Eur Arch Psychiatry Clin Neurosci (2009) 259:263–269 DOI 10.1007/s00406-008-0862-3

ORIGINAL PAPER

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Neurocognitive functioning in the early stages of bipolar disorder: visual backward masking performance in high risk subjects

Received: 23 May 2008 / Accepted: 28 November 2008 / Published online: 23 April 2009

Abstract *Introduction* Cognitive deficits, including deficits in early information processing, are associated with remitted bipolar disorder. The temporal relationship between these deficits and the clinical course is not known. The current study investigated whether or not deficits in early information processing were present before the onset and/or during the early stages of bipolar disorder. *Methods* Unaffected and remitted high risk offspring of well-characterized bipolar parents completed a visual backward masking task. For comparison we included a cohort of unaffected offspring of well parents and a clinically referred group of remitted bipolar patients. *Results* There was no evidence of a deficit in early information processing in well high risk subjects. As expected, the referred patient group had the highest error rates. After excluding the patients, interaction effect showed that the affected remitted high risk subjects performed differently in terms of error rates than unaffected high risk and control subjects. There were no significant differences in response times across study groups. Exploratory analyses revealed an association between a lifetime history of psychosis and increased errors on the task. *Conclusions* There was no evidence of a vulnerability in early information processing in offspring at risk for bipolar disorder. However, there were emergent changes in performance in the affected remitted high risk group. Psychosis appears to be an important clinical correlate associated with cognitive deficits. Mapping of the early course of bipolar disorder and associated changes in cognition has important implications for establishing critical periods for intervention.

Key words bipolar disorder · early stages · neurocognitive functioning · high risk · visual backward masking

Introduction

There is a substantial agreement in findings across a number of studies that even during periods of remission, adults diagnosed with bipolar disorder show deficits in neurocognitive functioning [26, 27]. This has in part been attributed to a burden of illness effect, likely representing a composite of neurobiological changes associated with repeated episodes and/or residual symptoms, complications of the disorder including substance use and perhaps to the effects of medications [20, 25, 30]. It is not clear how early in the course of illness neurocognitive deficits arise or if there is evidence of cognitive vulnerability predating the onset of a diagnosable mood disorder. Mapping the temporal association between cognitive deficits and the course of bipolar illness may assist with a more accurate early diagnosis and would have important implications for establishing critical periods for intervention and prevention.

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Deficits in early visual information processing as measured by visual backward masking (VBM), have been one of the most reliable neurocognitive findings in bipolar patients [10, 11, 23]. VBM is a procedure in which two brief stimuli are presented in rapid succession and the subject is required to identify the location of the first stimulus (the target) which is disrupted by the later stimulus (the mask) [31]. Under certain conditions, performance on the task is mediated by magnocellular visual pathways projecting to the dorsal occipito-parietal and frontal regions [8, 17], which have been implicated in structural and functional imaging studies of patients manifesting and at risk for mood disorders [15, 21].

The best way to distinguish between primary changes associated with the illness from abnormalities secondary to the burden of illness is through the use of a high risk study design. A number of studies have reported visual processing and perception deficits among the unaffected relatives of patients with schizophrenia [9, 17]. There have been two studies of early visual information processing using a VBM task in subjects at risk for bipolar disorder. In one study, Keri and colleagues reported that performance on a VBM task was similar between the unaffected relatives of bipolar patients and controls [18]. In a pilot study comparing performance on a VBM task between a small group of offspring of bipolar parents and controls [22], we reported that while all study subjects did worse on progressively shorter (more difficult) levels of the task, the affected remitted (lifetime depressive episodes) offspring made more errors at the hardest level of the task compared to unaffected high risk and control subjects.

These preliminary findings suggested to us that early information processing deficits may arise very early in the course of bipolar illness, prior to any full-blown episodes of mania. The current study was a further investigation of early visual information processing using a VBM task in a larger similarly recruited high-risk sample. We predicted that deficits in early information processing would not be present in the unaffected high risk subjects, but that differences in performance may be present early in the course of illness in the remitted affected high risk subjects. To examine for cognitive vulnerability in well but at risk offspring we included a control group of well offspring of well parents. In addition, to examine burden of illness effects we included a clinical comparison group of referred bipolar patients.

Methods

High risk families

Bipolar parents

Consenting offspring participating in a longitudinal study of the children of bipolar parents described elsewhere [4–6] participated in this neurocognitive study. Briefly, offspring were identified through their bipolar parent. Proband parents had been identified through their participation in genetic studies [32]. In accordance with research protocol, each proband completed a SADS-L [7] interview conducted by two research psychiatrists and met DSM-IV criteria for either bipolar I or bipolar II disorder. For this study, the other parent had no lifetime history of a major psychiatric disorder on the basis of SADS-L interviews.

The proband's response to long-term lithium was assessed in accordance with research protocol [1, 12]. Differences in long-term response to lithium is thought to identify a more homogenous subgroup of bipolar patients [1, 2] who have differences in clinical course and possibly therefore differences in underlying pathophysiology. Briefly, lithium responders had to have a highly recurrent illness prior to lithium, with no subsequent mood episodes while on therapeutic lithium (plasma level of at least 0.7 mmol/l). Lithium non-responders had to have at least two major recurrences associated with therapeutic lithium levels. Diagnosis and lithium response of the proband was based on blind consensus of at least two research psychiatrists utilizing all relevant clinical information.

High risk offspring

The offspring completed KSADS-PL [16] interviews conducted blind to familial association by a child and adolescent psychiatrist. DSM-IV diagnoses were made based on a blind consensus review, which included at least two additional psychiatrists, one being a child and adolescent psychiatrist. As part of the high-risk study, offspring were re-assessed annually or at any time symptoms developed. For this study, only those offspring deemed unaffected for a lifetime mood disorder or affected with a lifetime bipolar spectrum disorder (recurrent major depression, bipolar I or II disorder, bipolar nos or cyclothymia) in clinical remission were included. Remission was based on the absence of reported and observed clinically significant residual signs or symptoms (with no impairment of functioning) for at least two consecutive months prior to testing (in accordance with DSM-IV full remission criteria).

We included high risk subjects with a diagnosis of recurrent unipolar depression, given the parent history of clear-cut bipolar disorder and the wealth of evidence supporting the view that depression in first degree relatives of bipolar probands represent latent bipolar disorder especially if recurrent and/or early in the course of illness [3]. Bipolar not otherwise specified (bpnos) in this study referred to offspring with a lifetime history of recurrent major depression (full DSM-IV criteria) and full-threshold hypomanic episodes, but which fell short of the DSM-IV duration criteria.

Comparison groups

Low risk offspring

In order to compare to well individuals not at increased genetic risk for bipolar disorder, we selected psychiatrically well offspring of well parents recruited through two local schools in Ottawa already participating as control families in the ongoing longitudinal study previously described [4]. These families were initially identified on the basis of a demographic screening questionnaire the parent(s) completed that enquired about family composition and about the medical and psychiatric lifetime history of both parents and their children. Agreeable families completed a screening interview to verify the information on the psychiatric and medical health status of both parents. Identical to the high risk offspring, consenting children from control families completed a KSADS-PL interview

conducted by a child and adolescent psychiatrist and on the basis of a blind consensus review, were determined to be free from lifetime DSM-IV major psychiatric disorders (Axis I and II) at the time of neurocognitive testing.

Referred bipolar patients

Our main goal was to investigate whether subjects at genetic risk for mood disorders have a vulnerability in early information processing identifiable by abnormalities on VBM testing, therefore we investigated the offspring of bipolar parents, both affected and unaffected. In order to test the assay sensitivity of VBM, we also included a group of referred bipolar patients unselected for family history. Clinical patient populations are associated with higher burden of illness than are high risk populations, including an increased risk of neurocognitive impairment. Therefore, we recruited a consecutive series of patients referred to subspecialty outpatient clinics in Ottawa and Hamilton. Based on prospective longitudinal psychiatric assessment these patients met DSM-IV criteria for a bipolar disorder (bipolar I, II, nos) on the basis of consensus review and were in clinical remission (not acutely ill with non-impairing residual signs or symptoms) for a minimum of two consecutive months (in accordance with DSM-IV) at the time of testing.

Exclusion criteria for all subjects

The exclusion criteria for high risk and control subjects and referred patients included: (1) history of closed head injury resulting in loss of consciousness; (2) untreated active medical illness; (3) identified learning disability or diagnosis of ADHD; (4) lifetime history of substance dependence; (5) Prior electroconvulsive (ECT) treatment.

All participants in this study were properly informed about the study and signed a written consent form approved by the responsible research ethics board.

VBM task

The masking task was presented on an IBM compatible microcomputer with an SVGA3 monitor and circuitry capable of millisecond timing and following a method that we have previously employed in adults with established bipolar disorder and in our pilot high risk study [22, 24]. Visual angles subtended by the stimuli were approximately 0.57° on the vertical and horizontal dimensions. The target stimuli were letters (O, S, U, C) presented at one of four possible target locations (up, down, left or right, approximately 2.2° of visual angle away from fixation); the mask consisted of overlapping X's and Os. Subjects identified the location of the target by pointing in the correct direction using a joystick; they were not required to identify the target. This condition optimizes transient channel responses. Five blocks of 16 target location practice trials were presented prior to the task, followed by three blocks with increasingly short target-to-mask intervals and ending with a block of variable target-to-mask intervals identical to the format of the upcoming task.

Trials began with presentation of a fixation point followed 400 ms later by the appearance of a target 14 ms and then by a 14-ms mask. The target-mask inter-stimulus intervals (ISIs) were 14, 29, 43, 57, 86 and 114 ms. There were 48 non-practice trials at each ISI, distributed evenly across the four possible target locations, with an overall total of 368 trials including all practice trials. Percentage of incorrect responses and mean reaction time (RTs) at each ISI constituted the dependent measures.

Statistical analyses

We performed chi-square tests and one-way ANOVA tests for comparison of categorical and continuous demographic and clinical variables, respectively. Repeated measures analyses of variance compared RTs and error rates between groups at each ISI. In case of a significant interaction, we performed one way ANOVA for each inter-stimulus interval. Since already the nominal *P* values for these comparisons were non-significant, there was no need to control for multiple comparisons. We also calculated Cohen's d effect size for pairwise differences between groups.

Analyses of variance were also used to compare performance of high risk subjects with presence versus absence of family history of response to long-term lithium, personal history of psychotic symptoms and medication at the time of testing. Pearson's *r* was used to test for associations between RTs or error rates and age or clinical scales scores. For some of the exploratory analyses (ie differences in VBM performance between subjects with versus without lifetime history of psychotic symptoms, differences between medicated and non-medicated subjects at the time of testing, association between symptom scores and VBM performance), we combined the referred remitted patients and affected remitted high risk offspring in order to increase power. Multiple linear regression models were utilized to determine whether parent diagnosis, parent clinical course, parent lithium response, parent lifetime psychotic symptoms, parent hospitalization were associated with error rates in the high- risk offspring. For these analyses we looked at error rates at 14 ms, the most difficult level of the task.

Results

Sample description

The study sample consisted of 54 unaffected high risk offspring, 36 affected remitted high risk offspring, 79 unaffected offspring of well parents (controls) and 23 referred remitted bipolar patients (referred patients) in this study (refer to Table 1). There was a trend for differences in proportions of females between groups, with the largest proportion of females in the affected

Table 1 Descriptive characteristics of the subjects by group

	High risk affected subjects	High risk unaffected subjects	Referred bipolar patients	Controls	*P*
N	36	54	23	79	
Age (years)	22.0 (4.2)	18.5 (5.0)	17.87 (2.8)	17.3 (5.8)	0.01
Sex *n* (%) Females	26 (72.2)	25 (46.3)	12 (52.2)	49.0 (62.0)	0.08
HAMD	2.1 (2.3)	0.9 (1.5)	6.1 (6.8)	0.6 (1.0)	0.01
BDI	4.6 (3.6)	3.5 (3.7)	NA	3.7 (3.1)	NS
CGAS/GAF	84.8 (9.3)	87.3 (7.7)	74.3 (7.5)	90.6 (4.7)	0.01

Values are means and standard deviations in parentheses
NA not available

Table 2 Clinical characteristics of the high risk affected and bipolar patient groups

Variables	Affected remitted high risk subjects (n = 36)	Referred remitted bipolar patients (n = 23)	Significance
Mean age index mood episode years (standard deviation)	16.0 (3.4)	14.8 (2.1)	NS
Age at testing years (standard deviation)	22.0 (4.4)	17.9 (2.8)	$P < 0.01$
Mood diagnosis number (%)	BP I = 2 (5.6) BPII = 12 (33.3) BP NOS = 2 (5.6) Cyclothymia = 1 (2.8) Unipolar = 19 (52.8)	BP I = 9 (39.1) BPII = 4 (17.4) BP NOS = 10 (43.5) Cyclothymia = 0 Unipolar = 0	$P < 0.01$
Nature of the clinical course episodic/remitting number (%)	21 (58.3)	2 (10.5)	$P < 0.01$
Mood stabilizer ever number (%)	Yes = 12 (33.3) Anticonvulsant = 2 Atypical antipsychotic = 3 Lithium = 9 Combination = 1	Yes = 21 (81) Anticonvulsant = 5 Atypical antipsychotic = 16 Lithium = 7 Combination = 2	$P < 0.01$
Mood stabilizer at testing number (%)	Yes = 12 (33.3) Anticonvulsant = 1 Atypical antipsychotic = 0 Lithium = 8 Combination = 0	Yes = 19 (100) information about medication at the time of testing missing in 4 subjects Anticonvulsant = 1 Atypical antipsychotic = 11 Lithium = 1 Combination = 6	$P < 0.01$
Psychotic symptoms ever number (%)	Yes = 6 (16.7)	Yes = 12/19 (63.2) information about psychosis missing in four subjects	$P < 0.01$
Hospitalization ever number (%)	Yes = 6 (16.7)	Yes = 8 (34.8)	NS

high risk group and lowest proportion of females in the unaffected high risk group. There were differences between groups in age, with affected high risk subjects being the oldest and control subjects the youngest. The global functioning scores were lower in the referred patient group, whilst these were comparable between the high risk and control groups.

There were significant clinical differences between the high risk affected remitted group and the referred remitted patient group (Table 2). Specifically, the referred patients had more cases of bipolar I disorder, a higher proportion of cases with a non-episodic illness course and higher lifetime rates of psychotic features. Finally, the referred patients had higher rates of lifetime exposure to mood stabilizing medication and more of the patients were treated with mood stabilizers at the time of neurocogntive testing.

Neither Hamilton Depression Rating Scale scores (HAMD) nor the Beck Depression Rating Scale scores (BDI) correlated with numbers of errors or median response times for any of the groups. Therefore we did not use these as covariates for the final analyses. There was no association between age and median response times or error rates in a combined sample. Therefore we did not use age as a covariate.

Error rates between the groups

There was a significant main effect of group, such that the referred patients showed the highest numbers of errors across all ISIs (F = 6.32, df = 3; 188, $P < 0.001$), see Fig. 1. The number of errors increased with shortening of the ISI in all groups (main effect of ISI F = 173.93, df = 5; 940, $P < 0.001$). There was no interaction between ISI and group (F = 1.51, df = 15; 940, P = 0.10).

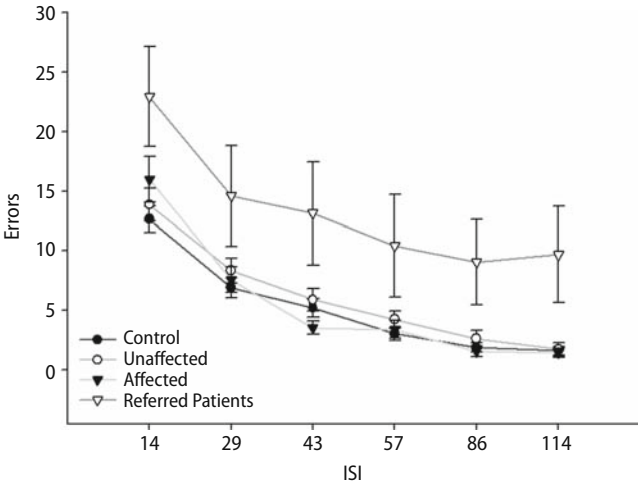

Fig. 1 Error rates across ISIs between groups on the VBM task, four groups (controls, high risk affected, high risk unaffected, referred bipolar patients)

Excluding the patient group resulted in comparable error rates between the affected high risk, unaffected high risk and control groups (F = 0.51, df = 2;166, P = 0.51). There was a main effect of ISI with more errors at shorter ISIs in all groups (F = 175.43, df = 5; 830, $P < 0.001$) and significant interaction between group and ISI (F = 2.02, df = 10; 830, P = 0.03). Visual inspection of Fig. 1 reveals that this interaction was likely driven by affected high risk subjects performing the worst at ISI of 14 ms, but the

best among the three groups at the ISI of 43 ms. In post hoc comparisons, none of these differences were statistically significant even at uncorrected p levels (ISI 14 ms, error rates between unaffected, affected, control subjects, $F = 1.33$; $df = 2$; 166, P uncorrected = 0.27, effect sizes for affected versus control subjects Cohen's d ES = −0.31, affected versus unaffected high risk subjects Cohen's d ES = −0.2, ISI 43 ms error rates between unaffected high risk, affected high risk, control subjects, $F = 1.56$; $df = 2$; 166, P = uncorrected 0.21, effect sizes—affected versus control subjects Cohen's d ES = 0.3, affected versus unaffected HR subjects Cohen's d ES = 0.43.).

Median response times

There were no significant differences in median response times between controls, unaffected high risk, affected high risk and referred patients ($F = 0.64$, $df = 3$; 188, $P = 0.59$). There was a main effect of ISI ($F = 306.31$, $df = 5$; 940, $P < 0.001$), with longer median response times at shorter ISIs and an interaction between ISI and group ($F = 3.73$, $df = 15$; 940, $P < 0.001$), such that referred patients had lower reaction times at easier levels of the task (see Fig. 2).

Excluding the patient group resulted in comparable median response times between the affected high risk, unaffected high risk and control groups ($F = 0.13$, $df = 2$; 166, $P = 0.88$). There was no ISI by group interaction ($F = 0.19$, $df = 10$; 830, $P = 0.99$). The prolongation of median response times with shortening of the ISIs remained significant ($F = 231.82$, $df = 5$; 830, $P < 0.001$).

Exploratory analyses

Twenty-nine (54%) of the unaffected high risk subjects and 21 (58%) of the affected high risk subjects derived from lithium responsive families. There were no differences in numbers of errors or median response times between high risk subjects from lithium responsive compared to lithium non-responsive families (error rates: $F = 0.00$, $df = 1$; 86, $P = 0.96$; median response times $F = 0.61$, $df = 1$; 86, $P = 0.44$), nor was there any interaction between lithium response in parents and status of the offspring (affected, unaffected) (error rates $F = 1.08$, $df = 1$; 86, $P = 0.30$; median response times $F = 1.12$, $df = 1$; 86, $P = 0.29$). Furthermore, there was no ISI by group interaction for error rates or median response times.

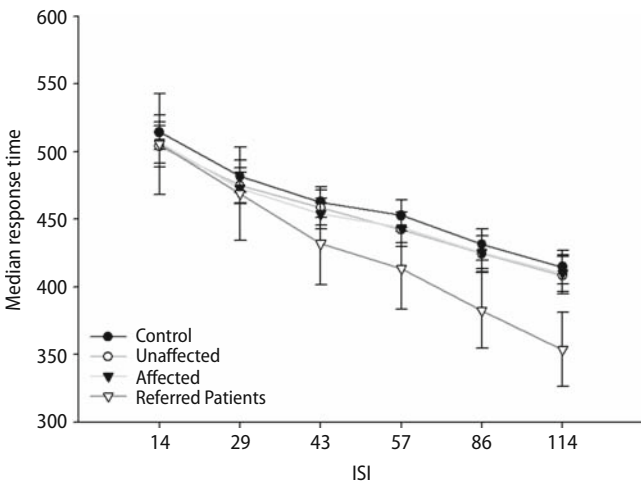

Fig. 2 Median response times across ISIs between groups on the VBM task, four groups (controls, high risk affected, high risk unaffected, referred bipolar patients)

In a multiple linear regression model, none of the clinical variables pertaining to the parent clinical phenotype, including parent diagnosis, parent clinical course, parent lithium response, parent lifetime psychotic symptoms and lifetime number of hospitalizations, were associated with error rates in the high risk offspring.

There were no differences in either response time or error rates between those high risk subjects with a lifetime diagnosis of recurrent unipolar versus bipolar disorder (error rates $F = 0.41$, $df = 1$; 34, $P = 0.53$; median response times $F = 0.05$, $df = 1$; 34, $P = 0.82$).

In establishing why referred bipolar patients showed poorer performance, we looked at following variables: severity of symptoms, lifetime history of psychosis, medication at testing. Since the HAMD scores fell within a narrow range, we combined all subjects in order to increase power to detect even small differences. There was no association between HAMD scores and either error rates ($r = -0.08$, $P = 0.42$) or median response times ($r = 0.09$, $P = 0.36$).

Affected remitted subjects (high risk + referred patients) with a prior history of psychosis made more errors relative to affected remitted subjects (high risk + referred patients) without a prior history of psychosis ($F = 4.56$, $df = 1$; 53, $P = 0.03$), with no ISI by group interaction ($F = 0.90$, $df = 5$; 265, $P = 0.90$). There were no differences between affected subjects (high-risk + referred patients) with a prior history of psychosis compared to those without psychosis in median response times ($F = 0.56$, $df = 1$; 53, $P = 0.46$), although there was an interaction between ISI and group ($F = 2.93$, $df = 5$; 265, $P = 0.01$) such that a history of psychosis was associated with increased response times at shorter ISIs.

There were no differences between affected subjects (high risk + referred) taking medication compared to affected subjects (high risk + referred) not medicated at the time of testing (error rates $F = 1.90$, $df = 1$; 53, $P = 0.17$; median response times $F = 0.25$, $df = 1$; 53, $P = 0.62$) and no interaction between medication and ISI for either error rates or median response times (error rates $F = 0.48$, $df = 5$; 265, $P = 0.79$; median response times $F = 0.90$, $df = 5$; 265, $P = 0.48$).

Discussion

The major aim of this study was to examine whether or not a genetic risk for bipolar disorder was associated with abnormalities in early information processing. The main finding from this study was no evidence of an early visual information processing deficit prior to the onset of bipolar disorder in a prospectively studied cohort of high risk individuals. That is, there was no significant difference in error rates or median response times on a visual backward masking task between unaffected high risk and control subjects. This finding replicates our pilot study [22] and suggests that a deficit in early information processing is not a vulnerability trait in those at familial risk for bipolar disorder.

Consistent with our previous report, affected remitted high risk subjects early in the course of bipolar disorder, had a different pattern of responding on the VBM task compared to unaffected high risk and control subjects. That is, the affected remitted high risk subjects made more errors than the unaffected high risk and control subjects at the shortest ISI (the hardest level of the task), but they made less errors than the other two groups at ISI of 43 ms. In post hoc analyses, these differences were not statistically significant and their biological significance remains unknown.

The findings in this study are in keeping also with our recent structural imaging investigations showing no differences in subgenual cingulate volumes or in concentrations of neurochemicals in the anterior cingulate, as measured by magnetic resonance spectroscopy between high risk (unaffected and affected) and control subjects [13, 14]. Taken together these data suggest that there is no evidence of a major neurological deficit in high risk individuals or in affected individuals early in the course of uncomplicated bipolar disorder. These findings also concur with findings of Keri and colleagues [18] and with other high risk studies reporting generally less severe developmental abnormalities compared to schizophrenia prior to and during the early stages of bipolar disorder [19, 28, 29].

In the case of a negative finding, it is crucial to demonstrate assay sensitivity or in other words to demonstrate that we can detect an abnormality if it exists. To this goal, we included a referred patient group typically associated with greater burden of illness. Compared to high risk affected subjects, the patient group had a greater proportion of medicated subjects, greater proportion of subjects with psychotic mood disorders, and thus greater likelihood of having neurocognitive impairments. Indeed the referred patients made more errors on the VBM task and showed a different pattern of timed reaction during the task. This finding demonstrates that we were able to detect VBM impairment in the patient group and reassures us that the lack of deficit in the high risk and control offspring is a true negative finding.

We also attempted to elucidate which variables may underlie the VBM deficits observed among some of the affected high risk subjects and the referred bipolar patients. Exploratory analyses revealed an association between a prior lifetime history of psychotic symptoms and increased error rates. None of the other variables provided an explanation to these differences. In particular, we detected no differences in median response times or error rates between medicated and unmedicated subjects at the time of testing. The significantly worse performance among referred patients was not caused by presence of unipolar patients among the high risk subjects, as there were no differences in any VBM measures between bipolar and unipolar offspring of bipolar parents. This is not surprising given the very high likelihood that depression in the high risk population is genetically related to the bipolar disorder segregating in the family [3]. Likewise severity of symptoms according to HAMD was no associated with VBM performance. The lack of association between symptom levels and VBM was likely due to narrow range of symptom scores, since we selected subjects in remission at the time of scanning.

Limitations of the current study include the confounding of illness course with prior and current exposure to mood stabilizers. Of relevance here is the fact that none of the subjects with established illness had prior ECT or a history of substance dependence. Secondly, it may be that more sensitive and specific neurocognitive tasks will be able to detect subtle differences in cognition in high-risk subjects or during the early stages of bipolar illness. This high risk cohort was highly selected and derived largely from intact middle class families therefore may not generalize to other high risk populations. Our post hoc exploratory analyses of variables underlying VBM deficits among referred bipolar patients are preliminary and require future replications.

A clear strength of this study lies in the fact that the parents of the high risk and control offspring were comprehensively assessed and that the offspring were followed and repeatedly prospectively studied. Therefore the stability and accuracy of the parent and offspring diagnoses, and of the assessment of clinical status at the time of testing, is at the best possible clinical standard. In addition, the high risk subjects were largely psychotropic drug naïve and all subjects were free from other potential confounders such as prior substance use disorder or learning disabilities and major neurological problems.

There is accruing evidence that bipolar disorder evolves through recognizable clinical stages from non-specific prodromes to early stages characterized largely by depressive episodes followed on average several years later by the onset of activated episodes [4]. Therefore the temporal mapping of neurocognitive deficits in the evolution of the illness is important. From this study and other findings, it appears that neurocognitive functioning is largely intact in

uncomplicated bipolar disorder until the clinical onset of illness. Furthermore, these findings highlight the importance of early intervention in order to prevent burden of illness effects. This appears especially true in individuals who experience psychotic symptoms. More research is needed to characterize the early stages of bipolar illness and to understand the mechanism underlying burden of illness effects.

Acknowledgment The authors would like to thank Ms Leah Crawford for her assistance with this manuscript.

Financial Disclosures Dr. Duffy was the recipient of an Intermediate Investigator Award from the National Alliance for Schizophrenia and Affective Disorders (NARSAD) and a Canada Research Chair Tier II in Child Mood Disorders (CRC). This study was sponsored by operating grants from the Ontario Mental Health Foundation (OMHF) and from the Canadian Institutes of Health Research (CIHR). The authors have no financial or potential conflict of interest to disclose with respect to the subject matter of this paper.

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