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BODY MASS INDEX, BUT NOT *FTO* GENOTYPE OR MAJOR DEPRESSIVE DISORDER, INFLUENCES BRAIN STRUCTURE

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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 the use of medication should ideally be measured and controlled for when conducting structural brain imaging research in MDD.

Key words: major depressive disorder, neuroimaging, genetics, body mass index, *FTO*, tensor-based morphometry.

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 etiology. 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

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Abbreviations: BDI, Becky Depression Inventory; BMI, body mass index; FDR, false-discovery rate; *FTO* gene, fat-mass and obesity-associated gene; ICV, intracranial volume; IQ, intelligence quotient; MDD, major depressive disorder; MDT, minimal deformation template; MP-RAGE, Magnetization-Prepared Rapid Gradient Echo; MRI, magnetic resonance imaging; SNP, single nucleotide polymorphism; TBM, tensor-based morphometry; VBM, voxel-based morphometry.

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comparable atrophic changes in the same regions (Ballmaier et al., 2004; Cole et al., 2010, 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% to 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 single nucleotide polymorphism (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 behavior 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.

EXPERIMENTAL PROCEDURES

Participants

Eighty-one recurrent MDD patients and 69 healthy control participants underwent magnetic resonance imaging (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, 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 meters. 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), intelligence quotient (IQ) (Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999), and medication use were acquired.

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 characterized 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 one genotype was not consistent, and this participant was excluded from the analysis.

MRI acquisition and analysis

Three-dimensional T1-weighted data were acquired on a 1.5T Signa HDx system (General Electric, WI, USA), using a Magnetization-Prepared Rapid Gradient Echo (MP-RAGE) protocol at the Institute of Psychiatry, King's College London. Acquisition parameters were: echo time = 3.8 ms, repetition time = 8.59 ms, flip angle = 8°, field of view = 24 cm × 24 cm, slice thickness = 1.2 mm, number of slices = 180, image matrix = 256 × 256. Full brain and skull coverage was required and quality control was assessed on all MR images (Simmons et al., 2009, 2011). Brain structure