Original article

The Maudsley Bipolar Disorder Project: insights into the role of the prefrontal cortex in bipolar disorder I

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INTRODUCTION

Episodes of mania or hypomania and periods of depression[1] are the hallmark of Bipolar disorder (BD). Specifically, manic episodes characterize Bipolar Disorder I (BDI) whereas hypomanic episodes define Bipolar Disorder II (BDII).[1]

Despite knowledge of the underlying pathophysiology of BD being rather incomplete, important advances in the fields of cognition and brain imaging have begun to determine the neural networks involved.

Neuroanatomical changes are mainly regional in BD, and involve the amygdala, prefrontal cortex (PFC), and anterior cingulate cortex (ACC). Reduced gray matter volume has been demonstrated in the dorsal PFC (DPFC), mostly on the left.[2-4] Similar changes are evident in the ventral PFC (VPFC), particularly in Brodmann Areas (BA) 44 and 47.[3,4] Some studies report a volume decrease in the left cingulate gyrus,[3,5] however this is not always the case.[4,6] In contrast, the amygdalae appear enlarged bilaterally or only on the left.[4,7,8]

Resting state functional imaging studies of depressive states have reported associated reductions in the activity of the DPFC[9] and increases in the amygdala.[10] Manic states have been associated with decreased activity in the VPFC and increased activity in the ACC.[11] Trait-related decreases in brain activation have also been reported within the left VPFC (BA47, 10).[12]

BD patients demonstrate a largely preserved general intellectual ability (IQ),[13] however, performance across domains is altered during acute episodes of depression or mania.[13] Naturally knowledge of the presence or absence of trait deficits is more useful in terms of understanding the pathophysiology of the disorder. In this regard, studies that have assessed cognitive function of patients during remission or euthymia have discovered persistent deficits in memory and aspects of executive function. Despite both of these domains being affected by current mood state, it also seems to be the case that some BD patients exhibit more enduring impairments which are independent of mood.[13-16] Cognitive deficits in BD also appear to be associated with longer duration of illness or increased number of episodes[17] as well as the presence of psychotic symptoms.[13]

Contributions from factors such as medication and family history of affective disorder have not been examined.

The Maudsley Bipolar Disorder Project commenced in 1999 and data is still being collected. It consists of a case-control design, and actually comprises several interconnected modules focusing on cognition, structural and functional neuroanatomy of BDI.[16,18,19] This article highlights the study's contribution to our understanding of the pathophysiology of BD, and presents some of the methodology utilized.

METHODS

We identified 63 patients with BDI from a one-month prevalence survey of all patients (n = 425) receiving treatment in a sector of the South London and Maudsley National Health Trust. Of these patients, 43 agreed to participate in the full study protocol. Subjects were matched to an equal number of healthy volunteers on age (within 2 years), gender, ethnicity and years of education. Diagnoses were assessed in patients by using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID).[20] Similarly, SCID was used to ensure the absence of a psychiatric diagnosis in the controls. Symptomatology was assessed using the 31-item Hamilton Depression Rating Scale (HAMD)[21] and the Mania Rating Scale from the Schedule for Affective Disorders and Schizophrenia – Change Version (MRS).[22] We used the Family Interview for Genetic Studies to gather information relating to family history. This was applied to each patient and one informant.

The same qualified psychologist conducted all cognitive assessments in a single session. The Wechsler Adult Intelligence Scale Revised (WAIS-R)[23] was used to appraise general intellectual ability (IQ), and the National Adult Reading Test (NART)[24] yielded estimates of predicted premorbid IQ. The Wechsler Memory Test III (WMS-III)[25] was used to assess memory. Executive function was assessed using the following tests: The Hayling Sentence Completion Test (HSCT),[26] which assesses speed of verbal planning and initiation; the Wisconsin Card Sorting Test (WCST),[27] a rule attainment and set shifting task; the Controlled Oral Word Association Test

(COWA);[28] and the Stroop Color Word Test (SCWT),[29] a measure of interference and inhibitory control. Patients were assessed whilst in remission. This was defined as a three-month period of clinical stability, without alteration of their medication regime, prior to the assessment. In addition, their total scores on the HAMD and MRS were below 10.

Subjects underwent a structural magnetic resonance imaging (MRI) scan on a 1.5T GE MR system. A 3-D spoiled GRASS T1-weighted dataset was acquired in the coronal plane with 1.5mm contiguous sections (TR = 35 ms, TE = 5 ms, flip angle = 20 degrees, one data average and a 256x256x128 pixel matrix). Image analysis was implemented in SPM99 operating under Matlab5 (Mathworks, Inc).

A sub-set of these subjects was selected for functional MRI (fMRI), which was used to assay patterns of brain activation during performance of executive function tasks. The following criteria were used to select patients: a) in clinical remission, b) receiving mood stabilizer monotherapy, and, c) a test performance less than 0.5 standard deviation below the control mean on all tests. Controls and patients were each matched for age, gender, years of education and IQ. fMRI data was obtained during performance of the N-back and Iowa gambling tasks, which were selected for their ability to specifically engage dorsal[30] and ventral PFC,[31] respectively. Subjects are required to detect a target letter during the N-back letter-sequencing task, which is a test of verbal working memory. In the 0-back condition, subjects indicate when a preselected target letter appears. In the 1-, 2- and 3- back conditions, the letter appearing in the preceding 1, 2 or 3 trials, respectively, represents the target. During the Iowa Gambling task, the subject selects a card from one of 4 decks in order to win 'pretend' money. Deck A has frequent, small magnitude punishments, deck B has infrequent, but higher punishments, deck C has frequent, small rewards, and deck D has infrequent, higher rewards. Gradient-echo echoplanar magnetic resonance images were acquired with a 1.5T GE Neurovascular Signa MR system (General Electric, Milwaukee, WI) fitted with 40 mT/m high speed gradients using a blocked periodic design incorporating alternating active and control conditions during the N-back and Gambling tasks. Image analysis was performed on a SPARC

Ultra 10 workstation (Sun Microsystems, Palo Alto, CA) using MATLAB (version 5.3, The Mathworks Inc, Natick, MA) and SPM99 software (Statistical Parametric Mapping, The Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm).

Analysis

Cognitive variables

A case–control comparison was performed using the cognitive test variables from the domains of general intellectual ability, memory, executive functioning, perception, and expressive language (naming). Multivariate tests (Wilk's tests) were used for this analysis. Subsequently, we examined the relationship between potential predictors and cognitive variables. The following predictors were analyzed: age at onset and duration of illness, total scores on the MRS and HAMD, the presence of any psychotic symptoms in the past, positive family history of affective disorder, and type of medication at the time of testing. Predictors that were associated with cognitive variables at the 5% significance level were entered into a multiple regression model.

Imaging

Structural. A regression model was fitted at each voxel in order to analyze between-group differences in regional grey matter volume. Permutation testing was utilized in order to assess statistical significance, and regional relationships were tested at the level of voxel clusters. A threshold of $p \leq 0.01$ was set, such that for all analyses less than one false positive cluster was predicted over that search volume.

Functional. A categorical design was used to analyze the active and control conditions for each task, i.e. 1/2/3-back vs. 0-back, and gambling vs. card selection. This utilizes a box-car function with haemodynamic response function to create the general linear model, which allows comparison of enhanced brain activation during the active conditions with that during the control element. A parametric design was used to investigate the 1, 2 and 3-back conditions. This

elucidated areas where activation was linearly positively correlated with working memory load. Corrections for multiple comparisons were made using voxel- and cluster-level statistics, with a threshold set at $p < 0.05$.

Between-group comparisons were used to assess for any significant differences between the patient and control groups in terms of the above analyses. A random effects model was used. The statistical parametric maps were thresholded at $p < 0.05$. Multiple comparisons were corrected for with cluster level statistics.

RESULTS

Subjects

Table 1 displays the clinical characteristics and demographics of the participants. Details of medication taken by patients at the point of neuropsychological assessment are provided in table 2. The mean dose of antipsychotic medication at the time of testing was 384.5 mg (SD = 457.4 mg) chlorpromazine equivalents. The mean doses of mood stabilizers were: lithium, 936.3 mg (SD = 222.3 mg), sodium valproate, 833.3 mg (SD = 321.4 mg), and carbamazepine, 800.0mg (SD = 400.0 mg).

Table 1 - Demographic and clinical characteristics of participants (n = 43)

Age in years	42.9 (11.1)
Gender (M:F)	20 (47%) : 23 (53%)
Mean years of education (SD)	13.12 (2.89)
Median duration of illness (IQR) in years	16.0 (19.0)
Mean age at onset (SD) in years	25.5 (9.2)
Median Mania Rating Scale [MRS] total score (IQR)	0.0 (1.0)
Median Hamilton total score (IQR)	7.0 (13.00)
Mean Global Assessment of Functioning [GAF] score (SD)	70.79 (15.07)
No. of patients (%) of patients with past psychotic episode	34 (79.1)
No. of patients (%) negative substance abuse	38 (88.4)
No. of patients (%) with positive family history for affective disorders	32 (74.4)

SD = standard deviation; IQR = inter-quartile range.

Table 2 - Current medication of participating patients

Type of medication	**N (%)**
Any antipsychotic	22 (51.2)
Atypical antipsychotic	12 (27.9)
Typical antipsychotics	10 (23.3)
Any mood stabilizer	30 (69.8)
Lithium	15 (34.9)
Sodium valproate	7 (16.3)
Carbamazepine	6 (14.0)
Other anticonvulsant	2 (4.7)
More than one mood stabilizers	5 (11.6)
Any antidepressant	8 (18.6)
Tricyclic antidepressant	3 (7.0)
SSRI antidepressant	5 (11.6)
Two or more psychotropics of different classes	20 (46.5)

SSRI = selective serotonin reuptake inhibitors.

Cognitive profile

In BD patients compared to controls, multivariate tests showed reductions across all cognitive domains, with effect sizes ranging from 0.2 to 1 standard deviations below the control mean (figure 1). However, the largest significant effects were demonstrated in variables relating to executive function (Wilk's tests; $F[12,28] = 2.6$; $p = 0.02$) for the BD group.

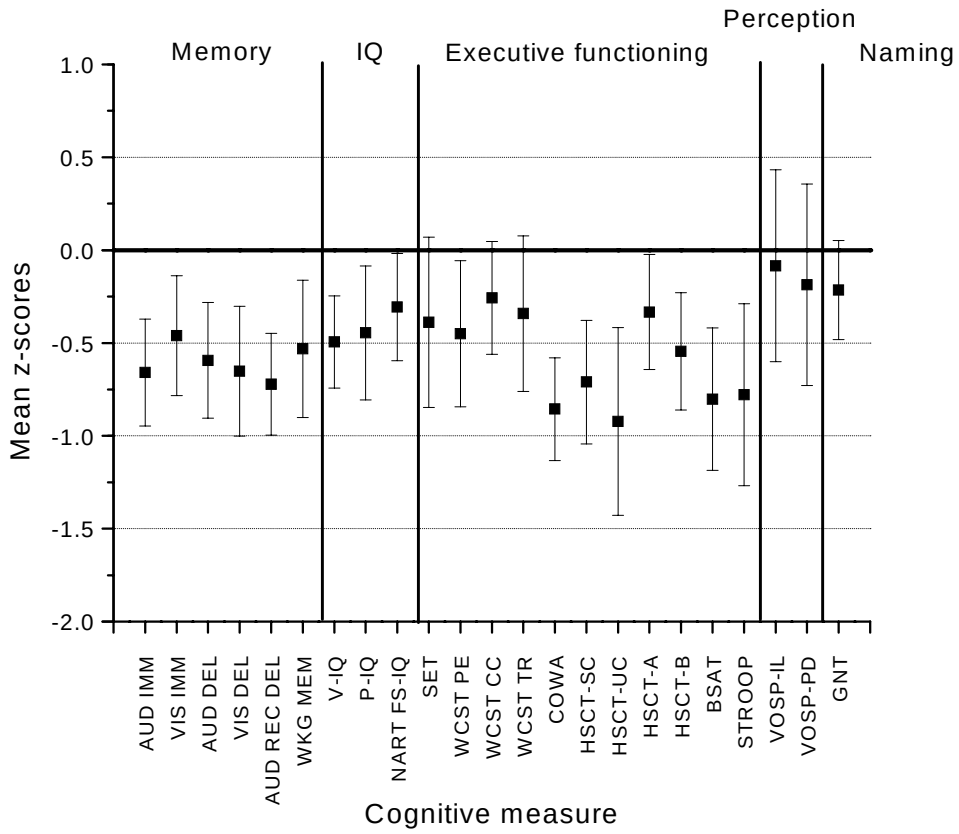

Figure 1 - Mean z-scores and approximate 95% CIs for neuropsychologic variables

Wechsler Memory Scale III: AUD IMM = auditory immediate memory; VIS IMM = visual immediate memory; AUD DEL = auditory delayed memory; VIS DEL = visual delayed memory; AUD DEC REL = auditory recognition delayed; WKG MEM = working memory. Wechsler Adult Intelligence Scale Revised: V-IQ = verbal IQ, P-IQ = performance IQ. National Adult Reading Test: NART FS-IQ = full scale IQ. Badley Dysexecutive Syndrome, Six elements test: SET = six elements, raw score. Wisconsin Card Sorting Test: WCST-PE = perseverative errors; WCST-CC = categories completed; WCST- TR = trials to complete first category. Controlled Oral Word Association: COWA = number correct. Hayling Sentence Completion test: HSCT-SC = sensible completion total time; HSCT-UC = unconnected sentences completion time; HSCT-A = Category A errors; HSCT-B = Category B errors. Brixton Spatial Anticipation Test: BSAT = test errors. Stroop Color Word Test: STROOP = total correct on interference condition. Visual object and

space perception: VOSP-IL = incomplete letters; VOSP-PD = position discrimination. Graded Naming Test: GNT = error score.

Predictors of cognitive function

Performance decrements in tests assessing general intellectual function (WAIS-R, NART), working memory (WMSIII) and cognitive set shifting (WCST, HSCT) were mainly associated with current use of antipsychotic medication. Duration of illness was negatively correlated with measures of response planning (HSCT errors), and general and working memory (WMSIII). Impairment in response initiation and inhibition (COWA, HSCT sensible completion time) was associated with antipsychotic use and a history of psychosis, but the effect of the latter became non-significant after adjustment. With regard to depression and mania, measures of response suppression (SCWT) were affected by symptom severity. In addition, there was reduced impairment in behavioral inhibition (as measured with the HSCT error score) in the presence of a family history for affective disorders, which was also associated with higher Full Scale IQ Scores.

Structural brain changes

In comparison with controls, BD patients had reduced grey matter bilaterally in orbitofrontal and inferior frontal gyri (BA11, 44, 45, 47), inferior and middle temporal gyri (BA37, 39), cuneus and thalamus, and in the left insula and dorsolateral prefrontal cortex (BA9, 46), right fusiform gyrus (BA36, 37) and inferior parietal lobe (BA7). BD patients had areas of increased grey matter bilaterally in the amygdala, temporal pole (BA38), middle and superior temporal gyri (BA21), left putamen and left post-central gyrus.

fMRI of prefrontal cortical function in BD

A total of seven patients, comprising five women and two men, from the entire pool of participants met the entry criteria for this module. The categorical analysis of the N-Back Task

(figure 2) revealed that both controls and patients displayed similar activation patterns in the parietal cortices (BA7, 40), the superior (BA6) and middle frontal gyri (BA9, 46) and the inferior temporal gyrus (BA37). No significant group differences were present.

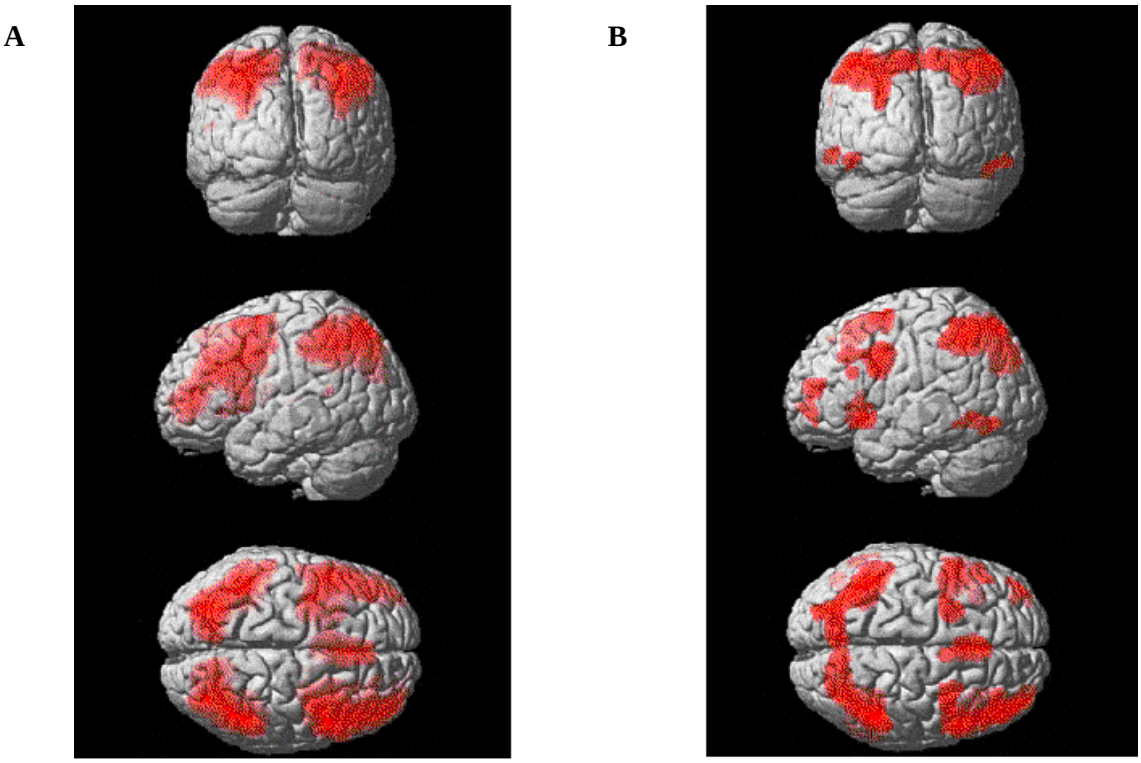

Figure 2 - Cerebral activation in controls (A) and patients (B) during the N-Back task (categorical analysis)

The parametric analysis of the N-Back Task showed that the effects of increasing memory load in control subjects were localized bilaterally to the superior (BA6) and middle frontal gyrus (BA 9, 46) and the anterior cingulate gyrus (BA32) as well as the right superior parietal lobule (BA7). In BD patients, these effects were localized to the left superior parietal lobule (BA7) and the right middle frontal gyrus (BA10).

During the Gambling Task, controls demonstrated brain activation associated with incentive decision making in the left superior frontal gyrus (BA6), the bilateral middle (BA8, 9, 46) and inferior (BA44, 45) frontal gyri, and the right superior parietal lobule (BA7) (figure 3).

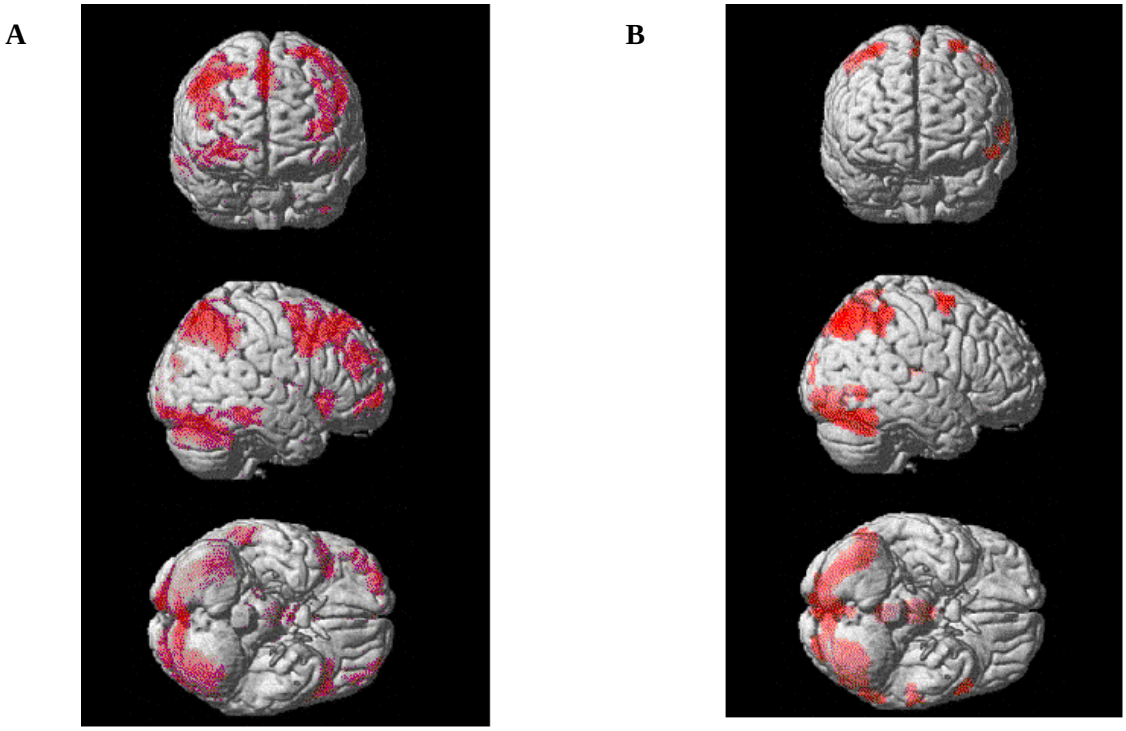

Figure 3 - Cerebral activation in controls (A) and patients (B) during the gambling task

In patients, activation took place in the left superior (BA7) and inferior (BA40) parietal lobules and the right superior frontal gyrus (BA10). Patients showed significantly less activation in the frontal cortices, in comparison with controls.

DISCUSSION

Cognitive profile of BDI

Patients with BDI, who were in remission, and recruited from a secondary care setting showed relatively specific reductions in executive function measures.

Current antipsychotic use was the only medication-related variable that showed an association with cognitive deficits even after adjusting for a history of psychosis. To our knowledge, this is the first study to report on the potential impact of antipsychotics on cognitive function in BD. Our findings are consistent with those of Abrams et al.[32] who found a negative association between antipsychotic use and IQ in BDI patients. It is possible that antipsychotic-

induced reduction in speed of information processing is responsible for some of these findings. In terms of other psychotropics, anticonvulsants, antidepressants and lithium cause only minor cognitive changes in healthy subjects[33-35] which is commensurate with the lack of an association between cognitive variables and treatment with "mood stabilizers" in this study. However, there was only a small number of individuals not taking mood stabilizers, so there may be insufficient power to detect an effect.

Decrements in Full Scale IQ, memory and in measures of response initiation or suppression were all associated with a history of psychosis. However this effect was not always statistically significant at the 5% level and was further confounded by the fact that it was common for patients with a history of psychosis to be taking antipsychotic treatments. General intellectual ability is within the normal range, even in BD patients with a history of psychosis, and is higher than that of patients with schizophrenia.[13] The effect of psychosis on IQ in BD should thus be deemed modest. Illness duration was a statistically significant predictor of greater cognitive decrements in General Memory and more errors in the HSCT. This would suggest that there is a deterioration over time in memory and inhibitory control in BD patients. Symptoms of either polarity negatively affected overall cognition; this is consistent with previous data,[13] but it only reached statistical significance for the SCWT.

A family history of affective disorder predicted higher current IQ and fewer errors in the HSCT. To our knowledge, this has not been investigated by other studies and this finding is in need of replication. The study be Tsuchiya et al.[36] reporting that higher parental education and wealth were associated with increased risk for BD in the Danish 1960 birth cohort provides indirect support for our study.

Structural and functional changes in BDI

Our observation that amygdala volume is increased is consistent with other reports of increased volume in these brain structures in chronic multi-episode patients. It may be that

amygdala enlargement results from chronicity; it is interesting that one study has reported that adolescents with BD had deficits in amygdala volume.[37] Reductions were found in the VPFC (orbital and inferior frontal gyri) bilaterally and in the dorsal prefrontal cortex on the left. Data from functional studies indicate that reduced DPFC activity is common in depressive states while activity in VPFC is decreased in mania and possibly in depression as well. In addition, there is evidence of residual dysfunction in the VPFC (BA10, 47) even in remitted patients.[12] In terms of cellular change, moderate reductions in neuronal and glial density have been recorded primarily in layer III in BA9/10. This is consistent with the reported gross volume reduction in gray matter. Currently, information is lacking about the rest of the PFC,[37] and the relationship of (macro- and micro-) PFC structure to the observed functional changes has yet to be clarified, in BD.

Increasing memory load in the N-Back Task resulted in differential brain activation patterns between patients and controls. Specifically, controls showed increased activity in the dorsal PFC and anterior cingulate, whilst patients appear to recruit the superior frontal PFC (BA10). In healthy controls, BA10 is associated with the ability to be cognizant of primary goals whilst processing secondary ones.[38] The latter may explain how the patients' are able to demonstrate adequate response levels. Success in the gambling task[31] relies on the ability to use emotion-guided reasoning for strategic planning. Data from human and primate studies suggest that the VPFC encodes incentive values only, while the DPFC may encode both incentive value and behavioral response. Neural activation peaks earlier in the VPFC which would suggest that this region generates incentive information, which subsequently enters the DPFC and modulates behavioral response.[39] Therefore, it is plausible that deficits in the ventral PFC should attenuate reward information in the DLPFC. The findings from the gambling task in this study appear to corroborate this hypothesis. During this task, no significant activation was observed in the VPFC and this was associated with attenuated activation within the DPFC. In addition, the results from the N-Back Task suggest that the DPFC itself is dysfunctional in BD. Brain activation patterns show that this DPFC dysfunction is relatively subtle during working memory tasks with an affective-neutral content, but more evident

when working memory demand increases. These findings support the idea that performance may be maintained via the recruitment of other cortical regions.

In summary, we have demonstrated that patients with BD from a secondary care setting display moderate performance reduction during cognitive tasks, and the biggest effect size is seen for measures of executive function. An interesting finding was that higher IQ and fewer errors in measures of interference and response generation were both predicted by a familial predisposition to affective disorder. The effect of familiality in BD has not been previously examined, and potential differences between BD patients with or without a family history requires further examination. We also discovered that there were significant negative effects on multiple cognitive domains due to medication; specifically antipsychotics. This study is the first to investigate this issue. The clinical implications of this finding are considerable and further replication is required. Medication is the single predictor of cognitive function that is readily amenable to change. The structural and functional MRI data draw attention to trait deficits in the PFC and suggest that both the DPFC and VPFC may be dysfunctional. This is independent of cognitive impairment or symptomatology, and leads to the possibility BD patients may display abnormal VPFC to DPFC interaction as a trait feature.

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ABSTRACT

Purpose: *The Maudsley Bipolar Disorder Project was set up in order to investigate the cognitive and structural/functional brain characteristics of Bipolar Disorder I (BDI).*

Methods: *Participating patients with BDI (n = 43) were recruited from a secondary care setting, while in remission. They were matched to healthy controls for age, gender, race and years of education. Each participant underwent extensive clinical review, cognitive assessment, and Magnetic Resonance Imaging (MRI) in order to obtain brain structural and functional data.*

Results: *When compared to controls, patients demonstrated subtle widespread impairment with executive function being more markedly reduced. Patients also displayed volume decrements in the ventral prefrontal cortex (VPFC) bilaterally and in the dorsal PFC (DPFC) on the left. The volume of the amygdala was bilaterally enlarged. Functional MRI of patients showed subtle*

abnormalities in their DPFC, with marked decrements in activity in both the DPFC and VPFC during tasks that rely on these regions functionally interacting.

Conclusions: *The results suggest that trait deficits in executive function occur in BDI, along with altered structure and function of the PFC*

Keywords: *Pathophysiology, imaging, cognition, bipolar disorder.*

Title: *The Maudsley Bipolar Disorder Project: insights into the role of the prefrontal cortex in bipolar disorder I*

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