Psychiatry Research: Neuroimaging 269 (2017) 43–47

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Metabolic correlate of memory-deficit awareness in dementia with Lewy bodies: Implication in cortical midline structure

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ARTICLE INFO

Keywords:
Dementia with Lewy bodies
Awareness
Memory deficit
FDG-PET
Cingulate island sign
DAT-SPECT
Cortical midline structure

ABSTRACT

The neural substrate of memory-deficit awareness has been studied in mild cognitive impairment and Alzheimer's disease (AD). However, little is known about that in dementia with Lewy bodies (DLB). To determine the neural substrates of memory-deficit awareness in DLB, we investigated the relationship between awareness of memory-deficit and glucose metabolism in DLB. Thirty-four patients with DLB were assessed by ^{18}F-FDG-PET and dopamine transporter (DAT)-SPECT. The awareness was evaluated using an awareness index that represents the discrepancy between objective and subjective memory scores. The association between awareness index and FDG uptake was analyzed using SPM12. Awareness index was significantly lower in DLB than in individuals with normal cognition and was associated with glucose metabolism in the bilateral posterior cingulate cortex and right orbitofrontal cortex. Moreover, the awareness index positively correlated with the cingulate island sign ratio but not with striatal DAT density. The findings suggested that the awareness of memory-deficit in DLB was to some extent impaired and its neural substrate was located in cortical midline structure. The concomitant AD-type pathology might have influenced memory-deficit awareness in DLB.

1. Introduction

Declining awareness of memory impairment and other cognitive functions is part of the natural history of dementia and represents cognitive incapacity rather than unwillingness to acknowledge a problem (McGlynn and Schacter, 1989). The findings of a longitudinal clinicopathological study have suggested that nearly all individuals with dementia eventually develop unawareness. This delays diagnosis and can cause difficulties with treatment, an increase in the burden of care and prognostic aggravation (Al-Aloucy et al., 2011). The symptom is described in all forms of progressive dementia but it is an early feature of Alzheimer's disease (AD) (Harwood et al., 2000; Starkstein et al., 1997a) and frontotemporal dementia (FTD) (Starkstein, 2014; Williamson et al., 2010). It occurs even during the prodromal stage of AD (MCI) (Roberts and Clare, 2009). Patients with MCI and unawareness have higher conversion rates to overt AD (Tabert et al., 2002). Although dementia with Lewy bodies (DLB) is the second most common neurodegenerative disease that causes dementia, little is known about awareness in this disease. The symptoms of DLB are more varied than those of AD, however, unawareness tends to be less prevalent among patients with DLB than with AD (Del Ser et al., 2001; Starkstein et al., 1996). Thus, unawareness in DLB has not been received much attention.

The neural substrates of unawareness in dementia are a matter of debate (Harwood et al., 2005; Mimura and Yano, 2006; Perrotin et al., 2015; Ries et al., 2007; Salmon et al., 2006; Shibata et al., 2008; Vogel et al., 2005). As awareness of a cognitive deficit occurs not only for one, but for several cognitive-function domains simultaneously, the corresponding neural substrate can differ among studies. Neuroimaging using ^{18}F-FDG-PET or brain perfusion SPECT has identified a relationship between memory-deficit unawareness in patients with AD and hypometabolism or hypoperfusion in the prefrontal cortex (PFC) involving the dorsomedial PFC and orbitofrontal cortex (OFC), as well as in the medial temporal lobe (MTL) and posterior cingulate cortex (PCC). A combined FDG-PET/resting-state fMRI analysis has revealed dysfunction of the cortical midline structure (CMS) including the OFC and PCC and the disconnection between these regions and MTL in terms of unawareness of a memory deficit in patients with AD (Perrotin et al., 2015). A neural substrate of unawareness such as that for AD has never been determined for DLB.

The present investigation evaluated associations between memory-deficit awareness and FDG uptake in the brains of patients with DLB to

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http://dx.doi.org/10.1016/j.pscychresns.2017.09.007
Received 24 February 2017; Received in revised form 29 May 2017; Accepted 8 September 2017
Available online 13 September 2017
0925-4927/

identify the neural substrate of awareness. We also examined pathological background of the awareness of memory deficit by assessing relationships between memory-deficit awareness and the cingulate island sign (CIS) (Lim et al., 2009) and the dopamine transporter (DAT) density in the striatum, because CIS and DAT binding reflect AD-type neurofibrillary-tangle (NFT) pathology (Graff-Radford et al., 2014) and striatal dopaminergic depletion that is associated with Lewy body (LB) pathology in the brainstem (Colloby et al., 2012), respectively.

2. Methods

2.1. Patients

The present study included 34 patients (age, > 65 years) who were diagnosed with probable DLB at Fukujuji Hospital, Tokyo between 2014 and 2016 according to the DLB consensus criteria (McKeith et al., 2005) and 18 individuals with normal cognition (NL). Cognitive function and short-term memory were assessed using the Mini-Mental State Examination (MMSE) and the Rey Auditory Verbal Learning Test (RAVLT) (Malloy-Diniz et al., 2007), respectively. Among core-features, fluctuation was evaluated using the clinician assessment of fluctuation (Walker et al., 2000). Hallucination and other symptoms were evaluated using the neuropsychiatric inventory (NPI). Parkinsonism was evaluated using the Unified Parkinson's Disease Rating Scale Motor Score (UPDRS-MS). Subjective and objective memory was evaluated with Memory Assessment Clinic-Q (MAC-Q) score (Crook et al., 1992) and the RAVLT, respectively. The MAC-Q scores were reversed so that a higher score represented better subjective memory. The awareness index (standardized delta-score) was calculated such that discrepancies between objective and subjective memory scores were standardized according to the mean and standard deviation of NL. All study participants were also assessed by MRI, FDG-PET and DAT-SPECT at the time of cognitive assessment. All procedures followed the clinical study guidelines of Fukujuji hospital and were approved by the hospital Ethical Review Board. Informed consent was obtained from all patients or their families for the patients to participate in the present study.

2.2. FDG-PET imaging

Patients fasted for at least six hours before assessment by FDG-PET using a Biograph Duo PET/CT instrument (Siemens AG., Munich, Germany) and blood sugar levels were measured to ensure the absence of hyperglycemia (> 150 mg/dL). A standard dose of 185 MBq of 18F-FDG was intravenously injected 45–50 min before image acquisition. Each image comprised a computed tomography (CT) transmission scan of the head (50 mAs for 16 s) followed by a three-dimensional (3D) static emission of 15 min with the resolution of the PET system set at 5 mm full-width half-maximum (FWHM). The PET sections were reconstructed using an iterative ordered-subset expectation maximization (OSEM) algorithm (4 iterations and 16 subsets), corrected for scatter and attenuation using density coefficients derived from a low-dose CT image of the head acquired in the same scanner. The 18F-FDG PET images were spatially normalized using SPM12 (Wellcome Department of Cognitive Neurology, London, UK) and FDG images were atlas-based parcellated into regions of interest (ROI) using a three dimensional stereotactic (3D-SRT) ROI template (Fuji Film RI Pharma, Tokyo Japan) (Takeuchi et al., 2002). Group differences in voxel-wise FDG uptake were assessed by a two-sided *t*-test using SPM12. The mean value in the ROI of the PCC was divided by the mean value in that of the precuneus plus cuneus to derive CIS ratios from FDG-PET images. The FDG-PET protocol is described elsewhere (Iizuka and Kameyama, 2016). Images of patients with DLB generated by FDG-PET were assessed using an awareness index that served as a single-vector regressor in a voxel-wise regression analysis using SPM12. Age, MMSE and education were used as nuisance variables in the analysis.

2.3. DAT-SPECT

Projection data were acquired in a 128 × 128 matrix on an E-CAM gamma camera (Toshiba Medical Corp, Otawara, Japan) with a fan beam collimator three hours after injecting ^{123}I-ioflupane (185 MBq). The images were reconstructed using a filtered back-projection algorithm with a Butterworth filter of cut-off frequency of 0.1 cycle/cm. Attenuation was corrected using Chang's method (attenuation coefficient = 0.1 cm^{-1}) and scatter radiation was corrected with a triple energy window. A specific binding ratio (SBR) that reflects striatal DAT binding was semi-quantified using DAT VIEW software (Nihon Medi-Physics, Tokyo, Japan) based on Bolt's method (Tossici-Bolt et al., 2006). We used the SBR as the mean value of right and left SBRs.

2.4. Statistical analysis

The mean age, education, MMSE, RAVLT and MAC-Q of NL, as well as patients with DLB were assessed using two-sample *t*-test. Correlations between memory-deficit awareness, cognitive functions, core features, CIS ratios and DAT binding were analyzed using the Pearson product-moment correlation coefficient with Bonferroni correction. All statistical tests were two-sided, and all data were statistically analyzed using SAS (The SAS Institute, Cary, NC, USA).

3. Results

The MMSE, RAVLT and MAC-Q scores were significantly lower in DLB than individuals with NL (Table 1). Awareness index was significantly lower in DLB than NL (Fig. 1). The FDG-uptake in DLB patients was compared with that in NL and the hypometabolism was obviously observed in the bilateral occipital and parietal association cortices and slightly in bilateral temporal cortex, precuneus and PCC in DLB (Table 2a, Fig. 2). Awareness of memory-deficit expressed by the awareness index was associated with glucose metabolism in the bilateral PCC and right OFC in DLB patients (Table 2b, Fig. 3). The CIS ratio was significantly associated with the awareness index (r = 0.455, p = 0.007; Fig. 4A), whereas striatal DAT binding in DAT-SPECT images was not (r = 0.220, p = 0.211; Fig. 4B). Delusion and apathy among DLB symptoms significantly and inversely correlated with the awareness index (Table 3).

4. Discussion

Awareness of memory deficit was evaluated by using awareness index that represents discrepancy between objective and subjective memory in the present study. The awareness index in DLB was significantly lower than in NL (Fig. 1). This suggested that awareness of memory deficit was to some extent impaired in DLB, whereas unawareness tends to be less prevalent among patients with DLB than with AD (Del Ser et al., 2001; Starkstein et al., 1996). This study also

Table 1
Demographic features of patients with DLB who were aware and unaware of a memory deficit and persons with normal cognition.

	DLB	NL	*p*-score
Number (n)	34	18	–
Male/Female	18/16	9/9	0.84 (chi-square test)
Age	76.9 ± 2.3	77.1 ± 1.3	0.81
Educational years	13.4 ± 1.9	12.8 ± 1.3	0.32
MMSE	23.6 ± 2.3	29.3 ± 0.5	< 0.01
RAVLT	25.1 ± 4.1	34.2 ± 2.4	< 0.01
MAC-Q	25.4 ± 3.1	27.2 ± 1.1	< 0.01
Awareness index	− 1.514 ± 1.693	0.000 ± 1.548	< 0.01
DAT binding	2.38 ± 0.88	NA	–
CIS ratio	1.05 ± 0.20	1.11 ± 0.23	0.31

Mean ± SD; NA, not assessed; two-sample *t*-test except gender (two-tailed).