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Research paper

Association of obesity with cognitive function and brain structure in patients with major depressive disorder

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ABSTRACT

Background: Obesity has been implicated in the pathophysiology of major depressive disorder (MDD), which prompted us to examine the possible association of obesity with cognitive function and brain structure in patients with MDD.

Methods: Three hundred and seven patients with MDD and 294 healthy participants, matched for age, sex, ethnicity (Japanese), and handedness (right) were recruited for the study. Cognitive function was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS). Gray and white matter structures were analyzed using voxel-based morphometry and diffusion tensor imaging in a subsample of patients (n = 114) whose magnetic resonance imaging (MRI) data were obtained using a 1.5 T MRI system.

Results: Verbal memory, working memory, motor speed, attention, executive function, and BACS composite scores were lower for the MDD patients than for the healthy participants ($p < 0.05$). Among the patient group, working memory, motor speed, executive function, and BACS composite scores were lower in obese patients (body mass index ≥ 30, n = 17) than in non-obese patients (n = 290, $p < 0.05$, corrected). MRI determined frontal, temporal, thalamic, and hippocampal volumes, and white matter fractional anisotropy values in the internal capsule and left optic radiation were reduced in obese patients (n = 7) compared with non-obese patients (n = 107, $p < 0.05$, corrected).

Limitations: Sample size for obese population was not very large.

Conclusions: Obesity is associated with decreased cognitive function, reduced gray matter volume, and impaired white matter integrity in cognition-related brain areas in patients with MDD.

1. Introduction

Body mass index (BMI) is an important nutritional parameter (Bailey and Ferro-Luzzi, 1995), and obesity, the state of abnormally increased BMI (Fabricatore and Wadden, 2006), originates from multiple biological and environmental factors (Campfield and Smith, 1999; Guyenet and Schwartz, 2012). Obesity has been suggested to be associated with the pathomechanism of various psychiatric disorders (Lopresti and Drummond, 2013; Nousen et al., 2013), including major depressive disorder (MDD) (Stunkard et al., 2003). Overlapping pathoetiologies (i.e., chronic inflammation, disturbed metabolic homeostasis, and hypothalamic-pituitary-adrenal axis dysregulation) have been suggested in obesity and MDD (Jantaratnotai et al., 2016). Furthermore, weight loss interventions, including bariatric surgery for

Abbreviations: ANCOVA, analysis of covariance; BACS, Brief Assessment of Cognition in Schizophrenia; BMI, body mass index; CPeq, chlorpromazine-equivalent dose; DTI, diffusion tensor imaging; FA, fractional anisotropy; FDR, false discovery rate; FSL, Functional MRI of the brain Software Library; FWE, family-wise error; HAMD, Hamilton Depression Rating Scale; HAMD-21, 21-item version of the HAMD; IMIeq, imipramine-equivalent dose; JART, Japanese version of National Adult Reading Test; JHU, Johns Hopkins University; MDD, major depressive disorder; MRI, magnetic resonance imaging; M.I.N.I., Mini International Neuropsychiatric Interview; NCNP, National Center of Neurology and Psychiatry; ROI, region of interest; SD, standard deviation; SPM, Statistical Parametric Mapping; TBSS, Tract-Based Spatial Statistics; VBM, voxel-based morphometry; WFU, Wake Forest University

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severe obesity (Yen et al., 2014), have been reported to improve depressive symptoms (Fabricatore et al., 2011).

Obesity has also been involved in cognitive dysfunction in memory, attention, executive function, and processing speed in aged MDD patients (Liu et al., 2014). Referring to BMI-based studies, peripheral inflammatory markers were associated with decreased psychomotor speed that was measured using several neuropsychological tasks in depressed patients who showed relatively high BMI scores (Goldsmith et al., 2016). A continuous BMI score correlated negatively with dominant hand fine motor skills measured by the Purdue pegboard test in individuals who had a history of MDD (Wroolie et al., 2015).

Although neuroimaging studies have reported an association between obesity and structural abnormalities in the brain, including those in gray and white matter (Kullmann et al., 2015; Soczynska et al., 2011), such an association has not been studied in subjects who presented with clinical depression. Cognitive dysfunction in MDD has been discussed particularly in relation with the hippocampal volume reduction accompanied by stress, which has been supported by animal studies (Brown et al., 2004; Campbell and Macqueen, 2004; McEwen, 2004; McEwen et al., 2002). In addition, brain imaging analyses have suggested that obesity is involved in the hippocampal atrophy and cognitive decline in human subjects (Shefer et al., 2013). Magnetic resonance imaging (MRI) studies of patients with MDD found negative effects of a continuous BMI score on the widespread subcortical and white matter volumes through tensor-based morphometry (Cole et al., 2013). Subsequently, Opel et al. (2015) reported that BMI scores negatively correlated with medial prefrontal, orbitofrontal, caudate nucleus, and thalamic volumes through voxel-based morphometry (VBM) (Opel et al., 2015). However, the association of obesity (BMI $\geq$ 30), rather than correlation with BMI, has not yet been examined. In addition, and to our knowledge, the possible effects of BMI-based variables on white matter integrity have not been analyzed by diffusion tensor imaging (DTI) in patients with MDD.

Although the involvement of continuous BMI scores in neurocognition has been suggested, there is a possibility that any nonlinear relationship such as u-shaped associations between BMI and depression scores (de Wit et al., 2009; Noh et al., 2015) underlies; which implies that obesity and underweight may have their risk-increasing effects. Furthermore, one reason for the difficulty in investigating the effects of obesity is that the prevalence of obesity is not generally large among a certain population (Bailey and Ferro-Luzzi, 1995; World Health Organization, 2000). We aimed to examine the association between obesity and cognitive function in MDD patients and healthy people in a relatively large Japanese sample. We also analyzed gray matter, including the hippocampus as a region of interest (ROI), and white matter structures, using VBM and DTI, to examine the pathology of obesity in the brain of MDD patients.

2. Methods

2.1. Participants

The participants consisted of 307 patients with MDD (mean age: 41.2 ± 11.3 years, 142 males) and 294 healthy people (mean age: 40.1 ± 12.9 years, 138 males). The participants were matched for age, sex, ethnicity (all Japanese), and handedness. All participants were recruited at the National Center of Neurology and Psychiatry (NCNP) hospital, were under 65 years old, and self-reported right handedness. Participants were recruited through advertisements in a free local magazine, and an announcement in our laboratory homepage. The participants were screened for any axis I psychiatric disorders using the Mini International Neuropsychiatric Interview (M.I.N.I.) (Otsubo et al., 2005; Sheehan et al., 1998) and additional non-structured interviews were conducted by a trained psychiatrist. A diagnosis for the participants' mental state was made based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (American Psychiatric Association, 1994), and clinical records if available. Participants that had a medical history of neurological diseases, severe head injury, substance abuse, or mental retardation were excluded. The purpose of the study was explained to each participant and written informed consent was collected from all participants. The study protocol was approved by the ethics committee at the NCNP, and was carried out in accordance with the Declaration of Helsinki (World Medical Association, 2013).

2.2. Clinical and psychological assessments

The symptoms in patients with MDD were assessed by the GRID-Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960; Williams et al., 2008). The cognitive functions were assessed by the Brief Assessment of Cognition in Schizophrenia (BACS) (Kaneda et al., 2007; Keefe et al., 2004). The BACS composite score was calculated as mean of *z* scores that were calculated from each BACS score based on mean and standard deviation (SD) of scores for the healthy people. The premorbid intelligence quotient was assessed by the Japanese version of National Adult Reading Test (JART) (Matsuoka et al., 2006). Daily doses of antipsychotics and antidepressants were converted to the chlorpromazine-equivalent dose (CPeq) and imipramine-equivalent dose (IMIeq) respectively, based on previous guideline (Inada and Inagaki, 2015).

2.3. Statistical analysis

Categorical variables were compared by the chi-square test, while continuous clinical variables between the two independent groups were compared using the Student's or Welch's t-test. Comparisons in BACS scores between groups were assessed by the analysis of covariance (ANCOVA), controlling at least for age and sex. BMI values were classified according to the World Health Organization criteria (World Health Organization, 2000) (i.e., underweight [BMI $<$ 18.5], normal [18.5 $\leq$ BMI $<$ 25], overweight [25 $\leq$ BMI $<$ 30], and obese [BMI $\geq$ 30]). The correlation was assessed by the Pearson's partial correlation coefficient, controlling for age and sex. The *post-hoc* analyses were conducted using the Bonferroni correction for multiple comparisons in ANCOVA and Person's partial correlation analysis. The effect sizes were evaluated using *Cramer's V* for the chi-square test, *Cohen's d* for the unpaired two-sample *t*-test, and η^2 for the ANCOVA. The statistics were calculated using the Statistical Package for the Social Sciences version 23.0 (SPSS Japan, Tokyo, Japan). All the statistical tests were two-tailed, and $p < 0.05$ was deemed significant.

2.4. MRI data acquisition and processing

High spatial resolution, 3-dimensional T1-weighted images and DTI data were obtained using the Magnetom Symphony 1.5-tesla (Siemens, Erlangen, Germany); MRI parameters were set up based on previous studies (Ota et al., 2013). Individuals with any aberrant findings were not enrolled in the study. VBM analyses were performed using Christian Gaser's toolbox (http://dbm.neuro.uni-jena.de/vbm8/) running within the Statistical Parametric Mapping (SPM) software package version 12 (http://www.fil.ion.ucl.ac.uk/spm). Gray matter images were smoothed with an 8-mm full-width at half-maximum Gaussian kernel. ROI analysis in VBM was conducted using the MarsBaR ROI toolbox for SPM (http://marsbar.sourceforge.net) after identifying the hippocampus based on the Wake Forest University (WFU) PickAtlas software (http://fmri.wfubmc.edu/software/pickatlas). DTI data were processed using Tract-Based Spatial Statistics (TBSS) (Smith et al., 2006). To exclude peripheral tracts, the fractional anisotropy (FA) threshold was set to 0.20. The skeletonized FA values from the DTI were analyzed by using a Functional MRI of the brain Software Library (FSL) "Threshold-Free Cluster Enhancement" option with 10,000 permutations in the "randomize" menu (Nichols and Holmes, 2002; Smith and Nichols,