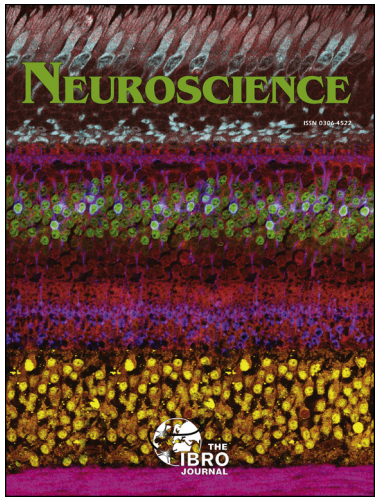

Body Mass Index, but not FTO genotype or Major Depressive Disorder, influences brain structure

James H. Cole, Christina P. Boyle, Andrew Simmons, Sarah Cohen-Woods, Margarita Rivera, Peter McGuffin, Paul M. Thompson, Cynthia H.Y. Fu

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Title

Body Mass Index, but not *FTO* genotype or Major Depressive Disorder, influences brain structure.

Authors

James H. Cole[a,b], Christina P. Boyle[c], Andrew Simmons[d,e], Sarah Cohen-Woods[a,f], Margarita Rivera[a,g], Peter McGuffin[a], Paul M. Thompson[c,h], Cynthia H. Y. Fu[a,i]

Affiliations

[a] Social, Genetic & Developmental Psychiatry Research Centre, Institute of Psychiatry, King's College London, De Crespigny Park, Denmark Hill, London SE5 8AF, UK.

[b] Computational, Cognitive, and Clinical Neuroimaging Laboratory, Division of Brain Sciences, Imperial College London, Burlington Danes Building, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK.

[c] Imaging Genetics Center, Laboratory of Neuro Imaging, Department of Neurology, UCLA School of Medicine, 225E Neuroscience Research Building, 635 Charles Young Drive, Westwood, Los Angeles, CA 90095, USA.

[d] Department of Neuroimaging, Institute of Psychiatry, King's College London, De Crespigny Park, Denmark Hill, London SE5 8AF, UK.

[e]NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London SE5 8AF, UK.

[f] Discipline of Psychiatry, University of Adelaide, Adelaide, Australia.

[g] CIBERSAM, University of Granada, Section of Psychiatry, Institute of Neurosciences, Biomedical Research Centre (CIBM), Avda. del Conocimiento, s/n - 18100, Armilla, Granada, Spain.

[h]Dept. of Psychiatry, Semel Institute, UCLA School of Medicine, 760 Westwood Plaza, Los Angeles, CA 90095, USA.

[i] Department of Psychological Medicine, Institute of Psychiatry, King's College London, De Crespigny Park, Denmark Hill, London SE5 8AF, UK.

Corresponding Author

Dr. James Cole, UCL Institute of Neurology, Queen Square, London, UK, WC1N 3BG.Email: james.cole@ucl.ac.uk; Tel: +44 207 242 0038; Fax: +44 207 611 0129

Abbreviations

BDI: Becky Depression Inventory

BMI: Body mass index

DNA: Deoxyribonucleic acid

FDR: False-discovery rate

FTO gene: Fat-mass and obesity associated gene

IQ: Intelligence Quotient

MDD: Major depressive disorder

MNI: Montreal Neurological Institute

MP-RAGE: Magnetisation-Prepared Rapid Gradient Echo

MRI: Magnetic Resonance Imaging

SNP: Single nucleotide polymorphism

TBM: Tensor-based morphometry

Abstract

Obesity and major depressive disorder (MDD) are highly prevalent and often comorbid health conditions. Both are associated with differences in brain structure and are genetically influenced. Yet, little is known about how obesity, MDD, and known risk genotypes might interact in the brain. Subjects were 81 patients with MDD (mean age 48.6 years) and 69 matched healthy controls (mean age 51.2 years). Subjects underwent 1.5T magnetic resonance imaging, genotyping for the fat mass and obesity associated (*FTO*) gene rs3751812 polymorphism, and measurements for body mass index (BMI). We conducted a whole brain voxelwise analysis using tensor-based morphometry (TBM) to examine the main and interaction effects of diagnosis, BMI and *FTO* genotype. Significant effects of BMI were observed across widespread brain regions, indicating reductions in predominantly subcortical and white matter areas associated with increased BMI, but there was no influence of MDD or *FTO* rs3751812 genotype. There were no significant interaction effects. Within MDD patients, there was no effect of current depressive symptoms; however the use of antidepressant medication was associated with reductions in brain volume in the frontal lobe and cerebellum. Obesity affects brain structure in both healthy participants and MDD patients; this influence may account for some of the brain changes previously associated with MDD. BMI and use of medication should ideally be measured and controlled for when conducting structural brain imaging research in major depressive disorder.

1. Introduction

Major depressive disorder (MDD) and obesity are among the most important health concerns currently facing society. Long-term predictions suggest that their prevalence, and thus impact on public health, will further increase (Mathers and Loncar, 2006). Rates of obesity (defined as body mass index (BMI) > 30) are 24% in MDD patients compared to 10% in controls (Farmer et al., 2008), depression during childhood is associated with a significant increase in adult BMI (Pine et al., 2001), and obese individuals in a population study were more likely to be at risk of depression at 18%) compared to non-obese individuals at 12% (Johnston et al., 2004). A meta-analysis of longitudinal studies supports a reciprocal relationship between MDD and obesity, with baseline obesity predicting future MDD and baseline MDD increasing the risk of obesity at follow-up (Luppino et al., 2010).

Common pathophysiological features have been observed in MDD and obesity (Soczynska et al., 2011), supporting the idea of a shared aetiology. Both are associated with structural brain abnormalities (Gunstad et al., 2008, Koolschijn et al., 2009). For example, higher BMI is associated with reductions in global brain volume (Ward et al., 2005, Pannacciulli et al., 2006), prefrontal lobes (Walther et al., 2010) and hippocampi (Raji et al., 2010), while depression is associated with comparable atrophic changes in the same regions (Ballmaier et al., 2004, Cole et al., 2010, Cole et al., 2011a).

MDD and obesity may share common genetic components. Both are significantly heritable; quantitative genetic studies estimate the variance due to genetic factors for BMI as ranging from 50%-90% (Stunkard et al., 1986, Allison et al., 1996, Maes et al., 1997) and between 37%-75% for a diagnosis of MDD (McGuffin et al., 1996, Sullivan et al., 2000). Twin research indicates some shared genetic aspects between MDD and obesity (Afari et al., 2010), and this is supported by findings from molecular genetic research. In particular, the fat mass and obesity associated (*FTO*) gene, shown to directly impact BMI (Dina et al., 2007, Frayling et al., 2007, Chang et al., 2008, Loos and Bouchard,

2008, Thorleifsson et al., 2009), has been assessed, our group finding that a diagnosis of MDD increases the effect of the *FTO* gene on BMI (Rivera et al., 2012). The *FTO* gene rs3751812 risk allele was strongly associated with BMI in two independent MDD patient groups, while there was no corresponding effect in the control groups. These results indicate that depression-related alterations in key biological processes may interact with the *FTO* risk allele to increase obesity (Rivera et al., 2012).

The combined effects of *FTO* and BMI are evident in the brain (Ho et al., 2010b). In a sample of healthy older adults, we replicated the association between the *FTO* risk allele and increased BMI and the relationship of increased BMI resulting in volumetric brain reductions identified using tensor-based morphometry (TBM). We also reported the novel finding that a SNP in the *FTO* gene is associated with brain volume alterations as having an increased BMI and carrying the risk allele at rs3751812 were associated with similar patterns of frontal and occipital volumetric reductions (Ho et al., 2010b). This supports the idea that *FTO* not only affects BMI but also affects the brain, either directly or indirectly by increasing BMI or affecting behaviour that impacts the brain.

MDD and obesity both influence brain structure, but the relationship between *FTO* and BMI has not been examined in MDD. In the present study, we employed TBM (as per Ho et al., 2010b) to investigate whether MDD and BMI share neuroanatomical correlates and whether MDD moderates the neuroanatomical overlap between the effects of *FTO* and BMI.

2. Experimental procedures

2.1 Participants

Eighty-one recurrent MDD patients and 69 healthy control participants underwent MRI scanning at the Institute of Psychiatry, King's College London. All participants had taken part in previous genetic association studies, including the investigation of MDD and *FTO* (Rivera et al., 2012), so all participants were of white European ancestry to reduce population stratification effects. Previous

imaging findings on portions of this sample have also been reported (Cole et al., 2011b, Cole et al., 2012). The study was approved by the Bexley & Greenwich Research Ethics Committee, and all participants provided written informed consent.

All MDD patients had experienced two or more depressive episodes of at least moderate severity, diagnosed using the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990). Healthy controls had no depressive history. Participants were excluded if they or a first-degree relative ever fulfilled criteria for mania, hypomania, schizophrenia or mood incongruent psychosis. Additional exclusion criteria were: a history of alcohol or substance abuse, depression secondary to medical illness or medication, a diagnosis of mania or psychosis in first- or second-degree relatives, any history of neurological or brain-related disease, or contraindications to MRI scanning.

Body mass index (BMI) was defined as weight in kilograms divided by height squared in metres. The determination of BMI was made by weight and height measurements at the original assessment and updated on or near the day of the MRI scan. Data on current mood, using the Beck Depression Inventory (BDI - Beck et al., 1961), IQ (Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999), and medication use were acquired.

2.2 Genotyping

Genotypes for rs3751812 were derived from genome-wide microarray data. DNA samples from the MDD cases and controls were genotyped using the Illumina HumanHap610-Quad BeadChips (Illumina Inc., San Diego, CA, USA) by the Centre National de Génotypage (Lewis et al., 2010). The SNP rs3751812 was selected for analysis due to the previous associations with brain structure (Ho et al., 2010b) and with BMI (Rivera et al., 2012). Genotype frequencies were computed (**Table 1**) and Hardy-Weinberg equilibrium was tested using PLINK v1.07 (Purcell et al., 2007). Due to the relatively low frequency of minor (T) allele homozygotes, *FTO* status was characterised as a binary variable, as in prior studies (Ho et al., 2010b), with G allele homozygotes representing the non-risk group and heterozygotes and T allele homozygotes the risk group. Genotypes were confirmed using a standard

Taqman genotyping assay (C_27476887_1) as per manufacturer's instructions. Only 1 genotype was not consistent, and this participant was excluded from the analysis.

2.3 MRI acquisition and analysis

Three-dimensional T1-weighted data were acquired on a 1.5T Signa HDx system (General Electric, WI, USA), using a Magnetisation-Prepared Rapid Gradient Echo (MP-RAGE) protocol at the Institute of Psychiatry, King's College London. Acquisition parameters were: echo time = 3.8ms, repetition time = 8.59ms, flip angle = 8º, field of view = 24cm x 24cm, slice thickness = 1.2mm, number of slices = 180, image matrix = 256 x 256. Full brain and skull coverage was required and quality control was assessed on all MR images (Simmons et al., 2009, 2011). Brain structure was assessed using a TBM approach - a deformation-based technique that quantifies differences in brain structure based on the voxelwise expansion and contraction factor necessary to spatially normalise brain images (Ashburner et al., 1998). In some situations, TBM can be more sensitive to subtle differences in brain structure than some other methods such as voxel-based morphometry. The TBM procedure involves pre-processing MP-RAGE images by correcting for intensity non-uniformities using a bias field correction procedure (Sled et al., 1998), then linearly registering those images to the Montreal Neurological Institute standard brain image template (MNI-152) using a nine-parameter registration to account for global position and scale differences across individuals, including head size (Hua et al., 2008). Globally aligned images were re-sampled to a final voxel size of 1 mm^3.

A minimal deformation template (MDT), or 'average' brain image, was created using data from a subsample of 20 MDD patients and 20 controls (Hua et al., 2008). The template was designed to be an unbiased representation of the sample and included equal numbers of males (N = 20) and females (N = 20). There was no statistical difference (p = 0.65) in the age of the subjects used in the MDT (49.03 ± 9.3 SD years of age) relative to the other subjects in the sample (49.77 ±8.7 SD years of age).

To quantify 3D patterns of volumetric brain atrophy based on statistical analysis of individual differences, all individual brains were non-linearly aligned to the MDT (Leow et al., 2005, Lepore et al., 2007). As all images were registered to the same template, they share a common anatomical coordinate defined by the common template. The local expansion factor of the 3D elastic warping transform, known as the Jacobian determinant, was plotted for each subject. These 3D Jacobian maps show relative volume differences between each individual and the common template and reveal areas of structural volume deficits or expansions. These can be tested for voxelwise statistical associations.

2.4 Statistical analysis

Initial analysis was conducted using Stata (Release 11, StataCorp LP, College Station, TX, USA) to test for relationships between demographic and clinical variables (i.e., age, sex, IQ, BDI) and the dependent variables: BMI, diagnostic group and *FTO* SNP genotype group. We used t-tests, χ^2 tests and Pearson's correlations, as appropriate. We also conducted statistical tests of the association between intracranial volume (ICV) and the dependent variable, to ascertain whether there were any underlying associations that could potentially bias the results. Subsequently, as per Rivera et al. (2012), we conducted a linear regression on $\log_{10}$ transformed BMI and *FTO* genotype, with age, sex and IQ as covariates, in combined samples and then separately in each group.

Regression analyses were run on the derived Jacobian maps by fitting a linear regression at each voxel to model relationships between brain volume and variables of interest. Predictors and covariates included: age of the subject (B1), sex (B2), IQ (B3), diagnosis (B4) and BMI (B5), e.g.:

$$Volume\ (Jacobian) = B_0 + B_1 \cdot Age + B_2 \cdot Sex + B_3 \cdot IQ + B_4 \cdot Diagnosis + B_5 \cdot BMI$$

Main effects of diagnosis, BMI and *FTO* rs3751812 genotype were tested, along with interaction terms between diagnosis and BMI, diagnosis and *FTO* genotype, and BMI and *FTO* genotype. We also tested for a three-way interaction effect, between diagnosis, BMI and *FTO* genotype, on brain

structure to see if diagnosis moderated the relationship between BMI and *FTO*. We used these voxelwise multiple regressions to assess whether the predictions of volume differences were significant, along with the influence of potential confounders. Medication status (i.e., whether a person was currently taking anti-depressant medication or not) was not included as a covariate as it was strongly associated with diagnosis ($p < 0.001$). Statistical *p*-value maps were generated to visualise patterns of voxelwise significance. To control for multiple testing, a standard false discovery rate (FDR) correction (Benjamini and Hochberg, 1995) was enforced voxelwise, using the conventionally accepted false-positive rate of 5% (q=0.05).

3. Results

3.1 Demographics

There were no significant differences in the sex ratio between groups, although there were trends towards controls being older and having higher IQ (Table 1). These 3 factors (sex, age, IQ) were included as covariates in the subsequent analyses. As expected, MDD patients had significantly higher BDI scores and were more likely to be taking anti-depressant medication, with 1 healthy control subject taking a low dosage of amitriptyline for migraines. MDD patients had significantly higher BMI compared to controls, consistent with the larger sample from which this group of participants was drawn, in terms of the relationship between BMI and MDD (Rivera et al., 2012).

Genotype frequencies of rs3751812 were in Hardy-Weinberg equilibrium ($p > 0.01$) and did not differ between groups ($p = 0.42$). When comparing demographics based on *FTO* genotype status (G-risk allele and TT homozygotes), the genotype groups did not differ in age ($p = 0.34$), sex (p =0.338), IQ ($p = 0.65$), medication usage ($p = 0.64$) or BDI ($p = 0.96$).

There was no significant main effect of *FTO* on BMI across all subjects ($p = 0.83$), nor in the linear regression of *FTO* genotype on $\log_{10}$ BMI across all subjects or on each diagnostic group separately,

perhaps due to the reduced size of the present sample compared to the overall cohort (N = 3251) in Rivera et al. (2012).

BMI showed a significant negative correlation with IQ (r = -0.19, p = 0.023). There were no correlations with age (p = 0.63), and BMI was similar between males and females (p = 0.34). Within the MDD patients, BMI showed a significant correlation with BDI (r = 0.26, p = 0.017), but not with medication use (p = 0.59).

ICV did differ significantly between males and females; males had higher ICV (t = 11.02, p < 0.01), but ICV was not correlated with age (p = 0.37), BMI (p = 0.27), or BDI score (p = 0.11). ICV was also not significantly associated with *FTO* rs3751812 genotype (p = 0.94) or a diagnosis of MDD (p = 0.16).

3.2 Effects on brain structure

The full regression model of the effects of BMI, MDD diagnosis and *FTO* genotype on regional brain volumes revealed significant effects of BMI (p = 0.0008), but no significant effect of *FTO* genotype or MDD, which was approaching significance. None of the interaction terms between the three factors were significant, nor was the three-way interaction effect. A reduced regression model was re-run without *FTO*, in which an effect of BMI on brain structure remained significant (p = 0.02), whereas diagnosis was not significant after FDR correction; nor was the interaction between BMI and MDD. This indicates that some of the variance in the Jacobian brain structural model is explained by BMI. All models were adjusted for age, sex and IQ.

Regions associated with BMI were visualised using unstandardized beta coefficient maps derived from the significant regression model in order to indicate the direction of change (expansion or contraction). Higher BMI was associated with reduced brain volumes in diverse regions of the brain: the involvement of frontal, temporal, parietal and occipital regions was confirmed quantitatively by using lobar regional masks (frontal: p = 0.0179; parietal: p = 0.0230; temporal: p = 0.0161; occipital: p

= 0.0198). As displayed in **Figure 1**, the regional contractions associated with increasing BMI are generally in the subcortical nuclei and white matter, as opposed to the cortical surface.

An exploratory analysis restricted to the MDD patient group assessed whether medication status or BDI score, as a measure of current self-reported depressive symptoms, were associated with brain structure. Medication status was found to be significant (p = 0.0019), though only in the frontal lobe region (p = 0.0020), where those currently taking antidepressant medication had reductions in volume. This indicates that within the MDD patient group, both BMI and medication status are important determinants of brain structure. To investigate this further, a conjunction analysis was run, to determine which voxels are significantly associated with both factors (as per Ho et al., 2010b). Reductions in frontal and cerebellar voxels were associated with higher BMI and taking antidepressants, with some expansions of CSF spaces also evident (p = 0.0009) (see **Figure 2**). The BDI score did not significantly relate to brain structure, though BMI, which was retained in the model, was still a strong predictor (p = 0.0175). When removing BMI from the model, the association between BDI and brain structure was still not significant. Age, sex and antidepressant use were used as covariates in the models.

4. Discussion

The relationship between major depressive disorder, *FTO* genotype and body mass index on regional brain structure revealed significant widespread effects of BMI and no significant effect of MDD diagnosis or *FTO* genotype for SNP rs3751812. The association of high BMI with brain volume reductions is well replicated (Ward et al., 2005, Pannacciulli et al., 2006, Gunstad et al., 2008, Raji et al., 2010, Ho et al., 2011), and the pattern of brain volume reductions is consistent with that previously reported by Ho et al., (2010b).

Our finding of high BMI impacting on brain structure in patients with depression is novel. In particular, our findings indicate that BMI may account for the reduced brain volumes that are generally observed in depression (Koolschijn et al., 2009) because BMI showed a significant

independent effect while there was no significant effect of diagnosis and BMI was significantly greater in MDD patients. An association of brain structure with BMI has been noted in other neuropsychiatric samples, such Alzheimer's Disease and mild cognitive impairment (Ho et al., 2010a) and after a first manic episode in bipolar disorder (Bond et al., 2011). The fact that these participants had all been diagnosed with recurrent MDD and had a significant lifetime burden of illness, but did not show alterations in brain structure is generally contrary to research in MDD samples (Koolschijn et al., 2009, Kempton et al., 2011) and does not lend support to the idea of a shared neuroanatomical aetiology explaining the common comorbidity of the two disorders. If previous studies had accounted for BMI in their study design, less conclusive results of structural brain abnormalities might have been found. However, the use of TBM in MDD is not common, and TBM may be more sensitive to the widespread effects of obesity (Ho et al., 2010b), whereas other methods (e.g., manual hippocampal volumetry or ROI-based approaches) may be more specific to depressive effects. Two studies that did use TBM in MDD samples (Ahdidan et al., 2011, Soriano-Mas et al., 2011) reported structural abnormalities in patients in the medial temporal lobe and brain stem, both of which were associated with the BMI model in our study (see Figure 1). Neither study accounted for BMI in their analysis, and this may have influenced these findings to some extent.

Furthermore, no influence of *FTO* SNP rs3751812 genotype was found on the brain volumes in contrast to Ho et al. (Ho et al., 2010b). This may reflect a slightly smaller sample size in the present study (N = 168 versus N = 206), the inclusion of a patient sample, and younger age of the present sample (mean age 50 years versus mean age 76 years (Ho et al., 2010b)). Age-related factors may influence the effect of *FTO* in the brain and it is possible that the effect of *FTO* on obesity (or BMI) may be evident earlier in life than the effect of *FTO* on the brain. One of the early tenets of imaging genetics was that brain measures might offer greater power to detect genetic effects than behavioural or physiological phenotypes (Bigos and Weinberger, 2010). That premise has not been borne out in genome-wide association studies, which required the aggregation of over 20,000 MRI scans to find and replicate common genetic variants implicated in hippocampal and intracranial

volumes (Bis et al., 2012, Stein et al., 2012). Moreover, while a number of genetic effects on the brain in MDD have been reported (Taylor et al., 2005, Frodl et al., 2007, Frodl et al., 2008b, Zobel et al., 2008, Bermingham et al., 2012, Murphy et al., 2012), they are yet to be robustly replicated, potentially due to small effects of genes and underpowered sample sizes. Interestingly, Ho and colleagues (Ho et al., 2010b) did not find a genetic effect when BMI was controlled for, further illustrating the strength of the relationship between BMI and brain structure.

The biological relationship between obesity and MDD is complex, but despite strong epidemiological evidence of comorbidity (Pine et al., 2001, Johnston et al., 2004, Farmer et al., 2008, Pan et al., 2012) our results do not reveal any shared aetiology. What is apparent from the present study is that the effect of BMI on brain structure is substantially greater than that of MDD. Careful study design is required to tease out the independent influence of depressive factors on the brain, which are unrelated to obesity-related factors. BMI was higher in MDD patients than in controls, and the severity of the self-reported depressive symptoms as measured by the BDI scale correlated with BMI in the patients, although there was no significant association between BDI and brain volume. To examine this further, future studies could match MDD and controls participants on BMI or restrict analysis to those subjects within the 'healthy' BMI range (i.e., 18.5-25).

Other factors that may have led to a lack of significant MDD effects include the degree of heterogeneity in the MDD patient group. These included a mixture of ages, current depressive status and a history of electroconvulsive therapy (ECT) in 4 patients. The pattern of brain differences associated with medication status also makes it difficult to establish depression-specific factors. Contractions in brain volume were found in those MDD patients taking antidepressants at the time of the study, and some of these reductions overlapped spatially with those areas associated with BMI - particularly in the frontal lobe and cerebellum. This is perhaps a controversial finding as previous research has associated antidepressant medication with a 'normalisation' (i.e. volume increase) in remitted MDD patients, in cross-sectional (Lavretsky et al., 2005, Malykhin et al., 2012,

Zeng et al., 2012) and longitudinal (Frodl et al., 2008a, Smith et al., 2013) studies. However, the picture is not clear cut, as some studies have found no effect of medication on brain structure (MacMillan et al., 2003, Vythilingam et al., 2004, Janssen et al., 2007) and others have found regional volume reductions associated with antidepressant medication in MDD patients (Young et al., 2008) or older adults with increased depressive symptoms (Geerlings et al., 2012). An alternative explanation is that those patients who currently receive antidepressant medication are potentially more likely to have a severe history of MDD and a higher lifetime burden. This may result in accumulated atrophy and the apparent reductions in volume. Medication status may indirectly index disease burden, rather than directly causing volume changes, though detailed investigation of previous depressive episodes and recurrence rates would be necessary to establish this. What is clear however, is that focused research on this subject is necessary, as the current sample were highly heterogeneous in terms of type of antidepressant prescribed, dosage, lifetime history of medication and treatment resistance. Intriguingly, some antidepressants, particularly tricyclics and monoamine oxidase inhibitors, have been linked to weight gain (Schwartz et al., 2004) and therefore increased risk of obesity (Serretti and Mandelli, 2010), so there may be common neurobiological factors underlying the spatial correspondence between BMI and medication effects detected in the present study.

Some other limitations of the study were a trend towards higher age and IQ in the control participants, although these factors were included in our statistical models. Despite being a well-validated method (e.g. Leow et al., 2006), tensor-based morphometry (TBM) is not as commonly used as alternatives such as voxel-based morphometry (VBM) or volumetric segmentation, which as mentioned, may offer different sensitivity to effects under investigation.

4.1 Conclusions

The widespread negative influence of increased BMI on brain structure has been demonstrated in both healthy participants and in depression. Independent effects of MDD diagnosis or rs3751812

genotype in the *FTO* gene were not detected by the analysis. Within MDD patients, the use of antidepressants was associated with lower regional brain volume, both in conjunction and independently of BMI, and this requires further investigation. Given high levels of comorbidity, the influence of obesity on brain structure in MDD indicates the necessity of assessing BMI and obesity and the careful consideration of medication effects in neuroimaging investigations in depression.

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Figure Captions

Figure 1.

Panel A) Orthogonal p-value maps of the effect of BMI on the brain in healthy controls and MDD patients (N = 150). Shaded voxels depicted are the significant results (FDR corrected $p < 0.05$) from the full model, which included a main effect of BMI, MDD diagnosis and genotype, and covaried for age, sex and IQ. Images are displayed on a study-specific average brain template (mean deformation template, or MDT). Panel B) Maps show areas where regional brain tissue volumes were significantly associated with BMI. In the significant areas, Cohen's effect size is shown at each voxel ($p = 0.0202$). For every unit increase in BMI, a subject moves 0.1 * standard deviations away from the mean brain volume, after statistically controlling for effects of age, sex, IQ and diagnosis on brain structure.

Figure 2.

Panel A) Cohen's effect size maps of localised changes from the MDD-only model ($N = 81$) associated with BMI, controlling for age, sex and medication. This panel shows axial, sagittal and coronal views to demonstrate significant decrease in overall brain volume in MDD patients ($p = 0.0178$). Panel B) Cohen's effect size maps of localised changes from the MDD-only model ($N = 81$) associated with medication, controlling for age, sex and BMI. This panel shows axial, sagittal and coronal views to demonstrate significant decrease in brain volume in MDD patients being treated with medication, predominately in the frontal lobe ($p = 0.0020$). Panel C) Orthogonal p-value maps of the effects of BMI and medication on the brain in MDD patients ($N = 81$). Shaded voxels depicted are the significant results (FDR corrected $p < 0.05$) resulting from a conjunction analysis identifying the overlapping areas of significant brain volume change from BMI and medication, independently, while covarying for age and sex. Images are displayed on a study-specific average brain template (mean deformation template, or MDT).

Table 1. Demographic, clinical and genetic characteristics

Group	Recurrent MDD patients	Healthy controls	Group comparison
N	81	69	-
Age	48.56 (9.19)	51.19 (7.99)	t = 1.86, p = 0.066
Sex (male/female)	27/54	31/38	χ^2 = 2.11, p = 0.15
IQ	117.37 (11.49)	120.54 (9.26)	t = 1.84, p = 0.068
BMI	26.39 (4.70)	24.14 (3.16)	t = -3.38, p< 0.001
Antidepressants use (yes/no)	60/21	1/68	χ^2 = 81.45, p< 0.001
BDI	15.04 (11.02)	1.75 (2.12)	t = -9.86, p< 0.001
Years since illness onset	29.32 (11.91)	-	-
History of ECT (yes/no)	4/77	-	-
rs3751812 genotype (TT & TG/GG)	51/30	39/30	χ^2 = 0.64, p = 0.42

Figures presented in mean (standard deviation) format.

Highlights

Cole et al., Body Mass Index, but not FTO genotype or Major Depressive Disorder, influences brain structure.

- BMI has significant influences on brain structure in patients and controls
- MDD diagnosis and rs3751812 SNP of the FTO gene had no effect on brain structure
- Taking antidepressant medication was associated with brain volume reductions
- Future neuroimaging studies of MDD should account for BMI as a confounding factor

Figure 1

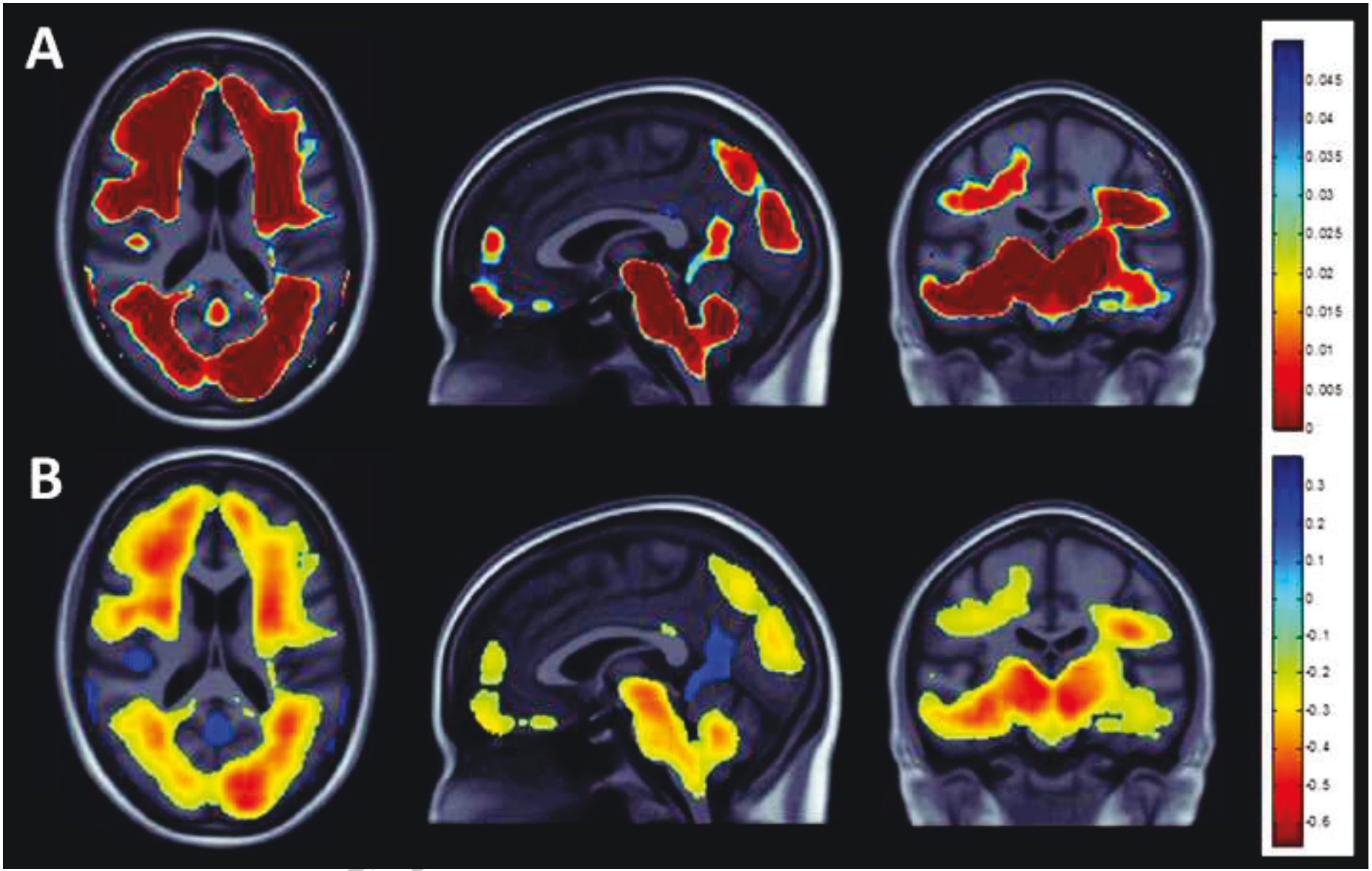

Figure 2