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Depressive symptoms and neuroanatomical structures in community-dwelling women: A combined voxel-based morphometry and diffusion tensor imaging study with tract-based spatial statistics

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ABSTRACT

Depressive symptoms, even at a subclinical level, have been associated with structural brain abnormalities. However, previous studies have used regions of interest or small sample sizes, limiting the ability to generalize the results. In this study, we examined neuroanatomical structures of both gray matter and white matter associated with depressive symptoms across the whole brain in a large sample. A total of 810 community-dwelling adult participants underwent measurement of depressive symptoms with the Center for Epidemiologic Studies Depression Scale (CES-D). The participants were not demented and had no neurological or psychiatric history. To examine the gray and white matter volume, we used structural MRI scans and voxel-based morphometry (VBM); to examine the white matter integrity, we used diffusion tensor imaging with tract-based spatial statistics (TBSS). In female participants, VBM revealed a negative correlation between bilateral anterior cingulate gray matter volume and the CES-D score. TBSS showed a CES-D-related decrease in fractional anisotropy and increase in radial and mean diffusivity in several white matter regions, including the right anterior cingulum. In male participants, there was no significant correlation between gray or white matter volume or white matter integrity and the CES-D score. Our results indicate that the reduction in gray matter volume and differences in white matter integrity in specific brain regions, including the anterior cingulate, are associated with depressive symptoms in women.

1. Introduction

Major depressive disorder is associated with decreased brain volume or changes in white matter integrity, particularly in frontal areas (Abe et al., 2010; Bremner et al., 2002; Egger et al., 2008; Kieseppä et al., 2010; Shimony et al., 2009) and in medial temporal areas such as the hippocampus (Abe et al., 2010; Campbell et al., 2004; Videbech and Ravnkilde, 2004). Recently, depressive symptoms that do not meet the criteria for major depression have received increased attention. Understanding this preclinical state precisely is important for preventing major depressive disorder (Cuijpers et al., 2004). Several previous reports have suggested that depressive symptoms at a subclinical level have some of the same neural correlates as those in major depression (Hayakawa et al., 2013; Lavretsky and Kumar, 2002; Lyness et al., 1999). However, most previous studies on this issue have been based on regions of interest or small sample sizes, limiting the ability to draw firm conclusions from them.

The purpose of this study was to investigate brain structures associated with depressive symptoms in gray and white matter across the whole brain in a large sample. We used voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) with tract-based spatial statistics (TBSS). Both VBM and TBSS enable the global analysis of brain volume or white matter integrity without a priori identification of a region of interest. White matter integrity was represented by four DTI measures: fractional anisotropy (FA), mean diffusivity

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; DTI, diffusion tensor imaging; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity; TBSS, tract-based spatial statistics; VBM, voxel-based morphometry.

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(MD), axial diffusivity (AD), and radial diffusivity (RD). The diffusivity of water molecules in white matter is more limited in the direction of neuronal fibers. Although the histological reasons for this limitation are not well understood, FA is believed to reflect the degree of myelination and axonal density (Arfanakis et al., 2002; Harsan et al., 2006;Song et al., 2002, 2003). Recently, more discrete analysis of the AD and RD has provided potential measures of the mechanisms that underlie white matter pathology and disease processes (Song et al., 2002; Wozniak and Lim, 2006). AD reflects diffusivity parallel to axonal fibers. Increases in AD are thought to reflect pathology of the axon itself, such as from trauma or ischemic changes (Song et al., 2003). RD reflects diffusivity perpendicular to axonal fibers and appears to be more strongly correlated with myelin abnormalities—either dysmyelination or demyelination—such as in multiple sclerosis (Song et al., 2005). All analyses were performed not only for all participants combined but also for each sex separately, because there is evidence that the brains of males and females with major depression have structural differences (Lorenzetti et al., 2009), suggesting that the sex difference may be present even at the subclinical level. In support of this hypothesis, in our preliminary study of 21 community-dwelling adults (Hayakawa et al., 2013), we found brain structural differences between subjects with subclinical depression and controls only in females.

2. Materials and methods

2.1. Participants

The participants were 1148 volunteers who underwent private health screening at the University of Tokyo hospital from 2008 to 2009. Depressive symptoms were measured with the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) during a visit to screen for depression. The CES-D (range, 0–60) is a widely used 20-item self-report inventory that assesses the frequency and severity of depressive symptoms experienced in the past week. Adequate validity of the CES-D in elderly community-dwelling adults has been demonstrated (Haringsma et al., 2004).

The exclusion criteria were missing data from the CES-D or mini-mental state examination (MMSE); past or current history of neuropsychiatric disorders, including major depression diagnosed with the Diagnostic and Statistical Manual for Mental Disorders IV criteria; central nervous system disease; serious head trauma; or medication with antipsychotic drugs. Two trained neuroradiologists (one with 4 years, and the other with 10 years of experience) reviewed all scans (including T2-weighted, fluid-attenuated inversion recovery images and magnetic resonance angiography) and excluded participants who had gross abnormalities such as infarct, hemorrhage, brain tumor, or aneurysm. Participants with a Fazekas score of 3 (irregular periventricular hyperintensity extending into the deep white matter) were also excluded (Fazekas et al., 1987).

The ethical committee of our institute approved this study. After a complete explanation of the study was provided to each participant, written informed consent was obtained.

2.2. Image acquisition

MRI data were obtained on two 3 T Signa HDx scanners (GE Medical Systems, Milwaukee, WI, USA) of the exact same model with an 8-channel brain phased-array coil. For the VBM analysis, T1-weighted images were acquired by using three-dimensional spoiled-gradient recalled acquisition in the steady state (3D SPGR) in 124 axial slices (repetition time: 6.4 ms; echo time: 2.0 ms; flip angle: 151; field of view: 250 mm; slice thickness: 1 mm with no gap; acquisition matrix: 256 × 256; number of excitations: 0.5). The voxel dimensions were 0.977 × 0.977 × 1.0 mm. For the DTI analysis, diffusion tensor images were acquired by using a single-shot spin-echo echo-planar sequence in 50 axial sections (repetition time: 13,200 ms; echo time: 62 ms; field of view: 288 mm; slice thickness: 3 mm with no gap; acquisition matrix: 96 × 96; number of excitations: 1). Diffusion weighting was applied along 13 noncollinear directions with a b-value of 1000 s/mm^2, and a single volume was collected with no diffusion gradients applied (b = 0). The reconstructed voxel dimensions were 1.125 × 1.125 × 3.0 mm. Parallel imaging (array spatial sensitivity encoding technique) was used with an acceleration factor of 2.0.

2.3. Image processing

2.3.1. VBM analysis

All 3D SPGR images were processed and examined using the Statistical Parametric Mapping version 8 software (Wellcome Department of Imaging Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm), where we applied VBM implemented in the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) with default parameters in MATLAB 7.7.0.471 (The MathWorks, Natick, MA, U.S.A.) running on a Windows computer. A 'nonlinear only' modulation was performed on all images during spatial normalization so that values in resultant images are expressed as volume corrected for brain size. The resultant modulated images were smoothed with a Gaussian kernel of 8 mm (full width at half maximum).

2.3.2. DTI analysis

We performed an unbiased whole-brain TBSS analysis (Smith et al., 2006), which is part of FSL (FMRIB software library) 4.1 (http://www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004). First, the raw diffusion data were corrected for eddy current distortion and head motion by using FDT (FMRIB's Diffusion Toolbox) 2.0 (Smith et al., 2004) and corrected for spatial distortion due to gradient nonlinearity by using grad_unwarp (Jovicich et al., 2006). Following brain extraction by using BET2.1 (Smith, 2002), FA, MD, AD, and RD maps were created by fitting a tensor model to the diffusion data by using FDT. The FA data of all participants were then aligned into Montreal Neurological Institute (MNI) 152 space by using FNIRT 1.0 (Smith et al., 2004), which uses a b-spline representation of the registration warp field. The FMRIB58_FA standard-space image was used as the target. Next, a mean FA image was generated and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. The mean FA skeleton image was thresholded at an FA value of 0.2 to prevent inclusion of nonskeleton voxels. The aligned FA data of each participant were then projected onto this skeleton. The MD, AD, and RD data were also aligned into MNI 152 space and projected onto the mean FA skeleton by using the FA data to find the projection vectors.

2.4. Statistical analysis

Relationships between four variables, CES-D, sex, age, and MMSE score, were tested by Pearson product moment correlation for all participants in the VBM analysis group and all participants in the TBSS analysis group.

2.4.1. VBM analysis

We performed voxel-wise correlation analyses by using the multiple regression function of SPM8 for all participants combined and for each sex separately. The CES-D score was treated as a covariate of interest. As nuisance variables, individual values for sex, age, and MMSE score were included for analysis of all participants combined, and age and MMSE for analysis of each sex. Two linear contrasts (1, −1) were made for positive and negative correlations, respectively. The significance level was set at family-wise error (FWE)-corrected $P < 0.05$.