Psychological Medicine (2016), **46**, 745–758. © Cambridge University Press 2015
doi:10.1017/S0033291715002147

ORIGINAL ARTICLE

Neuropsychological and social cognitive function in young people at genetic risk of bipolar disorder

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Background. Impairments in key neuropsychological domains (e.g. working memory, attention) and social cognitive deficits have been implicated as intermediate (endo) phenotypes for bipolar disorder (BD), and should therefore be evident in unaffected relatives.

Method. Neurocognitive and social cognitive ability was examined in 99 young people (age range 16–30 years) with a biological parent or sibling diagnosed with the disorder [thus deemed to be at risk (AR) of developing BD], compared with 78 healthy control (HC) subjects, and 52 people with a confirmed diagnosis of BD.

Results. Only verbal intelligence and affective response inhibition were significantly impaired in AR relative to HC participants; the BD participants showed significant deficits in attention tasks compared with HCs. Neither AR nor BD patients showed impairments in general intellectual ability, working memory, visuospatial or language ability, relative to HC participants. Analysis of BD-I and BD-II cases separately revealed deficits in attention and immediate memory in BD-I patients (only), relative to HCs. Only the BD (but not AR) participants showed impaired emotion recognition, relative to HCs.

Conclusions. Selective cognitive deficits in the capacity to inhibit negative affective information, and general verbal ability may be intermediate markers of risk for BD; however, the extent and severity of impairment in this sample was less pronounced than has been reported in previous studies of older family members and BD cases. These findings highlight distinctions in the cognitive profiles of AR and BD participants, and provide limited support for progressive cognitive decline in association with illness development in BD.

Received 17 April 2015; Revised 15 September 2015; Accepted 22 September 2015; First published online 1 December 2015

Key words: Bipolar affective disorder, cognitive ability, endophenotypes, family studies, inhibition, social cognition.

Introduction

Having an affected first-degree relative is the strongest determinant of risk for severe psychiatric disorders – including individuals with an affected family member with bipolar disorder (BD), who are estimated to be 5–10% more likely to develop this condition (Craddock & Sklar, 2013). The study of young, genetically at-risk (AR) samples is therefore relevant to the validation of candidate intermediate (endo-) phenotypes, for which similar deficits should be present in a higher proportion of unaffected relatives than in the general population, although expected to be of lesser severity than those found in affected patients (Gottesman & Gould, 2003).

Neuropsychological deficits have been implicated as candidate endophenotypes for BD following substantial evidence for impairments in working memory, executive functioning and attention (e.g. Martinez *et al.* 2004; Frangou *et al.* 2005; Langenecker *et al.* 2010; Levy & Weiss, 2010); these deficits are evident in the euthymic phases of illness, and in unaffected family members (e.g. Ferrier *et al.* 2004; Clark *et al.* 2005; Arts *et al.* 2008; Balanza-Martinez *et al.* 2008), in partial fulfilment of criteria for endophenotype status (Gottesman & Gould, 2003). However, evidence from both prospective longitudinal and cross-sectional studies of unaffected relatives of subjects with BD provides mixed evidence for cognitive deficits prior to the onset of illness. While a series of studies of unaffected relatives of BD patients has suggested that verbal learning, memory and working memory are among the most likely candidate cognitive endophenotypes for BD (Glahn *et al.* 2007; Arts *et al.* 2008; Balanza-Martinez *et al.* 2008; Olvet *et al.* 2013), more general estimates of premorbid intellectual functioning typically are not impaired (Olvet *et al.* 2013; Trotta *et al.* 2014); notably, if only prospective studies are examined, no deficit

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in intelligence quotient (IQ) is evident (Trotta *et al.* 2014).

In addition to neuropsychological functioning, emotion processing and higher-order social cognitive impairments (such as face processing and theory of mind deficits) have been identified in BD irrespective of mood state (Olley *et al.* 2005; Montag *et al.* 2010; Schenkel *et al.* 2014) and in a few studies of unaffected relatives of bipolar-I disorder (BD-I) patients (McClure *et al.* 2005; Brotman *et al.* 2008). There is also some evidence that social cognitive performance may be worse in BD-I relative to bipolar-II disorder (BD-II) (Schenkel *et al.* 2014). With regard to emotional inhibitory deficits, these have been reported as commonly mood-congruent in BD (e.g. Elliott *et al.* 2004; Gopin *et al.* 2011) and are also evident in unaffected relatives (Brand *et al.* 2012). Aberrant brain function during this process has also been demonstrated in BD (Wessa *et al.* 2007) as well as in a subsample of the AR group being investigated in this current paper (Roberts *et al.* 2013). However, the potential for emotional and social cognitive deficits to be endophenotypic markers of BD has not been extensively examined, and current evidence remains equivocal.

The aim of the present study was therefore to examine neuropsychological functioning in a sample of young people at high genetic risk for BD (i.e. those with at least one affected first-degree relative but who have not yet developed BD themselves), compared with healthy controls (HCs), and a group of participants with established BD. It was hypothesized that neurocognitive and social cognitive functioning would be impaired in BD patients (in particular, those with BD-I) and, to a lesser extent (in terms of domains affected and severity), young unaffected relatives of BD patients, compared with HCs.

Method

Participants

Participants included young people (aged 16–30 years) at high genetic risk for developing BD who had not yet developed BD themselves (AR, $n = 99$), young adults already diagnosed with BD ($n = 52$) and age-matched controls with no history of severe psychiatric illness (i.e. never diagnosed, hospitalized, or treated for a mood or psychotic disorder) during their own lifetime, or in a first-degree family member (HCs, $n = 78$). There were a total of 188 unique family groups represented in the sample. There were 87 participants from 73 families in the AR cohort, and 32 of the AR participants had at least one other sibling also in the AR cohort. The AR and established BD participants were recruited from an existing BD genetic family study (see Mitchell *et al.* 2011), a specialized BD research clinic (see Mitchell *et al.* 2009), contact with clinicians of local area health services, mental health consumer organizations, and from the community via print and electronic media and noticeboards in universities and local communities. HC participants were recruited from the community using print and electronic media and noticeboards in universities and local communities. Exclusion criteria included not having spoken English as their first language, and history of neurological illness or significant head injury. Further details of this sample have been reported elsewhere (Perich *et al.* 2015).

Materials

Clinical interviews

The Family Interview for Genetic Studies (FIGS) (Maxwell, 1992) was administered to all participants at baseline entry to determine any family history of affective disorders, and was thus used here both as a screening tool for exclusion of potential control participants and to ascertain family history of psychiatric conditions (Maxwell, 1992). Participants aged between 16 and 21 years were administered an adapted version of the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children – Bipolar Disorder version (K-SADS-BP). The K-SADS-BP was developed specifically for use in the US–Australian collaborative study of young people at genetic risk for BD. It combines items from the K-SADS – Present and Lifetime version (K-SADS-PL; Kaufman *et al.* 1997), and extends sections on depression, mania and attention-deficit/hyperactivity disorder (ADHD) derived from the Washington University in St Louis K-SADS (WASH-U-KSADS) to elicit detailed information on the presence of prepubertal mania, rapid cycling and ADHD (Geller *et al.* 2001). It differs from the K-SADS-PL in that it identifies specific episodes and duration of each symptom assessed. For participants aged between 22 and 30 years and for parents or adult siblings of AR participants, the Diagnostic Interview for Genetic Studies (DIGS) version 4 (Nurnberger *et al.* 1994) was administered. Similarly, parents of the HC participants completed the DIGS to confirm eligibility into the study. Consent forms to release medical records were posted to BD participants and BD probands.

Using the best estimate methodology (Leckman *et al.* 1982), lifetime diagnoses and age of onset were determined by the consensus of two independent raters (psychiatrists) who were blind to the family status of participants. This approach combined information from the DIGS version 4 (Nurnberger *et al.* 1994) or the K-SADS-BP (Kaufman *et al.* 1997; Nurnberger

https://doi.org/10.1017/S0033291715002147 Published online by Cambridge University Press

et al. 2011), the FIGS (Maxwell, 1992) and medical records (where available) in order to determine whether the participant met diagnostic criteria for a lifetime Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000) diagnosis and its age of onset. For each diagnosis, the independent rater rated their diagnostic confidence based on a four-point scale [1 = diagnosis asserted without supporting symptoms; two possible; some criteria met (both informants) or all criteria met (one informant) with some supporting information; 3 = probably; all criteria met, no supporting documentation; 4 = definite; meets criteria and has supporting documentation]. For this paper, only diagnoses achieving a confidence level of 3 or 4 were considered.

Clinical symptom assessments

Current mood state was assessed by the researcher-administered Montgomery–Åsberg Depression Rating Scale (MADRS), Bipolar Depression Rating Scale (BDRS) and the Young Mania Rating Scale (YMRS). The Children's Depression Inventory (CDI) was administered to 16- to 18-year-old participants (Kovacs, 1992).

Neuropsychological test battery

A comprehensive neuropsychological battery including the following domains of function was administered to all participants. Age-adjusted, normative *Z*-scores were used for between-groups analyses for each measure, unless otherwise stated.

General intellectual ability. General intellectual ability was assessed using the Wechsler Abbreviated Scale of Intelligence – two subtest version [WASI: including the vocabulary and matrix reasoning subtests of the Wechsler Adult Intelligence Scale (WAIS)] (Wechsler, 1999).

Working memory. Working memory was assessed using two memory subtests (immediate and delayed) from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph *et al.* 1998), as well as the digit span task and letter–number sequencing tasks from WAIS-III (Wechsler, 1999). There were no age-appropriate norms available for the RBANS measures.

Visuospatial ability, attention and language. Visuospatial ability, attention and language were assessed using subscales from the RBANS (Randolph *et al.* 1998).

Executive functioning. Executive functioning was measured using two tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB): the Intradimensional/Extradimensional (IED) Set Shift Task which measures attentional set-shifting; and the Stockings of Cambridge (SOC) task which measures planning ability, and is based on the Tower of London task.

Inhibition of emotional material. Inhibition of emotional material was assessed using the Affective Go-No-Go (AGN) task from the CANTAB, where errors of omission reflect a failure to respond to target words and more errors of commission reflect worse response inhibition. Individual trials alternate between using target words with a negative, positive or neutral valence. Trials are either 'shift' trials, in which the target valence is different to the previous trial, or 'non-shift', where the target valence is the same as in the previous trial. Shift trials are considered to be more difficult as they require participants' attention to shift from one emotional valence to another. No age-appropriate normative data were available for the AGN task; raw scores were thus used for analysis of performance on this task.

Social cognition. Social cognition was assessed using the Ekman 60-Faces emotion recognition test from the 'Facial Expressions of Emotion: Stimuli and Tests' (FEEST; Young *et al.* 2002), and version A of The Awareness of Social Inference Test (TASIT; McDonald *et al.* 2004). The Ekman 60-Faces task is a computerized task in which participants are presented with photographic images of faces displaying six basic emotions – happiness, sadness, surprise, fear, disgust or anger – and are required to identify the emotion being displayed. TASIT is a more complex measure of social cognition. Similar to the Ekman 60-Faces task, part one requires participants to identify the same six basic emotions; however, short video vignettes are presented rather than static images. Part two of TASIT presents 15 vignettes of interactions, and requires participants to interpret social cues beyond dialogue text to determine whether characters are sincere or insincere. The enriched subtest (TASIT part three) contains 16 vignettes, half of which feature a character that is lying to the main protagonist. In these cases, evidence the character is lying is presented through either subtle paralinguistic cues, or straightforward visual cues embedded in the scene.

Procedure

Participants completed the neuropsychological test battery individually in a laboratory setting. The battery took approximately 2 h to administer. Testing occurred

https://doi.org/10.1017/S0033291715002147 Published online by Cambridge University Press

as part of one full day of assessment for a longitudinal study, for which sample details have been reported previously (Perich *et al.* 2015).

Statistical analyses

All statistical analyses were implemented in SPSS v21; the α level was set at $p = 0.01$ with consideration of the number of tests conducted. We used the generalized estimating equation method to test for difference between groups on neurocognitive and social cognitive measures, owing to the relatedness of some cases among the AR and BD groups; this procedure controls for clustering of outcomes that may occur when data points may not be independent, as is the case when several members (children or siblings of a BD proband) of a family are included. Seven participants in the AR group had a sibling proband in the BD group, and 46 participants in the AR group had at least one other AR sibling in the study. Two participants in the BD group were also related, as well as two HCs.

Ethical standards

The study was conducted with the approval of the University of New South Wales Human Research Ethics Committee (HREC protocol 09/104) and the South Eastern Sydney Illawarra Health Service HREC (protocol 09/097) in Sydney, Australia. Written informed consent from all participants was obtained for involvement in an ongoing longitudinal study; additional parental consent was obtained for participants under the age of 16 years. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Participant characteristics

Demographic and clinical information for each group is provided in Table 1. The groups differed significantly in age ($F_{2,213} = 7.123$, $p = 0.001$), with the BD group being older than both the AR ($p = 0.003$) and HC ($p = 0.014$) groups; age was thus entered as a covariate in any pairwise comparisons with the BD group. There were no group differences in sex distribution or education levels. Because the overarching inclusion/exclusion criteria for participants in the AR and HC groups were based on a family history of BD (or lack thereof), some participants met lifetime criteria for a major depressive disorder (34 AR and 16 HC; further details of the clinical status of these participants are described in Perich *et al.* 2015). Three HC and 11 AR participants were removed from the analyses because they were taking prescribed psychoactive medications, and one AR participant experiencing a current major depressive episode was removed. Most of the AR participants had a proband with a BD-I diagnosis ($n = 70$, 80.5%), and 36 of these BD-I probands (51%) reported a definite lifetime history of psychosis.

Participants in the BD group were found to have significantly higher depressive, hypomanic and anxiety symptom severity scores than both HC and AR groups, as shown in Table 1. HC and AR groups did not differ from each other in terms of current mood severity on the MADRS, BDRS and/or YMRS; also there were no differences in depressive severity among AR and HC participants aged younger than 18 years, as measured with the CDI.

Psychiatric co-morbidities for each participant group are reported in Table 1. The BD group had higher rates of anxiety disorders and substance use disorders than both HC and AR groups, as well as higher rates of behavioural disorders compared with the HC but not the AR group. The AR group had higher rates of anxiety and behavioural disorders than the HC group. While 18 of the BD patients had experienced psychotic symptoms on at least one occasion, there was no history of psychotic symptoms in the HC or AR groups.

Of the BD participants, 27 were diagnosed with BD-I and 25 with BD-II; the majority were medicated ($n = 35$). Table 2 presents the mean age of onset, as well as the number of mood episodes for the BD group. The mean age of onset for any mood episode in the BD sample was 15.3 (S.D. = 3.2) years, and the mean total number of lifetime mood episodes of any type experienced by this group was 17.7 (S.D. = 15.7). Global assessment of functioning ratings were also significantly lower in BD relative to AR ($t = 4.23$, $p < 0.001$) and HC ($t = 9.08$, $p < 0.001$) groups, and AR participants had lower ratings than HCs ($t = -4.89$, $p < 0.001$).

Neurocognition

Group means and statistics for each neurocognitive domain are reported in Table 3.

Comparison of AR v. *HC*

The AR participants performed significantly worse than the HC group ($p = 0.011$) on the WASI vocabulary subtest and exhibited more errors of commission than HCs during all trials of the CANTAB AGN task when the stimuli were of negative or neutral target valence (p values ranging from 0.002 to 0.024); however, there were no differences between these groups in the capacity to inhibit stimuli of a positive target valence.

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Table 1. *Demographic characteristics and clinical diagnoses*

	Group descriptives			Statistical values for pairwise comparisons		
	HC	AR	BD	HC *v.* AR	HC *v.* BD	AR *v.* BD
n	75	87	52			
Mean age, years (S.D.)	22.4 (3.9)	22.0 (4.5)	24.6 (3.8)	$t = 0.436$, $p = 0.664$	$t = -3.035$, $p = 0.003$*	$t = -2.483$, $p = 0.014$*
Male, %	45.3	42.5	32.7	$\chi^2 = 0.129$, $p = 0.720$	$\chi^2 = 2.042$, $p = 0.153$	$\chi^2 = 1.326$, $p = 0.250$
Mean duration of education, years (S.D.)	14.7 (2.7)	15.0 (2.9)	15.2 (2.9)	$t = 0.323$, $p = 0.474$	$t = -0.934$, $p = 0.352$	$t = -0.649$, $p = 0.517$
Mean global assessment of functioning rating (S.D.)	91.4 (4.2)	85.6 (9.7)	76.3 (12.8)	$t = 4.89$, $p < 0.001$***	$t = 9.08$, $p < 0.001$***	$t = 4.23$, $p < 0.001$***
Lifetime clinical diagnosis, *n*						
Bipolar I	–	–	27	–	–	–
Bipolar II	–	–	25	–	–	–
Other affective primary diagnosis	13	27	–	$\chi^2 = 5.48$, $p = 0.019$*	–	–
Any anxiety disorder	5	21	25	$\chi^2 = 9.117$, $p = 0.003$**	$\chi^2 = 31.32$, $p < 0.001$***	$\chi^2 = 9.83$, $p = 0.002$**
Any behavioural disorder	0	7	7	$\chi^2 = 6.375$, $p = 0.012$*	$\chi^2 = 11.45$, $p = 0.001$**	$\chi^2 = 1.31$, $p = 2.52$
Any substance use disorder	6	7	15	$\chi^2 = 0.00$, $p = 0.991$	$\chi^2 = 10.02$, $p = 0.002$**	$\chi^2 = 10.95$, $p = 0.001$**
History of psychosis	0	0	18	$\chi^2 = 0$	$\chi^2 = 31.16$, $p < 0.001$***	$\chi^2 = 0$
Current mood severity						
Mean MADRS (S.D.)[a]	1.9 (3.1)	2.6 (3.7)	11.4 (11.3)	$t = 0.989$, $p = 0.325$	$t = -5.130$, $p < 0.001$***	$t = -4.730$, $p < 0.001$***
Mean BDRS (S.D.)[a]	1.6 (2.1)	2.6 (3.4)	10.2 (10.2)	$t = 1.64$, $p = 0.102$	$t = -5.291$, $p < 0.001$***	$t = -4.571$, $p < 0.001$***
Mean YMRS (S.D.)[a]	0.7 (1.0)	0.8 (1.4)	4.5 (4.4)	$t = 0.573$, $p = 0.568$	$t = -5.367$, $p < 0.001$***	$t = -5.116$, $p < 0.001$***
Mean DASS anxiety (S.D.)[a]	2.3 (3.4)	3.5 (4.8)	9.2 (8.9)	$t = 1.221$, $p = 0.226$	$t = -4.382$, $p < 0.001$***	$t = -3.622$, $p < 0.01$**
Mean DASS depression (S.D.)[a]	4.9 (9.7)	3.5 (5.1)	12.0 (12.0)	$t = -0.805$, $p = 0.423$	$t = -2.777$, $p = 0.007$**	$t = -4.172$, $p < 0.001$***
Mean CDI (S.D.)[b]	5.3 (2.5)	7.75 (5.6)	8.00 (0)	$t = 0.714$, $p = 0.485$	$t = -0.918$, $p = 0.456$	$t = -0.043$, $p = 0.966$
Proband diagnosis, *n*						
Proband – bipolar I	–	70	–			
Proband – bipolar II	–	17	–			
Proband history of psychosis	–	36	–			

HC, Healthy control; AR, at-risk; BD, bipolar disorder; S.D., standard deviation; MADRS, Montgomery–Åsberg Depression Rating Scale; BDRS, Bipolar Depression Rating Scale; YMRS, Young Mania Rating Scale; DASS, Depression Anxiety Stress Scale; CDI, Children's Depression Inventory.

[a] Participants aged 18 years and older.

[b] Participants aged under 18 years.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 2. *History of mood episodes in the bipolar disorder group*

	Mean (S.D.)	
Age at onset, years		
First depression	15.6 (3.4)	
First hypomania	18.1	(4.1)
First mania	19.8	(4.9)
First elevated mood	18.1	(4.2)
Any mood	15.3	(3.2)
Number of episodes		
Depression	9.4	(9.8)
Hypomania	9.4	(10.8)
Mania	2.7	(2.0)
Any elevated mood	8.6	(10.0)
Any mood	17.7	(15.7)

S.D., Standard deviation.

Comparison of BD v. *AR and HC*

The BD group was significantly impaired on the attention domain of the RBANS, relative to the HC group ($p = 0.001$). However, the BD patients showed no significant deficits in general intellectual functioning, working memory, visuospatial ability, language domains or executive function measures of planning (SOC) or attentional set-shifting (IED Set Shift Task), in comparison with the HC or AR participant groups.

Comparison of BD-I v. *BD-II*

Post-hoc analyses were conducted to explore the possibility that cognitive deficits may be evident in BD-I participants, following the lack of deficits in the entire BD group. Mean scores on neurocognitive and social cognitive measures are presented separately for BD-I and BD-II participants in Table 4. The BD-I participants showed significantly impaired attention, relative to both BD-II ($p = 0.007$) and HC ($p = 0.003$) participants, and also showed significant deficits in immediate memory ($p = 0.011$), relative to HC subjects.

Cognitive functioning and psychosis history

We also examined the relevance of history of psychosis for cognitive performance of BD participants, and, in the case of AR participants, whether the affected proband had a history of psychosis, via comparison of cases with and without such psychosis history. There were no significant differences in cognitive function between BD participants with and without psychosis history, or between AR participants who had probands with a history of psychosis and those who did not.

Social cognition

Group means and statistics for performance on the social cognition measures are reported in Table 5. The BD group demonstrated higher accuracy for recognition of disgust facial expressions on the Ekman task ($p = 0.011$), relative to HC participants. After correction for multiple testing, no other significant differences were found for BD patients compared with HCs on the Ekman or TASIT measures of social cognition; however, there was a trend toward a deficit in the recognition of fear faces in BD-II patients relative to HCs ($p = 0.014$; summarized in Table 6). BD participants with history of psychosis showed significantly greater deficits in the recognition of 'sadness' expressions on the Ekman task (mean = 7.89), relative to BD participants without psychosis history (mean = 9.37; $\chi^2 = 20.288$, $p < 0.001$).

Illness features and neuropsychological functioning

There were no significant associations between illness duration, or the number of mood episodes, with any neuropsychological outcomes that were found to be impaired within the BD group (including the RBANS attention, TASIT mental state reasoning, or the number of correctly identified fearful or disgust facial expressions on the Ekman task). However, the total number of mood episodes was negatively associated with the number of correctly identified fearful facial expressions ($r = -0.157$, $p = 0.025$). While WASI vocabulary *Z*-scores did not differ between participant groups, there was a moderate negative correlation between WASI vocabulary *Z*-scores and the total number of mood episodes experienced ($r = -0.347$, $p = 0.000$), but not illness duration ($r = -0.065$, $p = 0.456$).

Discussion

This study examined neuropsychological and social cognitive functioning in young people (<30 years of age) at genetic risk for BD (i.e. with a first-degree relative with BD) compared with HC and established BD groups. Those at increased genetic risk for BD exhibited deficits in verbal ability and the inhibition of emotional material – particularly of negative valence, while the BD participants showed selective impairments on cognitive domains of attention and immediate memory.

While these results of selective cognitive impairments in our relatively young sample of BD patients are consistent with previous reports of deficits in attention and memory in BD and their unaffected relatives (e.g. Clark *et al.* 2005; Glahn *et al.* 2007; Arts *et al.* 2008; Balanza-Martinez *et al.* 2008; Bora *et al.* 2008; Levy & Weiss, 2010; Olvet *et al.* 2013), they differ

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Table 3. *Neuropsychological variables and pairwise comparisons for the HC, AR and BD groups*

	Group mean (standard deviation)			Statistical values for pairwise comparisons[a]					
				HC *v.* AR		HC *v.* BD		AR *v.* BD	
Measure	HC ($n = 75$)	AR ($n = 87$)	BD ($n = 52$)	χ^2	p	χ^2	p	χ^2	p
Intellectual ability									
WASI IQ	119.3 (10.7)	116.5 (10.1)	118.4 (10.7)	2.956	0.086	1.066	0.302	0.010	0.920
WASI vocabulary T-score	64.4 (7.3)	61.4 (8.1)	58.9 (24.3)	6.480	0.011**	2.656	0.103	0.752	0.382
WASI matrix reasoning T-score	57.4 (7.9)	56.9 (6.3)	57.6 (5.9)	0.145	0.703	0.586	0.445	0.371	0.542
Working memory									
WAIS digit span, age-scaled score	10.5 (2.6)	10.6 (3.0)	10.5 (3.2)	0.009	0.922	0.156	0.693	0.059	0.809
WAIS letter–number sequencing	10.0 (2.3)	9.9 (2.9)	10.3 (3.1)	0.144	0.704	0.064	0.801	0.014	0.905
RBANS immediate memory index score	93.0 (13.8)	92.8 (14.9)	91.5 (14.0)	0.011	0.917	0.475	0.491	1.541	0.214
RBANS delayed memory index score	92.1 (12.3)	91.5 (11.0)	92.0 (11.7)	0.103	0.748	0.000	0.994	0.060	0.806
Visuospatial ability									
RBANS visuospatial/constructional index score	95.5 (14.0)	95.7 (14.1)	96.2 (14.8)	0.012	0.912	0.002	0.961	0.165	0.685
Language									
RBANS language index score	104.3 (12.7)	102.3 (12.9)	106.3 (11.3)	1.112	0.292	0.047	0.828	1.164	0.281
Attention									
RBANS attention index score	101.0 (15.6)	98.3 (15.0)	97.8 (15.6)	1.238	0.266	10.259	0.001**	0.800	0.371
Executive functioning									
IED number of stages completed	8.6 (1.3)	8.6 (1.2)	8.6 (1.1)	0.035	0.851	0.004	0.951	0.092	0.761
IED total errors adjusted	23.0 (29.3)	23.3 (28.8)	21.3 (18.6)	0.004	0.947	0.006	0.938	0.139	0.710
IED pre-EDS errors	8.2 (5.7)	8.0 (5.3)	7.9 (3.8)	0.000	0.990	0.045	0.833	0.246	0.620
IED EDS errors	6.4 (8.2)	7.2 (8.4)	7.2 (9.6)	0.291	0.589	0.427	0.514	0.000	0.938
SOC problems solved in minimum moves	8.7 (1.8)	8.7 (5.3)	8.6 (1.8)	0.044	0.834	1.339	0.247	0.481	0.488
SOC time spent thinking before making five move problems, ms	7253.6 (4971.6)	6074.4 (3927.5)	6387.9 (4407.3)	4.838	0.028*	2.643	0.104	0.040	0.841
AGN errors of omission – negative valence trials	6.3 (12.4)	5.8 (9.6)	2.5 (17.1)	0.063	0.801	1.563	0.211	0.787	0.375
AGN errors of omission – positive valence trials	8.2 (12.0)	8.0 (9.5)	4.2 (17.5)	0.030	0.863	1.607	0.205	0.973	0.324
AGN errors of omission – neutral valence trials	11.4 (12.2)	11.3 (10.3)	6.7 (18.3)	0.004	0.951	2.033	0.154	1.335	0.248
AGN errors of omission – non-shift trials	12.8 (17.9)	12.3 (14.2)	7.4 (20.2)	0.036	0.850	1.781	0.182	0.940	0.332
AGN errors of omission – shift trials	13.1 (18.0)	12.8 (14.2)	8.1 (20.2)	0.020	0.887	1.719	0.190	0.921	0.337
AGN errors of omission – all trials	25.9 (35.7)	25.0 (28.1)	17.5 (30.3)	0.028	0.867	1.523	0.217	0.651	0.420
AGN errors of commission – negative valence trials	4.3 (4.4)	6.9 (5.7)	5.2 (17.0)	9.889	0.002**	0.335	0.563	0.001	0.973
AGN errors of commission – positive valence trials	5.9 (5.3)	7.2 (5.2)	6.3 (17.5)	2.530	0.112	0.110	0.740	0.037	0.847
AGN errors of commission – neutral valence trials	8.9 (5.4)	11.4 (6.5)	10.7 (18.2)	6.847	0.009**	0.630	0.428	0.062	0.804
AGN errors of commission – non-shift trials	10.1 (6.8)	12.9 (8.3)	12.4 (20.1)	5.119	0.024*	0.981	0.322	0.339	0.560

Table 3 (*cont.*)

Measure	Group mean (standard deviation)			Statistical values for pairwise comparisons[a]					
				HC *v.* AR		HC *v.* BD		AR *v.* BD	
	HC ($n = 75$)	AR ($n = 87$)	BD ($n = 52$)	χ^2	p	χ^2	p	χ^2	p
AGN errors of commission – shift trials	9.0 (7.6)	12.6 (8.3)	11.9 (19.8)	8.082	0.004**	1.378	0.241	0.234	0.628
AGN errors of commission – all trials	19.1 (13.7)	25.5 (15.9)	26.3 (29.0)	7.133	0.008**	3.615	0.057	4.440	0.230

HC, Healthy control; AR, at-risk; BD, bipolar disorder; WASI, Wechsler Abbreviated Scale of Intelligence; IQ, intelligence quotient; WAIS, Wechsler Adult Intelligence Scale; RBANS, Repeated Battery for the Assessment of Neuropsychological Status; IED, Intradimensional/Extradimensional Set Shift Task; EDS, Extradimensional Shift; SOC, Stockings of Cambridge; AGN, Affective Go/No-Go Task.

[a] Pairwise comparisons used *Z*-scores as the dependent variable where available.

* $p < 0.05$, ** $p < 0.01$ (Wald χ^2 from generalized linear model).

with respect to the extent to which neuropsychological abilities are impaired; notably, we did not find evidence of these same cognitive impairments in the AR participant group. Instead, the AR participants showed deficits in verbal ability and affective inhibition. The notable exclusion of executive function and working memory deficits, emerging in recent literature as the most promising candidates for endophenotypic status in BD (Bora *et al.* 2009; Glahn *et al.* 2007; Arts *et al.* 2008; Balanza-Martinez *et al.* 2008; Olvet *et al.* 2013), may be due to the younger age of the sample.

The present findings are largely consistent with a recent review (Olvet *et al.* 2013) which highlights little evidence of global intellectual impairment in people at familial risk of BD. There was neither strong support for the status of social cognitive abilities as endophenotypes for BD, despite some evidence for more severe impairments in the recognition of negative (sad) expressions in BD-I participants with a history of psychosis. This was found in the context of other, erroneous findings in the whole BD sample (enhanced recognition of disgust expressions).

Perhaps most interestingly, the finding of impaired inhibition in the context of an emotional go/no-go task in the AR group, in the negative and neutral, but not positive, valence conditions, is consistent with previous evidence of mood-congruent biases in the inhibition of emotional material in established BD (e.g. Elliott *et al.* 2004; Gopin *et al.* 2011) and AR samples (Brand *et al.* 2012). We note also that a subsample of the present AR group showed abnormal activation of the inferior frontal cortex during the inhibition of negative (fearful) stimuli during a facial emotion go/no-go task (Roberts *et al.* 2013). The accumulating evidence thus suggests that emotion-related cognitive disturbances may be intermediate processes in the development of BD. Longitudinal follow-up of this sample is required to determine whether these deficits predict later development of disorder. It remains curious as to why the present BD sample showed no evidence of similar inhibitory deficits for negative (or neutral) stimuli on this task, and it is possible that the use of medication in this group may be assisting in the correction of any such affective-inhibitory bias.

In considering the implications of the present findings it is important to note the substantial variability in the severity of cognitive deficits among cases with established BD in the broader literature (Burdick *et al.* 2014) in relation to their potential utility as intermediate phenotypes. Recent cluster-analytic studies of cognitive deficits in large groups of BD subjects have revealed the existence of subgroups (approximately 30% of BD cases) who show severe impairments in all neurocognitive domains, relative to a group of patients who show relatively spared cognitive

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Table 4. *Neuropsychological variables and pairwise comparisons for the HC, BD-I and BD-II groups*

	Group mean (standard deviation)			Statistical values for pairwise comparisons[a]					
				HC *v.* BD-I		HC *v.* BD-II		BD-I *v.* BD-II	
Measure	HC ($n = 75$)	BD-I ($n = 27$)	BD-II ($n = 25$)	χ^2	p	χ^2	p	χ^2	p
Intellectual ability									
WASI IQ	119.3 (10.7)	120.0 (9.1)	117.0 (12.4)	0.117	0.732	1.046	0.306	1.198	0.274
WASI vocabulary T-score	64.4 (7.3)	62.2 (8.5)	55.5 (34.3)	1.420	0.233	1.862	0.172	0.298	0.335
WASI matrix reasoning T-score	57.4 (7.9)	59 (5.2)	56.1 (6.5)	0.043	0.835	0.579	0.447	3.468	0.063
Working memory									
WAIS digit span, age-scaled score	10.5 (2.6)	10.1 (2.9)	11.1 (3.6)	1.516	0.218	0.327	0.567	1.098	0.295
WAIS letter–number sequencing	10.0 (2.3)	10.1 (2.9)	10.6 (3.3)	0.000	0.986	0.699	0.403	0.456	0.499
RBANS immediate memory index score	93.0 (13.8)	87.1 (13.9)	96.0 (12.9)	2.847	0.092	1.132	0.287	6.436	0.011**
RBANS delayed memory index score	92.1 (12.3)	92.0 (13.2)	93.0 (12.4)	0.044	0.834	0.102	0.749	0.102	0.749
Visuospatial ability									
RBANS visuospatial/constructional index score	95.5 (14.0)	98.8 (13.2)	93.4 (16.4)	0.516	0.473	0.385	0.535	2.300	0.129
Language									
RBANS language index score	104.3 (12.7)	104.9 (10.8)	107.8 (12.1)	0.184	0.668	1.581	0.209	.989	0.320
Attention									
RBANS attention index score	101.0 (15.6)	92.3 (14.5)	103.8 (15.0)	8.830	0.003**	0.517	0.472	7.271	0.007**
Executive functioning									
IED number of stages completed	8.6 (1.3)	8.6 (0.85)	8.8 (0.59)	0.713	0.398	1.571	0.210	1.410	0.235
IED total errors adjusted	23.0 (29.3)	24.6 (21.1)	17.5 (15.4)	1.012	0.315	1.955	0.162	1.944	0.163
IED pre-EDS errors	8.2 (5.7)	7.6 (4.0)	8.1 (3.7)	0.101	0.751	0.044	0.833	0.339	0.560
IED EDS errors	6.4 (8.2)	9.1 (11.1)	5.1 (7.6)	1.589	0.208	0.744	0.389	2.360	0.124
SOC problems solved in minimum moves	8.7 (1.8)	8.0 (1.7)	8.7 (2.4)	5.492	0.019*	0.064	0.800	1.202	0.273
SOC time spent thinking before making five move problems, ms	7253.6 (4971.6)	6151.1 (4575.7)	4343.8 (5789.0)	1.314	0.252	3.740	0.053	0.214	0.644
AGN errors of omission – negative valence trials	6.3 (12.4)	2.6 (2.2)	2.3 (26.0)	4.164	0.041*	0.515	0.473	0.002	0.965
AGN errors of omission – positive valence trials	8.2 (12.0)	4.2 (2.8)	4.2 (26.6)	5.612	0.018**	0.494	0.482	0.001	0.982
AGN errors of omission – neutral valence trials	11.4 (12.2)	6.5 (4.9)	6.9 (27.5)	6.126	0.013**	0.576	0.448	0.004	0.947
AGN errors of omission – non-shift trials	12.8 (17.9)	6.2 (4.3)	9.0 (30.4)	6.111	0.013**	0.347	0.556	0.195	0.659
AGN errors of omission – shift trials	13.1 (18.0)	7.1 (4.0)	9.2 (30.6)	5.444	0.020*	0.355	0.551	0.104	0.747
AGN errors of omission – all trials	25.9 (35.7)	13.2 (7.8)	22.9 (45.0)	5.896	0.015**	0.105	0.746	1.001	0.317
AGN errors of commission – negative valence trials	4.3 (4.4)	6.5 (5.5)	3.6 (25.2)	6.846	0.009**	0.011	0.916	0.269	0.604
AGN errors of commission – positive valence trials	5.9 (5.3)	7.8 (8.3)	4.5 (24.9)	1.637	0.201	0.065	0.799	0.352	0.553
AGN errors of commission – neutral valence trials	8.9 (5.4)	11.5 (7.2)	9.8 (26.6)	3.440	0.064	0.024	0.876	0.085	0.771
AGN errors of commission – non-shift trials	10.1 (6.8)	13.4 (10.2)	11.3 (28.6)	3.230	0.072	0.033	0.857	0.107	0.744

Table 4 (*cont.*)

Measure	Group mean (standard deviation)			Statistical values for pairwise comparisons[a]					
				HC *v.* BD-I		HC *v.* BD-II		BD-I *v.* BD-II	
	HC ($n = 75$)	BD-I ($n = 27$)	BD-II ($n = 25$)	χ^2	p	χ^2	p	χ^2	p
AGN errors of commission – shift trials	9.0 (7.6)	12.3 (10.1)	11.2 (28.1)	3.806	0.051	0.179	0.672	0.027	0.870
AGN errors of commission – all trials	19.1 (13.7)	25.7 (20.0)	27.3 (38.3)	3.699	0.054	1.013	0.314	0.031	0.860

HC, Healthy control; BD, bipolar disorder; WASI, Wechsler Abbreviated Scale of Intelligence; IQ, intelligence quotient; WAIS, Wechsler Adult Intelligence Scale; RBANS, Repeated Battery for the Assessment of Neuropsychological Status; IED, Intradimensional/Extradimensional Set Shift Task; EDS, Extradimensional Shift; SOC, Stockings of Cambridge; AGN, Affective Go/No-Go Task.

[a] Pairwise comparisons used *Z*-scores as the dependent variable where available.

* $p < 0.05$, ** $p < 0.01$ (Wald χ^2 from generalized linear model).

functioning (Hall *et al.* 2012; Burdick *et al.* 2014; Lewandowski *et al.* 2014). It is thus possible that these cognitive profiles will be found to run in families – with only the unaffected offspring of BD cases with severe cognitive deficits demonstrating (less severe) cognitive impairments in similar cognitive domains. However, the low number of sibling pairs in the present study was not sufficient to provide reliable estimates of concordance of cognitive deficits. It is also possible that more homogeneous samples enriched for severe cognitive deficit, such as probands with a family history of BD and schizophrenia, may yield greater cognitive deficits in offspring, given that cognitive deficits in the unaffected relatives of schizophrenia patients appear to be more robust than those reported for the unaffected relatives of BD (Sitskoorn *et al.* 2004).

This study provides additional evidence to the small number of existing studies of cognitive function in young adults (mean age < 30 years) with BD (Fleck *et al.* 2003; Strakowski *et al.* 2004; Larson *et al.* 2005; Nehra *et al.* 2006). It is notable that the cognitive deficits in this young BD sample are not as extensive as those reported previously for older BD cases (Bora *et al.* 2010), consistent with a recent meta-analysis which showed that the magnitude of post-illness-onset decline in intellectual functioning was greater in chronic BD than in first-episode patients (Trotta *et al.* 2014). Taken together, these findings suggest that cognitive decline may increase with the progression of illness, or could reflect the early onset of age-related cognitive decline (Schneider *et al.* 2012). Neurocognitive deficits frequently observed in BD may thus increase with illness progression, possibly as a function of repeated mood episodes (Post *et al.* 2012), or age. It is also possible that severe cognitive deficits are more apparent in BD patients with a history of psychosis (Glahn *et al.* 2004), though we found no evidence of this in our study. While we found no association between illness duration or the number of mood episodes and cognitive function for the BD patients in this study, this is perhaps not surprising as this relatively young group had a shorter illness duration and fewer mood episodes than participants in most other studies; notably, the meta-analysis of cognitive deficits in studies of BD (Arts *et al.* 2008) included mostly middle-aged adult relatives of BD probands (Kremen *et al.* 1998; Gourovitch *et al.* 1999; Keri *et al.* 2001; Ferrier *et al.* 2004; Zalla *et al.* 2004; McIntosh *et al.* 2005), with 37 of the 41 BD patient groups having a mean age >30 years. It should be noted that the AR group was shown to be impaired relative to HCs in some measures, yet did not differ from the BD group. This could be a function of medication, as many participants in the BD group were taking prescribed psychoactive medications yet participants in the AR group

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Table 5. *Social cognitive variables and pairwise comparisons for the HC, AR and BD groups*

	Group mean (standard deviation)			Statistical values for pairwise comparisons[a]					
				HC *v.* AR		HC *v.* BD		AR *v.* BD	
Measure	HC ($n = 75$)	AR ($n = 87$)	BD ($n = 52$)	χ^2	p	χ^2	p	χ^2	p
TASIT 1 total score	25.3 (2.2)	25.1 (1.8)	25.1 (1.8)	0.518	0.472	1.048	0.306	0.029	0.865
TASIT 2 total score	54.4 (5.1)	54.8 (3.9)	54.0 (5.0)	0.415	0.519	0.862	0.353	4.326	0.038*
TASIT 3 total score	56.7 (4.3)	57.0 (3.47)	55.4 (5.2)	0.050	0.823	4.844	0.028*	4.911	0.027*
Ekman – correctly identified anger	8.3 (1.2)	8.0 (1.5)	8.1 (1.3)	3.097	0.078	2.483	0.115	0.016	0.900
Ekman – correctly identified disgust	7.4 (1.7)	7.4 (2.0)	7.9 (1.6)	0.064	0.801	6.533	0.011**	0.749	0.387
Ekman – correctly identified fear	7.8 (1.7)	7.7 (2.0)	7.1 (2.5)	0.225	0.635	3.963	0.047*	2.199	0.138
Ekman – correctly identified happiness	9.9 (0.3)	9.9 (0.7)	9.9 (0.2)	0.017	0.896	0.392	0.532	0.029	0.866
Ekman – correctly identified surprise	9.0 (1.3)	9.0 (1.2)	8.9 (1.3)	0.106	0.745	0.515	0.473	0.104	0.747
Ekman – correctly identified sadness	7.9 (1.7)	8.2 (1.3)	8.1 (1.4)	1.755	0.185	0.332	0.565	0.748	0.387
Ekman – total score	50.4 (3.9)	50.2 (4.1)	50.0 (4.1)	0.112	0.738	0.712	0.399	0.475	0.491

HC, Healthy control; AR, at-risk; BD, bipolar disorder; TASIT, The Awareness of Social Inference Test; Ekman, Ekman 60-Faces Task.

[a] Pairwise comparisons used *Z*-scores as the dependent variable where available.

* $p < 0.05$, ** $p < 0.01$ (Wald χ^2 from generalized linear model).

Table 6. *Social cognitive variables and pairwise comparisons for the HC, BD-I and BD-II groups*

	Group mean (standard deviation)			Statistical values for pairwise comparisons[a]					
				HC *v.* BD-I		HC *v.* BD-II		BD-I *v.* BD-II	
Measure	HC ($n = 75$)	BD-I ($n = 27$)	BD-II ($n = 25$)	χ^2	p	χ^2	p	χ^2	p
TASIT 1 total score	25.3 (2.2)	25.4 (1.6)	24.7 (2.0)	0.017	0.897	1.224	0.269	2.245	0.134
TASIT 2 total score	54.4 (5.1)	53.4 (5.1)	54.7 (4.8)	1.801	0.180	0.047	0.828	0.839	0.360
TASIT 3 total score	56.7 (4.3)	55.2 (6.0)	55.7 (4.3)	0.037	0.847	1.423	0.233	0.128	0.720
Ekman – correctly identified anger	8.3 (1.2)	8.2 (1.5)	7.8 (1.4)	1.196	0.274	1.430	0.232	0.662	0.416
Ekman – correctly identified disgust	7.4 (1.7)	8.2 (1.5)	7.6 (1.7)	4.008	0.045*	0.243	0.622	1.320	0.251
Ekman – correctly identified fear	7.8 (1.7)	7.6 (2.4)	6.7 (2.6)	0.710	0.399	6.028	0.014**	1.911	0.167
Ekman – correctly identified happiness	9.9 (0.3)	9.9 (0.3)	9.96 (0.2)	0.015	0.904	1.561	0.212	0.280	0.597
Ekman – correctly identified surprise	9.0 (1.3)	9.0 (1.3)	8.8 (1.3)	0.006	0.939	0.837	0.360	0.529	0.467
Ekman – correctly identified sadness	7.9 (1.7)	8.4 (1.3)	8.0 (1.5)	1.120	0.290	0.003	0.959	1.023	0.312
Ekman – total score	50.4 (3.9)	51.3 (4.1)	48.8 (4.1)	0.123	0.725	2.850	0.094	4.010	0.045*

HC, Healthy control; BD, bipolar disorder; TASIT, The Awareness of Social Inference Test; Ekman, Ekman 60-Faces Task.

[a] Pairwise comparisons used *Z*-scores as the dependent variable where available.

* $p < 0.05$, ** $p < 0.01$ (Wald χ^2 from generalized linear model).

were not. It could also again be indicative of the relatively high-functioning BD sample in this study, who have experienced a low number of lifetime mood episodes compared with other studies (for a review, see Bora *et al.* 2010).

The present results should be considered in light of a number of limitations. First, this report is limited to a cross-sectional comparison of participants at genetic risk for BD, for which it is impossible to predict who will go on to develop BD; longitudinal follow-up of this sample will be necessary to determine the predictive capacity of neuropsychological function in relation to the later onset of BD. Second, it is possible that the presence of other lifetime psychiatric diagnoses in some subjects in the AR group (such as major depressive disorder, and anxiety, behavioural and substance use disorders) may be driving the cognitive deficits reported here, rather than being related to their genetic

https://doi.org/10.1017/S0033291715002147 Published online by Cambridge University Press

risk for BD. However, the exclusion of AR participants with current mood episodes somewhat mitigates this possibility. Third, the RBANS is a relatively brief measure designed to detect neuropsychological impairment that may not be as sensitive to subtle differences expected to be observed in the unaffected relatives of BD patients. Finally, although some of the participants in our unaffected relative and BD proband groups were biologically related, the recruitment procedures did not invite 'families' to participate; as such, there were not enough related sets of participants to examine cognitive deficits which may have been specifically inherited within families. Future studies of cognitive deficits shared among affected and unaffected family members would be valuable in this regard. Similarly, comparisons of concordance between related *v.* unrelated pairs of AR participants may be informative in testing the heritability of patterns of cognitive deficits.

In summary, we have demonstrated evidence for impaired general verbal ability and inhibition of emotional cues in young people at genetic risk for BD, as well as evidence for selective impairments in attention and immediate memory in young individuals with BD (particularly those with BD-I). These results are consistent with other evidence that supports selective deficits in verbal and emotional processing as intermediate phenotypes for BD, though is at odds with the considerable evidence for executive functioning deficits as endophenotypes for BD. While it remains difficult to delineate the influences of age or illness progression on cognitive functioning in BD, our findings of selective deficits in a young adult group of BD participants may be seen as consistent with recent clinical staging models of BD (Berk *et al.* 2007) which propose increasing cognitive impairment and associated structural and functional changes to the brain, in conjunction and function with greater illness duration (Fries *et al.* 2012). However, not all findings of this study support this model of cognitive decline with illness progression. Specifically, the fact that impairments in different cognitive domains were seen in the AR group that were not observed in the BD group, and vice versa, suggests distinct patterns of functioning between groups that are not entirely consistent with the hypothesis of progressive decline from BD risk to illness. Future study of cognitive and social cognitive deficits across clinical stages of BD is warranted.

Acknowledgements

This study was funded by the Australian National Health and Medical Research Council (NHMRC) (program grant 1037196) and the Landsdowne Foundation. M.J.G. was supported by the R.D. Wright Biomedical Career Development Fellowship from the NHMRC (1061875) and a grant to the Netherlands Institute for Advanced Studies from the National Academy of Science, the Netherlands. The funding agencies played no role in the design, analyses or interpretation of this study.

We acknowledge the contribution of research assistants from the University of New South Wales School of Psychiatry in data collection, and thank the participants for their time participating in this research.

Declaration of Interest

None.

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