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Resting-state synchrony between the retrosplenial cortex and anterior medial cortical structures relates to memory complaints in subjective cognitive impairment

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ABSTRACT

Subjective cognitive impairment (SCI) is a clinical state characterized by subjective cognitive deficits without cognitive impairment. To test the hypothesis that this state might involve dysfunction of self-referential processing mediated by cortical midline structures, we investigated abnormalities of functional connectivity in these structures in individuals with SCI using resting-state functional magnetic resonance imaging. We performed functional connectivity analysis for 23 individuals with SCI and 30 individuals without SCI. To reveal the pathophysiological basis of the functional connectivity change, we performed magnetic resonance-diffusion tensor imaging. Positron emission tomography-amyloid imaging was conducted in 13 SCI and 15 nonSCI subjects. Individuals with SCI showed reduced functional connectivity in cortical midline structures. Reduction in white matter connections was related to reduced functional connectivity, but we found no amyloid deposition in individuals with SCI. The results do not necessarily contradict the possibility that SCI indicates initial cognitive decrements, but imply that reduced functional connectivity in cortical midline structures contributes to overestimation of the experience of forgetfulness.

1. Introduction

Subjective cognitive impairment (SCI) is a clinical state characterized by an individual's own perception that their cognitive abilities, including memory, are declining; importantly, individuals with SCI do not have overt cognitive deficits and their cognitive performance tends to be within the general normal range. SCI is presently a topic of active debate, especially with respect to its implications in the early diagnosis of Alzheimer's disease (AD). Epidemiological (Waldorff et al., 2012), clinical (Juncos-Rabadan et al., 2012), electrophysiological (Babiloni et al., 2010), and neuroimaging (Stewart et al., 2011) data suggest that a portion of SCI subjects is already on the path toward a neurodegenerative disease, mostly AD (Reisberg et al., 2008). However, other studies have found little or no correlation between subjective cognitive complaints and cognitive impairment (Jungwirth et al., 2004; Slavin et al., 2010), indicating that an individual's subjective evaluation of his/her cognitive functioning may not provide an accurate appraisal of actual cognitive deficits (Roberts et al., 2009).

The inconclusive results of previous studies may indicate that SCI could be due to various causes. Given that self-overestimation

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of cognitive disturbance is a major factor influencing SCI, dysfunction in self-referential processing might contribute to this phenomenon. Converging evidence suggests that self-referential processing is mediated by cortical midline structures such as the ventromedial and dorsomedial prefrontal cortex and the anterior and posterior cingulate cortex (Northoff et al., 2006). Therefore, we hypothesized that the resting-state functional connectivity among these regions in the cortical midline structures would be altered in SCI, and thought to underlie these patients' subjective memory complaints.

To test this hypothesis, we performed region of interest (ROI) seed-based functional connectivity analysis, to investigate the intrinsic neural network related to self-referential processing in individuals with SCI and in those without SCI (nSCI). In addition, to reveal the pathophysiological basis of any observed differences in functional connectivity, we performed magnetic resonance-diffusion tensor imaging (MRI-DTI) and positron emission tomography (PET) imaging with the ^{11}C-labeled Pittsburgh Compound-B ([^{11}C]PIB), and examined the association of white matter connectivity and amyloid deposition with changes in resting-state functional connectivity in SCI.

2. Methods

2.1. Participants

A total of 30 SCI and 38 nSCI individuals were recruited from the psychiatry unit of Osaka University Hospital. Individuals with SCI were included if they met the proposed Reisberg criteria for primary idiopathic SCI (Reisberg et al., 2008). This study was approved by the institutional review boards of all participating institutions, and all participants provided written informed consent.

All participants were screened for comorbid medical and psychiatric conditions by means of clinical, physical, and neurological examinations. Cognitive function was assessed according to a standardized battery of cognitive tests, including Raven's Colored Progressive Matrices (RCPM), Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive Component (ADAS-Cog), and the Logical Memory I/II subscale from the Wechsler Memory Scale (WMS-R LM I/II). To be classified into the SCI or nSCI groups, the individuals had to have normal memory function (scoring above the education-adjusted cutoff on WMS-R LM II, MMSE score $\geq$27), absence of significant levels of impairment in other cognitive domains, and essentially preserved activities of daily living. The education-adjusted cutoff scores of the WMS-R LM II (maximum score = 25) for a definition of clinically normal with no cognitive impairment are as follows: (1) education years $\geq$16, LM II score $\geq$12; (2) education years 10–15, LM II score $\geq$10; and (3) education years 0–9, LM II score $\geq$7.

After the medical examination and cognitive assessment, 7 individuals from the SCI group and 8 from the nSCI group were excluded because of the presence of overt cognitive deficits, and therefore 23 SCI and 30 nSCI individuals were included in the analysis. The presence of subjective memory deficit was evaluated with a standardized questionnaire system based on the everyday memory checklist (EMC) of Wilson et al. (1989). The EMC was translated into Japanese, and was slightly modified to fit Japanese culture. The EMC has been previously used to assess unawareness of memory impairment (Supplementary Table S1) (Kazui et al., 2003, 2006). The EMC scores for the subjects' own ratings were analyzed. All individuals in the SCI group had EMC scores greater than the standardized cutoff score of 9.

2.2. Neuroimaging analysis

2.2.1. MR image acquisition

All MRI examinations were performed using a 3-Tesla whole-body scanner (Signa Excite HD V12M4; GE Healthcare, Milwaukee, WI, USA) with an 8-channel phased-array brain coil. T1-weighted images were obtained using a 3-dimensional spoiled grass gradient recalled inversion-recovery sequence, and DT images were acquired with a locally modified single-shot echo-planar imaging sequence by using parallel acquisition at a reduction (ASSET) factor of 2 in the axial plane. The details are described in previous studies (Matsuoka et al., 2014; Yasuno et al., 2014). T2-weighted images were obtained using a fast-spin echo (TR = 4800 ms; TE = 101 ms; echo train length = 8; field of view = 256 mm; 74 slices in the transverse plane; acquisition matrix, 160 $\times$ 160, acquired resolution, 1 mm $\times$ 1 mm $\times$ 2 mm). To exclude subjects with significant microvascular disease, white matter hyperintensities and lacunar lesions were rated using the Scheltens scale, which is a semi-quantitative visual rating scale (Scheltens et al., 1993).

The resting-state functional MRI (fMRI) scan images were obtained by capturing 37 transverse slices of 4-mm thickness covering the entire brain with a temporal resolution of 3 seconds, using a T2*-weighted gradient echo-planar imaging pulse sequence (TR = 3000 ms, TE = 35 ms, flip angle = 85°, time frames = 88, number of images = 3256; acquisition time = 4 minutes 24 seconds). For resting-state image acquisition, participants were instructed to remain still with their eyes closed and to let their minds wander freely. To reduce blurring and signal loss arising from field inhomogeneity, an automated high-order shimming method based on spiral acquisitions (Kim et al., 2002) was used before acquiring DTI and fMRI scans. To correct for motion and distortion derived from the eddy current and B0 inhomogeneity, the FMRIB Software (v.5;//fsl.fmrib.ox.ac.uk/fsl) was used.

2.2.2. Image preprocessing for resting fMRI

Standard image preprocessing methods were conducted using the Statistical Parametric Mapping 8 (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/) with the conn toolbox (http://www.nitrc.org/projects/conn) for functional connectivity analysis. The functional images were corrected for slice time and motion, co-registered with a high-resolution anatomical scan, normalized into the Montreal Neurological Institute space, resampled at 2 mm^3, and smoothed with a Gaussian kernel of 8 mm^3 full-width half-maximum (Friston et al., 1995). In addition, the Artifact Detection Tool (http://www.nitro.org/projects/artifact_detect) was used to measure motion artifacts in all individuals of both groups (mean $\pm$ SD; nSCI: 0.042 $\pm$ 0.008, SCI: 0.047 $\pm$ 0.013, p = 0.13). Nonetheless, we controlled for any motion artifacts using realignment parameters detected by Artifact Detection Tool.

2.2.3. Seed region definition

A series of ROIs were defined on the cortical midline structures (Northoff and Bermpohl, 2004). A mask for the following distinct subdomains of the cortical midline structures was provided by the conn toolbox: the orbitomedial prefrontal cortex (BA11; Montreal Neurological Institute coordinates for the centroid of the ROIs, right and left: 18, 46, 29 and −16, 45, −29); dorsal medial prefrontal cortex (DMPFC, BA10: 26, 62, −3 and −23, 62, −3); anterior cingulate cortex (ACC, BA32: 11, 34, 14, and −8, 33, 16); posterior cingulate cortex (PCC, BA31: 14, −45, 35 and −9, −45, 35); and retrosplenial cortex (RSC, BA29: −9, −46, 13 and −6, −45, 13) (Fig. 1A).

2.2.4. Functional connectivity analysis

Following the preprocessing steps outlined in the previous section, the functional images were imported into the conn toolbox