionally, previously observed executive deficits were primarily related to deficits in verbal fluency and information manipulation that may have not been present in our BD sample (Thompson et al., 2005). Furthermore, the previously reported impulsivity in individuals with BD may differ from the construct evaluated by cognitive measures of impulsivity (Bauer et al., 2015c).

Rather than focusing on cognitive functions previously shown to be impaired in BD, in this study we chose a broad, exploratory analytical approach to capture a large range of potential cognitive markers of BD. Given our exploratory approach statistical significance was set at $p < .05$. For clarity purposes, we compared uncorrected and Bonferroni-corrected p-values for relevant tests. Notably, after correcting for multiple comparisons, differences in AGN latencies between HC and BD were maintained, while differences in the number of RVP hits between BD siblings and HC approached but did not reach statistical significance ($p=.066$). Thus, prior to correcting for current mood state, our findings appeared to confirm previous studies reporting deficits in affective processing in children with BD (Gopin et al., 2011), unaffected siblings (Brand et al., 2012) and offspring (Bauer et al., 2015a) of BD patients. This may indicate that our study was underpowered to detect such cognitive deficits and/or that there is weak evidence of attentional deficits in siblings of BD patients. However, both Trivedi et al. (Trivedi et al., 2008) and Maqbool et al. (Maqbool and Vinod Kumar Sinha, 2015) detected attentional deficits in relatives and remitted adolescents with BD. Further, it could be argued that, while Bonferroni corrections were applied to the groups on a per test basis, the experiment-wise error rate correction was not addressed. However, given the preliminary nature of this study and the small sample size of our groups this additional correction would have led to a loss of statistical power and penalized our tests. The experiment-wise error rate depends on both the number of tests and comparisons. However, this correction is necessary to decrease the overall risk of finding “false positives”. Thus, although promising, our current findings should be considered preliminary. A methodologically robust, large-scale study is needed to determine whether attentional deficits are markers of vulnerability to BD or rather “state effects” due to the individuals' current mood state.

A limitation of this exploratory study is the small number of participants included in each group. Given that the present study was a novel investigation of offspring of BD patients and we did not have expectations in terms of effect size, we undertook retrospective *post hoc* analyses with the view to informing future research design. These analyses showed that, assuming a large effect size ($f=.40$, $d=.80$, $\alpha=.05$), the current study was sufficiently powered to detect differences in cognitive performance across participant groups (power above 80%). Given that previous studies of neurocognitive findings in relatives of bipolar patients identified small effects deficits in working memory and attention ($ES=.16$), executive functions ($ES=.22$)(Bora et al., 2008) the current study may have been underpowered to detect cognitive deficits of smaller effect size. In sum, the effect size estimates reported in this study suggest that siblings of BD may display cognitive deficits of

small effect size. An accurate assessment of cognitive functioning in this population needs, therefore, a sample size much larger than that included in the current study.

In conclusion, this study provides preliminary evidence that subthreshold depressive symptoms are associated with deficits in sustained attention in healthy siblings of BD patients. These findings yield potential implications for the development of early prevention and intervention strategies addressing mood fluctuations and cognitive deficits in at-risk individuals. Large-scale, longitudinal studies are needed to confirm our conclusions and help consolidate normative references to assess cognition in vulnerable individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We compared cognition in individuals with BD, their biological siblings and HC
- We used the CANTAB - a validated computerized cognitive task
- Depressive symptoms may contribute to attentional deficits in siblings
- Large-scale studies are needed in sibling research.

Fig. 1.

Number of hits in the Rapid Visual Processing (RVP) task across participant groups. The number of correct responses to target sequences was greater in the HC group when compared to individuals with BD and siblings of individuals with BD ($p < .05$)

Table 1
Demographic and Clinical Characteristic of the Sample (mean $\pm$ 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	0.09 (0.29)	0.93 (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	0.22 (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- Asberg Depression Rating Scale, PD: Panic Disorder; PTSD: Post-traumatic Stress Disorder; SAD: Seasonal Affective Disorder; YMRS: Young Mania Rating Scale, WASI: Wechsler Abbreviated Scale of Intelligence.

Comparisons: BD vs HC,

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#BD vs siblings;
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Table 2
Mean reaction times (RT; in milliseconds) and accuracy estimates of variables showing significant differences across groups (mean $\pm$ standard deviation)

	HC n=23	BD n=26	Siblings n=15	F	p-value
<i>AGN RT Correct Trials</i>	491.695 $\pm$ 62.896	528.820 $\pm$ 62.256	520.292 $\pm$ 79.647	1.925	.151
<i>AGN RT shift</i>	488.399 $\pm$ 58.180	522.370 $\pm$ 60.360	516.280 $\pm$ 75.565	1.862	.164
<i>AGN RT Shift positive</i>	481.367 $\pm$ 61.249	533.700 $\pm$ 65.716	508.335 $\pm$ 59.319	4.180	.020 (^a)
<i>AGN RT Shift negative</i>	494.054 $\pm$ 59.509	512.476 $\pm$ 69.737	522.655 $\pm$ 100.327	.733	.485
<i>RVP Total hits</i>	19 $\pm$ 5.196	16 $\pm$ 4.931	16.071 $\pm$ 3.518	3.355	.041 (^{ab})

Abbreviations: AGN: Affective Go/No-Go; RVP: Rapid Visual Processing; RT: reaction time

^a Comparisons: =BD vs HC.

^b =siblings vs HC.