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ORIGINAL ARTICLE

Increased body mass index makes an impact on brain white-matter integrity in adults with remitted first-episode mania

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Background. Obesity is increasingly prevalent in bipolar disorder (BD) but data about the impact of elevated body mass index (BMI) on brain white-matter integrity in BD are sparse. Based on extant literature largely from structural magnetic resonance imaging (MRI) studies, we hypothesize that increased BMI is associated with decreased fractional anisotropy (FA) in the frontal, temporal, parietal and occipital brain regions early in the course of BD.

Method. A total of 26 euthymic adults (12 normal weight and 14 overweight/obese) with remitted first-episode mania (FEM) and 28 controls (13 normal weight and 15 overweight/obese) matched for age, handedness and years of education underwent structural MRI and diffusion tensor imaging scans.

Results. There are significant effects of diagnosis by BMI interactions observed especially in the right parietal lobe (adjusted $F_{1,48}$=5.02, p=0.030), occipital lobe (adjusted $F_{1,48}$=10.30, p=0.002) and temporal lobe (adjusted $F_{1,48}$=7.92, p=0.007). Specifically, decreased FA is found in the right parietal ($F_{1,23}$=5.864, p=0.023) and occipital lobes ($F_{1,23}$=4.397, p=0.047) within overweight/obese patients compared with normal-weight patients with FEM. Compared with overweight/obese controls, decreased FA is observed in right parietal ($F_{1,25}$=6.708, p=0.015), temporal ($F_{1,25}$=10.751, p=0.003) and occipital ($F_{1,25}$=9.531, p=0.005) regions in overweight/obese patients with FEM.

Conclusions. Our findings suggest that increased BMI affects temporo-parietal-occipital brain white-matter integrity in FEM. This highlights the need to further elucidate the relationship between obesity and other neural substrates (including subcortical changes) in BD which may clarify brain circuits subserving the association between obesity and clinical outcomes in BD.

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Key words: Bipolar disorder, body mass index, diffusion tensor imaging, first-episode mania, fractional anisotropy, obesity.

Introduction

Obesity is increasingly prevalent in bipolar disorder (BD), in that over 60% of patients with BD may be overweight or obese (Goldstein *et al.* 2011). Obesity has been associated with poor clinical outcomes in BD, including shorter time to recurrence during the maintenance phase of the illness (Fagiolini *et al.* 2003), more frequent depressive episodes and suicide attempts compared with the general population (Fagiolini *et al.* 2003, 2004). Furthermore, patients with BD who are overweight and obese often have poor medical outcomes including greater risk of suffering from metabolic disturbances such as diabetes and cardiovascular disease (Magalhães *et al.* 2012) and these are the leading causes of premature and excess mortality in BD (Osby *et al.* 2001).

In the general population, previous structural magnetic resonance imaging (MRI) studies have found either no change in white-matter volume (Pannacciulli *et al.* 2006) or decreased total brain volume, grey-matter volume in overweight/obese individuals (Taki *et al.* 2008; Soreca *et al.* 2009) as well as greater loss of brain volume over time compared with individuals with normal weight (Enzinger *et al.* 2005; Bobb *et al.* 2012). Recent studies using diffusion tensor imaging (DTI) in otherwise healthy adults found that obesity is associated with disruptions in white-matter integrity as indicated by reductions of fractional anisotropy (FA) within the corpus callosum (Mueller *et al.* 2011) and involving midbrain and brainstem white-matter tracts (Verstynen *et al.* 2012). Furthermore, individuals with high body mass index (BMI) exhibited deficits in

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attention, speed of processing, and executive functioning on neuropsychological testing compared with those with normal BMI (Gunstad *et al.* 2006, 2007), indicating that elevated BMI may have observable adverse impacts on neural substrates.

To the best of our knowledge, there is a paucity of neuroimaging studies that have specifically evaluated the underlying brain structural changes that may mediate the impact of BMI in BD. The only study was a recent structural MRI report by Bond *et al.* (2011) that documented decreased brain white-matter volume and temporal lobe volume in adults newly diagnosed with BD and with elevated BMI. There are to date no data on the effect of BMI on brain white-matter integrity in BD patients. However, in the context of pharmacotherapy, previous studies investigating the impact of psychotropic medication use on brain structures have found associations of grey-matter volume increase with use of mood stabilizers (Atmaca *et al.* 2008; Kempton *et al.* 2008) and increase of glial cell density and non-reduction of white-matter volume with antipsychotic administration (Selemon *et al.* 1999; Bartzokis *et al.* 2011). Thus, based on these sparse extant data, we sought to examine whether excess weight is associated with changes of brain white-matter integrity in adults with BD who have achieved symptomatic remission from a first episode of mania. The emphasis on newly diagnosed BD patients decreases the likelihood of confound by effects of illness, chronicity and treatment. In view of the findings of Bond *et al.* (2011) involving white-matter volume and temporal lobe volume in patients with first-episode mania (FEM) and elevated BMI, we hypothesized that increased BMI in remitted patients with FEM is associated with reduced FA in the frontal, temporal, parietal and occipital brain regions.

Method

Participants

The study sample comprised 54 participants (31 men and 23 women) who gave written informed consent to participate in the study after a detailed explanation of the study procedures between June 2008 and June 2010. A total of 26 patients with remitted FEM were recruited from the Institute of Mental Health, Singapore. All diagnoses were made by a psychiatrist (K.S.) using information obtained from the existing medical record, clinical history, mental status examination, interviews with the patients and their significant others as well as the administration of the Structured Clinical Interview for DSM-IV disorders (SCID) – Patient Version (First *et al.* 1994) and Young Mania Rating Scale (YMRS; Young *et al.* 1978). All patients were in remission from mania (i.e. YMRS score <10) at the time of recruitment and on the day of neuroimaging (Tohen *et al.* 2009; Chan *et al.* 2010), were maintained on a stable dose of psychotropic medication for at least 2 weeks prior to the recruitment and did not have their medication withdrawn for the purpose of the study. In addition, 28 age-, gender-, handedness- and education-matched healthy controls (HC) were administered the SCID – Non-Patient Version (First *et al.* 2002). None of the participants had a history of significant and/or unstable/untreated medical illnesses such as seizure disorder, head trauma or cerebrovascular accidents. Moreover, no subjects had a current or past history of substance use or alcohol use disorder, metabolic disorder such as diabetes, dyslipidaemia or previous diagnosis and/or treatment for another psychiatric disorder. This study was approved by the Institutional Review Boards of the Institute of Mental Health, Singapore, as well as the National Neuroscience Institute, Singapore.

BMI and weight evaluation

Each participant had their height and weight recorded. The BMI was calculated using the formula BMI = weight (kg)/height $(m)^2$. For the purpose of analyses, participants were categorized into normal weight (BMI of 18.5 to <23.0 kg/m^2; $n=25$), overweight (BMI 23.0 to <25.0 kg/m^2; $n=12$) and obese (BMI >25.0 kg/m^2; $n=17$) according to the International Association for the Study of Obesity (World Health Organization, International Association for the Study of Obesity, International Obesity Task Force, 2000) and the World Health Organization (WHO) proposed BMI cut-off points for obesity in adult Asians (WHO Expert Consultation, 2004).

Brain imaging acquisition and data processing

Brain imaging was performed using a 3-Tesla whole body scanner (Philips Achieva; Philips Medical Systems, The Netherlands) with a SENSE head coil at the National Neuroscience Institute, Singapore. High-resolution T1-weighted magnetization prepared rapid gradient recalled echo (MP-RAGE) images were required [repetition time (TR) = 7.2 ms; echo time (TE) = 3.3 ms; flip angle = 8°]. Each T1-weighted volume consisted of 180 axial slices of 0.9 mm thickness with no gap (field of view, 230 mm × 230 mm; acquisition matrix, 256 × 256 pixels). For DTI, single-shot echo-planar diffusion tensor images were obtained (TR = 3725 ms; TE = 56 ms; flip angle = 90°, $b=800$ s/mm^2) with 15 different non-parallel directions ($b=800$ s/mm^2) and the baseline image without diffusion weighting ($b=0$ s/mm^2). The acquisition matrix was 112 × 109 pixels with a field of view of 230 mm × 230 mm,

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which was zero-filled to 256×256 pixels. A total of 42 axial slices of 3.0 mm thickness were acquired parallel to the anterior–posterior commissure line. The T1-weighted and DTI data were sequentially acquired in a single session scan time without position change. Stability of a high signal to noise ratio was assured through a regular automated quality-control procedure.

The structural MRI images were processed using the Free Surfer software package to delineate the different brain regions (Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard University; http://surfer.nmr.mgh.harvard.edu/). The Free Surfer software reformatted each brain volume image into a 1 cubic mm isovoxel volume image (Fischl *et al.* 2002). Within each subject, the diffusion-weighted images (DWIs) of each subject were corrected for motion and eddy current distortions using affine transformation to the baseline image without diffusion weighting ($b=0$). FA maps were acquired from the DTI images using DTI Studio (Jiang *et al.* 2006) and were then co-registered automatically to the structural MP-RAGE images. Mean FA values in the frontal, parietal, temporal and occipital lobes were then computed and used in the following statistical analyses.

Statistical analyses

As the number of subjects who were categorized as overweight (BMI 18.5 to <23.0 kg/m^2) or obese (BMI ⩾ 23.0 kg/m^2) was relatively low, we combined the two groups and compared those with remitted FEM who were normal weight with those who were overweight/obese. Both groups were also compared with a HC group. Sociodemographic variables between FEM and HC were compared using the two-sample Student's t test and χ^2 test for continuous and categorical variables; respectively. The diagnosis effect, BMI effect and BMI × diagnosis interactions on brain white-matter integrity (FA) were examined using two-way analysis of variance. The BMI effect, diagnosis effect and diagnosis × BMI interactions were further analysed using two-way analysis of covariance to control for covariates such as age, gender, years of education and medications in terms of antipsychotic use (mean daily chlorpromazine equivalents) and prescription of mood stabilizer. When a significant diagnosis × BMI interaction was found, differences between the two groups of FEM and HC were further evaluated separately. All statistical tests were performed using PASW for Windows, version 18.0 (SPSS Inc., USA). The significance level for statistical tests was set at two-tailed $p<0.05$ as our analyses were exploratory on the different brain regions at this stage.

Results

Sociodemographic and clinical characteristics

There was no significant difference in age, gender, handedness, subject and parental years of education between patients with FEM and HC. Of the subjects, 46% ($n=25$, 12 patients with FEM and 13 controls) of the subjects had normal weight while the rest of the subjects were either overweight or obese ($n=29$; 14 patients with FEM and 15 controls). The majority of the patients received medications such as mood stabilizers, namely valproate ($n=12$) and lithium ($n=10$), as well as antipsychotics ($n=22$; two typicals, 20 atypicals), while the remaining four patients did not receive any medication at the time of recruitment. The sociodemographic and clinical features are shown in Table 1. Table 2 shows the details comparing between normal-weight and overweight/obese groups within both patients and HC. Essentially, there was no significant difference in terms of age, gender, years of education, parental years of education and handedness between normal-weight and overweight/obese groups within the patients and HC. Within the patient group, there was no significant difference between normal-weight and overweight/obese groups in terms of duration of illness, YMRS scores, lithium, mood stabilizers and antipsychotic medications prescribed.

Effect of BMI on brain white-matter integrity

There were significant effects of diagnosis × BMI interactions observed in the right frontal lobe ($F_{1,50}=4.92$, $p=0.031$), right parietal lobe ($F_{1,50}=5.90$, $p=0.019$), right occipital lobe ($F_{1,50}=9.02$, $p=0.004$) and temporal lobe ($F_{1,50}=8.81$, $p=0.005$). These interactions remained significant after controlling for covariates (right frontal lobe: adjusted, $F_{1,48}=5.69$, $p=0.021$; right parietal lobe: adjusted, $F_{1,48}=5.02$, $p=0.030$; right occipital lobe: adjusted, $F_{1,48}=10.30$, $p=0.002$; right temporal lobe: adjusted, $F_{1,48}=7.92$, $p=0.007$). As the diagnosis × BMI interactions were found to be significant for the right frontal, parietal, temporal and occipital lobes (Table 3), we analysed the effects of BMI on these four brain regions between patients with FEM and controls as well as separately within patients with FEM and controls (Fig. 1). Specifically, decreased FA was found in the right parietal ($F_{1,23}=5.864$, $p=0.023$) and occipital ($F_{1,23}=4.397$, $p=0.047$) lobes with standardized effect sizes of −1.1 and −1.2, respectively, within overweight/obese patients compared with normal-weight patients with FEM. Compared with overweight/obese controls, decreased FA was observed in right parietal ($F_{1,25}=6.708$, $p=0.015$), temporal ($F_{1,25}=10.751$, $p=0.003$) and occipital ($F_{1,25}=9.531$, $p=0.005$)

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Table 1. *Demographic and clinical characteristics of the participants*

Characteristic	Healthy controls (n=28)		First-episode mania (n=26)		t or χ^2 test	df	p
Mean age, years (S.D.)	33.46	(11.28)	34.27	(12.04)	$t=-0.254$	52	0.801
Mean subject's years of education (S.D.)	12.89	(1.99)	11.81	(2.23)	$t=1.892$	52	0.064
Mean mother's years of education (S.D.)	6.93	(4.82)	4.85	(4.5)	$t=0.598$	52	0.552
Mean father's years of education (S.D.)	7.86	(4.47)	7.23	(3.02)	$t=1.639$	52	0.107
Mean duration of illness, years (S.D.)	–	–	0.2	(0.2)	–	–	–
Mean YMRS score (S.D.)	–	–	4	(5.25)	–	–	–
Male, n (%)	16	(57.1)	15	(57.7)	$\chi^2=0.002$	1	0.967
Right-handed, n (%)	28	(100)	25	(96.2)	$\chi^2=1.097$	1	0.295
Overweight and obese, n (%)	15	(53.6)	14	(53.8)	$\chi^2=0.001$	1	0.984
Use of lithium[a]							
n (%)	–	–	10	(38.5)			
Mean (S.D.)	–	–	480.12	(269.74)			–
Use of other mood stabilizers[a]							
n (%)	–	–	12	(46.2)			
Mean (S.D.)	–	–	408.62	(391.55)			–
Antipsychotic use[b]							–
n (%)	–	–	22	(84.6)			
Mean (S.D.)	–	–	141.14	(110.69)			

df, Degrees of freedom; S.D., standard deviation; YMRS, Young Mania Rating Scale.
[a] Frequency and mean dose of lithium or other mood stabilizers prescribed.
[b] Frequency and mean dose of antipsychotic prescribed in mean daily chlorpromazine equivalents.

Table 2. *Demographic and clinical characteristics of the participants by weight group*

	Healthy controls						First-episode mania					
Characteristic	Normal weight (n=13)		Overweight/ obese (n=15)		t or χ^2 test	p	Normal weight (n=12)		Overweight/ obese (n=14)		t or χ^2 test	p
Mean age, years (S.D.)	34.46	(12)	32.6	(10.95)	$t=0.43$	0.67	34.17	(12.88)	34.36	(11.76)	$t=-0.04$	0.97
Mean subject's years of education (S.D.)	12.23	(1.92)	13.47	(1.92)	$t=-1.70$	0.10	11.5	(2.02)	12.07	(2.43)	$t=-0.64$	0.53
Mean mother's years of education (S.D.)	6.85	(4.79)	7	(5)	$t=-0.08$	0.94	5	(5.152)	4.71	(4.05)	$t=0.16$	0.88
Mean father's years of education (S.D.)	7.69	(4.07)	8	(4.93)	$t=-0.18$	0.86	6.92	(3.26)	7.5	(2.9)	$t=-0.48$	0.63
Mean duration of illness, months (S.D.)	–	–	–	–	–	–	3.24	(4.6)	2.93	(4.97)	$t=0.17$	0.87
Mean YMRS score (S.D.)	–	–	–	–	–	–	2.42	(3.29)	5.36	(6.3)	$t=-1.45$	0.16
Male, n (%)	7	(53.8)	9	(60)	$\chi^2=0.11$	0.74	7	(58.3)	8	(57.1)	$\chi^2=0.004$	0.95
Right-handed, n (%)	13	(100)	15	(100)	–	–	11	(91.7)	14	(100)	$\chi^2=1.21$	0.27
Prescription of lithium, n (%)	–	–	–	–	–	–	4	(33.3)	6	(42.9)	$\chi^2=0.25$	0.62
Prescription of other mood stabilizers, n (%)	–	–	–	–	–	–	6	(50)	6	(42.9)	$\chi^2=0.11$	0.72
Antipsychotic use, n (%)	–	–	–	–	–	–	9	(75)	13	(92.9)	$\chi^2=1.58$	0.21

S.D., Standard deviation; YMRS, Young Mania Rating Scale.

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Table 3. *Effect of BMI on brain white-matter integrity (mean fractional anisotropy)*

	First-episode mania ($n=26$)		Healthy controls ($n=28$)		ANOVA					ANCOVA (adjusted)[a]					
	Normal weight ($n=12$)	Overweight/ obese ($n=14$)	Normal weight ($n=13$)	Overweight/ obese ($n=15$)	Diagnosis effect		BMI effect		Interaction	Diagnosis effect		BMI effect		Interaction	
Brain regions	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	F	p	F	p	F p	F	p	F	p	F	p
Left frontal lobe	0.219 (0.06)	0.211 (0.04)	0.188 (0.02)	0.211 (0.03)	2.13	0.150	0.52	0.473	2.04 0.160	2.87	0.097	0.24	0.628	2.18	0.147
Left parietal lobe	0.217 (0.06)	0.206 (0.03)	0.202 (0.01)	0.214 (0.02)	0.14	0.711	0.01	0.946	1.60 0.212	0.32	0.572	0.04	0.838	2.02	0.162
Left occipital lobe	0.232 (0.06)	0.213 (0.04)	0.194 (0.03)	0.212 (0.03)	2.83	0.099	0.01	0.952	2.49 0.121	2.76	0.104	0.01	0.906	2.21	0.144
Left temporal lobe	0.242 (0.06)	0.224 (0.05)	0.198 (0.01)	0.22 (0.03)	4.60	0.037	0.04	0.838	2.99 0.090	5.58	0.022	0.00	0.972	3.15	0.083
Right frontal lobe	0.202 (0.03)	0.188 (0.02)	0.190 (0.02)	0.205 (0.03)	0.10	0.754	0.01	0.944	4.92 0.031	0.00	0.947	0.03	0.874	5.69	0.021
Right parietal lobe	0.204 (0.03)	0.183 (0.02)	0.194 (0.02)	0.202 (0.02)	0.77	0.384	1.37	0.247	5.90 0.019	1.11	0.298	0.96	0.333	5.02	0.030
Right occipital lobe	0.234 (0.07)	0.188 (0.04)	0.201 (0.03)	0.280 (0.03)	0.09	0.772	0.67	0.417	9.02 0.004	0.00	0.978	1.22	0.275	10.30	0.002
Right temporal lobe	0.212 (0.03)	0.195 (0.02)	0.201 (0.02)	0.228 (0.03)	2.25	0.140	0.45	0.508	8.81 0.005	2.23	0.142	0.43	0.513	7.92	0.007

BMI, Body mass index; ANOVA, analysis of variance; ANCOVA, analysis of covariance; S.D., standard deviation.
[a] Adjusted for age, gender and years of education.

regions with standardized effect sizes of −1.0, −1.65 and −2.3, respectively, in overweight/obese patients with FEM.

We performed additional analyses on the possible effect of medication on these brain regions including antipsychotic use (in mean daily chlorpromazine equivalents), use of lithium and valproate. Apart from the right frontal region ($F_{1,47}=3.068$, $p=0.086$), the diagnosis × BMI interactions remained largely unchanged in the other brain regions after including medication as covariates (right parietal: $F_{1,47}=4.668$, $p=0.036$; right occipital: $F_{1,47}=7.224$, $p=0.003$; right temporal: $F_{1,47}=8.017$, $p=0.007$). Backward regression was performed to further analyse the effect of medication in the right frontal region, in which we found that only mean daily chlorpromazine equivalents significantly predicted mean FA compared with lithium and valproate ($\beta=-0.460$, $t=-2.523$, $p=0.020$).

Discussion

To our knowledge, this is the first study to specifically examine the impact of weight status on brain white-matter integrity in patients with FEM. There were several observations in the sample examined herein. First, reductions of FA in the right parietal and occipital regions were found in FEM patients who were overweight/obese compared with those who had normal weight. Second, reductions of FA were seen in the right parietal, occipital and temporal regions within overweight/obese FEM patients compared with controls, suggesting that increased BMI early in the course of BD is associated with disruptions of white-matter integrity involving temporal–parietal–occipital brain circuitry.

The observed reductions in FA within FEM patients who were overweight/obese compared with normal weight occur in brain regions previously found to be implicated in the patho-aetiology of BD. Earlier structural MRI studies of patients with BD have reported increased rates of white-matter hyperintensities in BD, with a recent meta-analysis noting up to 2.5 times increased odds of having deep white-matter hyperintensities in patients with BD (Kempton *et al.* 2008). Structural MRI studies of FEM patients found reductions of brain white-matter volume but not grey-matter volume (Vita *et al.* 2009). DTI studies that specifically examine brain white-matter integrity have implicated disruptions in FA within parietal and occipital regions in patients with BD (Chan *et al.* 2010; Heng *et al.* 2010). Our findings of FA reductions specifically within parietal and occipital brain regions suggest that similar brain regions are affected early in the course of the illness in FEM patients who are overweight/obese.

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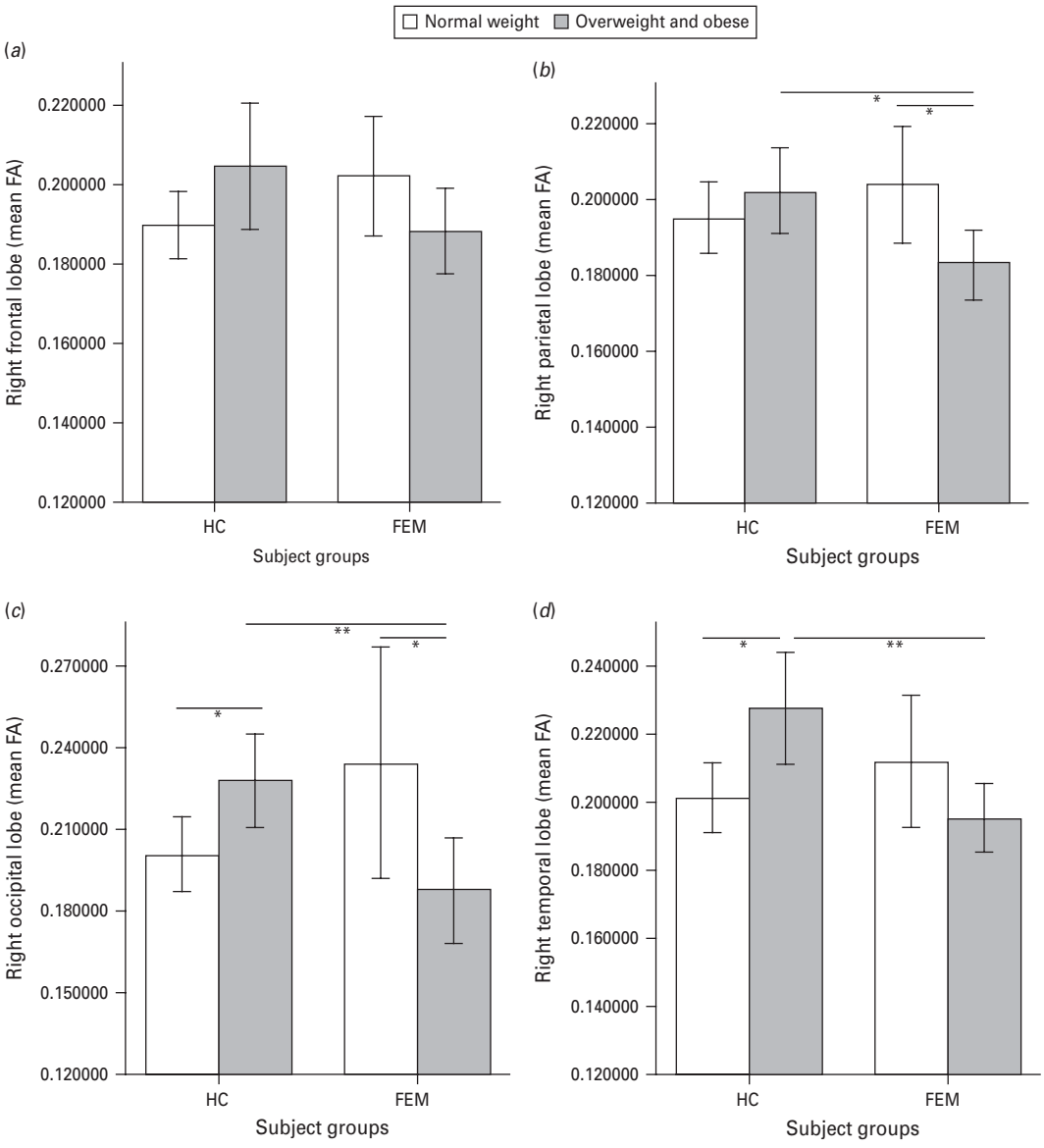

Fig. 1. Fractional anisotropy (FA) in the (*a*) right frontal, (*b*) parietal, (*c*) occipital and (*d*) temporal lobes in healthy subjects (HC) and first-episode mania patients (FEM). Values are means, with standard errors represented by vertical bars. Significant mean FA differences: * $p<0.05$, ** $p<0.01$.

Compared with the overweight/obese healthy adults, we also found FA reductions in right parietal, temporal and occipital regions in FEM patients who were overweight/obese, providing evidence that FEM patients with elevated BMI may be more susceptible to brain white-matter changes. Of note, the overweight/obese patients with FEM had lower FA in the right occipital and temporal lobes compared with normal-weight patients with FEM, but overweight/obese controls had higher FA in the similar brain regions compared with normal-weight controls. The observed higher FAs within the temporal and occipital lobes in overweight/obese controls compared with normal-weight controls need replication, although these results may be consistent with findings of an earlier MRI study which reported increased white-matter volume in temporal and occipital brain regions of obese subjects (Haltia *et al.* 2007). However, other studies have found no difference in brain white-matter volume (Pannacciulli *et al.* 2006), no difference in FA between overweight and normal-weight controls (Stanek *et al.* 2011), reductions in FA within the corpus callosum in obese female controls (Mueller *et al.* 2011) or especially found within midbrain and brainstem white-matter tracts (Verstynen *et al.* 2012). In this regard, elevated BMI may have differential aetiological mechanisms amongst individuals with FEM and controls and may be a marker of greater illness severity

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in BD, hence accounting for the FA differences in controls and FEM with elevated BMI compared with those individuals with normal weight. Future studies are needed to better determine the relationship between elevated BMI and brain white-matter structure as it may affect different brain structures differently in controls and within the context of BD.

The neurobiological pathways linking obesity, mania and brain white-matter changes are still unclear and await further elucidation. Earlier studies have found reduced white-matter integrity in patients with obesity-associated co-morbidity such as diabetes, hypertension, metabolic syndrome and stroke (Hoth *et al.* 2007; Kodl *et al.* 2008). Postulated biological mechanisms subserving the relationship between obesity and brain white-matter changes include endothelial dysfunction, insulin resistance and inflammatory processes (Hoth *et al.* 2007; Rosenberg, 2009; Katsumata *et al.* 2010). Genetic imaging studies have highlighted the relationship between risk alleles at rs1421085 and rs17817449 of the fat mass and obesity-associated (*FTO*) gene and volume reductions of 8% in the bilateral frontal and 12% in the bilateral occipital lobes, respectively (Ho *et al.* 2010), indicating that genetic factors relevant to obesity may contribute to susceptibility towards brain structural changes including brain white matter. In addition, there are some data to support the roles of the pleiotropic peptides insulin, insulin-like growth factor 1 (IGF-1) and incretins in neuronal and glial cell function including neurogenesis, myelination and modulation of synaptic plasticity (McIntyre *et al.* 2008). Alterations in insulin/IGF-1 signalling can result in downstream effects of decreased cellular integrity and survival in brain regions affecting neurocognition and other brain functions (McIntyre *et al.* 2008). BD is associated separately with disruptions in white-matter integrity in the putative regions (Heng *et al.* 2010), which may be further exacerbated in the context of elevated BMI. In addition, leptin from adipose tissue (Farooqi *et al.* 2007) and gut hormones such as ghrelin, peptide YY (peptide tyrosine-tyrosine) and glucagon-like peptide (Gibson *et al.* 2010) have been associated with activation of different cortical brain areas related to visual presentation of food, suggesting the complex inter-relationships between neurobiological factors within the gut–brain axis in affecting brain white matter.

In addition, the diagnosis × BMI interactions and reductions of FA occur mainly within brain regions in the right hemisphere, suggesting laterality effect. This laterality effect is consistent with the findings of a meta-analysis of 10 whole-brain DTI studies (Vederine *et al.* 2011), which reported significant clusters of decreased FA in the right hemisphere although not taking into account the weight status. One possible explanation is that brain white-matter composition may be dynamic (May, 2011) and altered white-matter fibres in the corpus callosum of patients with BD may have contributed to asymmetrical impact on white-matter integrity within the different brain regions. Reduced white-matter integrity in the corpus callosum has been observed in obese healthy adults (Stanek *et al.* 2011), and obesity may have additionally contributed to the laterality effect of affected brain white-matter regions.

There are several limitations in this study. First, the study sample is small and the findings need to be replicated in other populations and in a larger sample. Second, the findings may be confounded by the effects of medications such as mood stabilizers and antipsychotics. However, the patients with FEM were recruited at an early phase of their illness with no previous treatment with medications and had been receiving their treatment for a minimal period of time. In addition, available data suggest that psychotropic medications used such as lithium and valproate are associated with grey-matter volume increases and are less likely to contribute to changes in white matter (Moore *et al.* 2000; Atmaca *et al.* 2008; Kempton *et al.* 2008), as is also consistent with our findings which remained largely unchanged when we included medications as covariates in our analyses. Exposure to antipsychotics (typical and atypical) in animal models has been associated with an increase in glial cell density as well as promotion of oligodendrocyte differentiation and myelin repair (Selemon *et al.* 1999). Adherence to antipsychotic treatment with remission of illness is also thought to result in better trajectory of myelination and non-reduction of brain white-matter volume (Bartzokis *et al.* 2011). Third, this is a cross-sectional study and the longitudinal follow-up of these subjects would proffer further insights into the complex interaction between weight status, illness factors, treatment and changes in brain white-matter integrity. Fourth, the functional and behavioural implications of our findings may be relevant to neurocognitive function. Unfortunately, we did not include measures of neurocognitive function in our sample. Extant data indicate that individuals with BD exhibit clinically significant and broad-based neurocognitive deficits that often persist during periods of euthymia. Neurocognitive deficits in BD are known to cause and maintain functional impairment. A separate body of evidence has reported that obesity and diabetes are associated with cognitive deficits (McIntyre *et al.* 2010). Moreover, preliminary evidence indicates that the metabolic syndrome may be associated with neurocognitive deficits in bipolar populations (Yim *et al.* 2012).

In conclusion, we found that elevated BMI is associated with disruptions of brain white-matter integrity

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affecting right parietal, temporal and occipital regions in FEM patients who were overweight/obese. These findings add to a growing confluence of study results indicating that somatic health status is associated with alterations in central nervous system (CNS) structure and function. In addition to replication and extension of our results, elucidating effector systems that mediate the association between BD, obesity, and white-matter integrity would be a future research vista. Practitioners providing care for individuals with BD need to consider the CNS effects associated with overweight/obesity in BD and recommendations for screening, prevention, and treatment of excess weight and BMI are supported by these data.

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Declaration of Interest

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References

Atmaca M, Ozdemir H, Cetinkaya S, Parmaksiz S, Belli H, Poyraz AK, Tezcan E, Ogur E (2007). Cingulate gyrus volumetry in drug free bipolar patients and patients treated with valproate or valproate and quetiapine. *Journal of Psychiatric Research* **41**, 821–827.

Bartzokis G, Lu PH, Amar CP, Raven EP, Detore NR, Altshuler LL, Mintz J, Ventura J, Casaus LR, Luo JS, Subotnik KL, Nuechterlein KH (2011). Long acting injection *versus* oral risperidone in first-episode schizophrenia: differential impact on white matter myelination trajectory. *Schizophrenia Research* **132**, 35–41.

Bobb JF, Schwartz BS, Davatzikos C, Caffo B (2012). Cross-sectional and longitudinal association of body mass index and brain volume. *Human Brain Mapping*. Published online 24 September 2012. doi:10.1002/hbm.22159.

Bond DJ, Lang DJ, Noronha MM, Kunz M, Torres IJ, Su W, Honer WG, Lam RW, Yatham LN (2011). The association of elevated body mass index with reduced brain volumes in first-episode mania. *Biological Psychiatry* **70**, 381–387.

Chan WY, Yang GL, Chia MY, Woon PS, Lee J, Keefe R, Sitoh YY, Nowinski WL, Sim K (2010). Cortical and subcortical white matter abnormalities in adults with remitted first-episode mania revealed by Tract-Based Spatial Statistics. *Bipolar Disorders* **12**, 383–389.

Enzinger C, Fazekas F, Matthews PM, Ropele S, Schmidt H, Smith S, Schmidt R (2005). Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects. *Neurology* **64**, 1704–1711.

Fagiolini A, Kupfer DJ, Houck PR, Novick DM, Frank E (2003). Obesity as a correlate of outcome in patients with bipolar disorder. *American Journal of Psychiatry* **160**, 112–117.

Fagiolini A, Kupfer DJ, Rucci P, Scott JA, Novick DM, Frank E (2004). Suicide attempts and ideation in patients with bipolar I disorder. *Journal of Clinical Psychiatry* **65**, 509–514.

Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC (2007). Leptin regulates striatal regions and human eating behavior. *Science* **317**, 1355.

First MB, Spitzer RL, Gibbon M, Williams JBW (1994). *Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Version (SCID-P)*. American Psychiatric Press: Washington, DC.

First MB, Spitzer RL, Gibbon M, Williams JBW (2002). *Structured Clinical Interview for DSM-IV Axis I Disorders-Non-Patient Version (SCID-I/NP)*. New York State Psychiatric Institute: New York.

Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, van der Kouwe A, Killiany R, Kennedy D, Klaveness S, Montillo A, Makris N, Rosen B, Dale AM (2002). Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* **33**, 341–355.

Gibson CD, Carnell S, Ochner CN, Geliebter A (2010). Neuroimaging, gut peptides and obesity: novel studies of the neurobiology of appetite. *Journal of Neuroendocrinology* **22**, 833–845.

Goldstein BI, Liu SM, Zivkovic N, Schaffer A, Chien LC, Blanco C (2011). The burden of obesity among adults with bipolar disorder in the United States. *Bipolar Disorders* **13**, 387–395.

Gunstad J, Paul RH, Cohen RA, Tate DF, Gordon E (2006). Obesity is associated with memory deficits in young and middle-aged adults. *Eating and Weight Disorders* **11**, e15–e19.

Gunstad J, Paul RH, Cohen RA, Tate DF, Spitznagel MB, Gordon E (2007). Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. *Comprehensive Psychiatry* **48**, 57–61.

Haltia LT, Viljanen A, Parkkola R, Kemppainen N, Rinne JO, Nuutila P, Kaasinen V (2007). Brain white matter expansion in human obesity and the recovering effect of dieting. *Journal of Clinical Endocrinology and Metabolism* **92**, 3278–3284.

Heng S, Song AW, Sim K (2010). White matter abnormalities in bipolar studies: insights from diffusion tensor imaging studies. *Journal of Neural Transmission* **117**, 639–654.

Ho AJ, Stein JL, Hua X, Lee S, Hibar DP, Leow AD, Dinov ID, Toga AW, Saykin AJ, Shen L, Foroud T, Pankratz N, Huentelman MJ, Craig DW, Gerber JD, Allen AN, Corneveaux JJ, Stephan DA, DeCarli CS, DeChairo BM, Potkin SG, Jack CR Jr, Weiner MW, Raji CA, Lopez OL, Becker JT, Carmichael OT,

Thompson PM, Alzheimer's Disease Neuroimaging Initiative (2010). A commonly carried allele of the obesity-related FTO gene is associated with reduced brain volume in the healthy elderly. *Proceedings of the National Academy of Sciences USA* **107**, 8404–8409.

Hoth FK, Tate DF, Poppas A, Forman DE, Gunstad J, Moser DJ, Paul RH, Jefferson AL, Haley AP, Cohen RA (2007). Endothelial function and white matter hyperintensities in older adults with cardiovascular disease. *Stroke* **38**, 308–312.

Jiang H, van Zijl PC, Kim J, Pearlson GD, Mori S (2006). DtiStudio: resource program for diffusion tensor computation and fiber bundle tracking. *Computer Methods and Programs in Biomedicine* **81**, 106–116.

Katsumata T, Otori T, Nishiyama Y, Okubo S, Nishiyama Y, Nagayama H, Ueda M, Utsumi K, Yamazaki M, Komaba Y, Katsura K, Katayama Y (2010). Correlation between insulin resistance and white matter lesions among non-diabetic patients with ischemic stroke. *Neurological Research* **32**, 743–747.

Kempton MJ, Geddes JR, Ettinger U, Williams SC, Grasby PM (2008). Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. *Archives of General Psychiatry* **65**, 1017–1032.

Kodl CT, Franc DT, Rao JP, Anderson FS, Thomas W, Mueller BA, Lim KO, Seaquist ER (2008). Diffusion tensor imaging identifies deficits in white matter microstructure in subjects with type 1 diabetes that correlate with reduced neurocognitive function. *Diabetes* **57**, 3083–3089.

Magalhães PV, Kapczinski F, Nierenberg AA, Deckersbach T, Weisinger D, Dodds S, Berk M (2012). Illness burden and medical comorbidity in the Systematic Treatment Enhancement Program for Bipolar Disorder. *Acta Psychiatrica Scandinavia* **125**, 303–308.

May A (2011). Experience-dependent structural plasticity in the adult human brain. *Trends in Cognitive Sciences* **15**, 475–482.

McIntyre RS, Kenna HA, Nguyen HT, Law CW, Sultan F, Woldeyohannes HO, Adams AK, Cheng JS, Lourenco M, Kennedy SH, Rasgon NL (2010). Brain volume abnormalities and neurocognitive deficits in diabetes mellitus: points of pathophysiological commonality with mood disorders? *Advances in Therapy* **27**, 63–80.

McIntyre RS, Vagic D, Swartz SA, Soczynska JK, Woldeyohannes HO, Voruganti LP, Konarski JZ (2008). Insulin, insulin-like growth factors and incretins: neural homeostatic regulators and treatment opportunities. *CNS Drugs* **22**, 443–453.

Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK (2000). Lithium-induced increase in human brain grey matter. *Lancet* **356**, 1241–1242.

Mueller K, Anwander A, Möller HE, Horstmann A, Lepsien J, Busse F, Mohammadi S, Schroeter ML, Stumvoll M, Villringer A, Pleger B (2011). Sex-dependent influences of obesity on cerebral white matter investigated by diffusion-tensor imaging. *PLoS One* **11**, e18544.

Osby U, Brandt L, Correia N, Correia N, Ekbom A, Sparén P (2001). Excess mortality in bipolar and unipolar disorder in Sweden. *Archives of General Psychiatry* **58**, 844–850.

Pannacciulli N, Del Parigi A, Chen K, Le DS, Reiman EM, Tataranni PA (2006). Brain abnormalities in human obesity: a voxel-based morphometric study. *Neuroimage* **31**, 1419–1425.

Rosenberg GA (2009). Inflammation and white matter damage in vascular cognitive impairment. *Stroke* **40**, S20–S23.

Selemon LD, Lidow MS, Goldman-Rakic PS (1999). Increased volume and glial density in primate prefrontal cortex associated with chronic antipsychotic drug exposure. *Biological Psychiatry* **46**, 161–172.

Soreca I, Rosano C, Jennings JR, Sheu LK, Kuller LH, Matthews KA, Aizenstein HJ, Gianaros PJ (2009). Gain in adiposity across 15 years is associated with reduced gray matter volume in healthy women. *Psychosomatic Medicine* **71**, 485–490.

Stanek KM, Grieve SM, Brickman AM, Korgaonkar MS, Paul RH, Cohen RA, Gunstad JJ (2011). Obesity is associated with reduced white matter integrity in otherwise healthy adults. *Obesity* **19**, 500–504.

Taki Y, Kinomura S, Sato K, Inoue K, Goto R, Okada K, Uchida S, Kawashima R, Fukuda H (2008). Relationship between body mass index and gray matter volume in 1,428 healthy individuals. *Obesity* **16**, 119–124.

Tohen M, Frank E, Bowden CL, Colom F, Ghaemi SN, Yatham LN, Malhi GS, Calabrese JR, Nolen WA, Vieta E, Kapczinski F, Goodwin GM, Suppes T, Sachs GS, Chengappa KR, Grunze H, Mitchell PB, Kanba S, Berk M (2009). The International Society for Bipolar Disorders (ISBD) Task Force report on the nomenclature of course and outcome in bipolar disorders. *Bipolar Disorders* **11**, 453–473.

Vederine F, Wessa M, Leboyer M, Houenou J (2011). A meta-analysis of whole-brain diffusion tensor imaging studies in bipolar disorder. *Progress in Neuro-psychopharmacology and Biological Psychiatry* **35**, 1820–1826.

Verstynen TD, Weinstein AM, Schneider WW, Jakicic JM, Rofey DL, Erickson KI (2012). Increased body mass index is associated with a global and distributed decrease in white matter microstructural integrity. *Psychosomatic Medicine* **74**, 682–690.

Vita A, De Peri L, Sacchetti E (2009). Gray matter, white matter, brain, and intracranial volumes in first-episode bipolar disorder: a meta-analysis of magnetic resonance imaging studies. *Bipolar Disorders* **11**, 807–814.

WHO Expert Consultation (2004). Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* **363**, 157–163.

World Health Organization, International Association for the Study of Obesity, International Obesity Task Force (2000). *The Asia-Pacific Perspective: Redefining Obesity and its Treatment*. Health Communications Australia: Melbourne.

Yim CY, Soczynska JK, Kennedy SH, Woldeyohannes HO, Brietzke E, McIntyre RS (2012). The effect of overweight/obesity on cognitive function in euthymic individuals with bipolar disorder. *European Psychiatry* **27**, 223–228.

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978). A rating scale for mania: reliability, validity and sensitivity. *British Journal of Psychiatry* **133**, 429–435.