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Positive affect and regional cerebral blood flow in Alzheimer's disease

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ABSTRACT

Quality of life (QOL) has been recently recognized as the central purpose of healthcare, and positive affect is one of the core dimension of QOL. However, positive affect among patients with dementia or Alzheimer's disease (AD) has not received much attention in the medical research field. One hundred sixteen consecutive patients with AD were recruited from the outpatient units of the Memory Clinic of Okayama University Hospital. The positive affect score was evaluated using the positive affect domain of the Quality of Life questionnaire for Dementia (QOL-D). Patients underwent brain SPECT with 99mTc-ethylcysteinate dimer. Positive affect scores were inversely related to apathy scores, subjective depressive scores, and delusion scores. After removing the effects of age, sex, duration of education, and cognitive function, positive affect scores showed a significant correlation with regional cerebral blood flow in the left premotor and superior frontal gyri. The left premotor and superior frontal area is significantly involved in the pathogenesis of the decrease of positive affect in AD. Apathy and depression are closely related to the prefrontal area in AD, and they may affect the relationship between positive affect and the left prefrontal area.

1. Introduction

Alzheimer's disease (AD) is the leading cause of late-onset dementia worldwide. The pathophysiology of AD is being gradually clarified, but there is no treatment for the cause of the disease. Therefore, the maintenance or recovery of quality of life (QOL) is very important in the care of patients with AD.

Psychological wellbeing is thought to be the core dimension for QOL of patients with dementia (Jonker et al., 2004). It consists of both the presence of positive affect and the absence of negative affect, although the absence of depressive symptoms is not necessarily the presence of psychological wellbeing (Nierenberg et al., 2012). Until now, however, not much attention has been paid to positive affect among patients with dementia or AD in the medical research field (Kurisu et al., 2016).

Despite its importance, there have been only a few studies focusing on positive affect of dementia including AD. High positive affect and low negative affect are closely related with greater engagement in activity among nursing home residents with dementia (Kolanowski et al., 2014). Some studies reported that an increased level of positive affect is observed during participation in activity programs among dementia patients or long-term care residents (Schreiner et al., 2005; Materne et al., 2014; Casey et al., 2014). Further, behavioral intervention or exercise induces higher positive affect and mood among patients with dementia or AD (Beck et al., 2002; Williams and Tappen, 2007).

Positive affect is decreased in mild to moderate AD compared to cognitively intact older adults (Cotrell and Hooker, 2005), but there have been no studies focusing on what characteristics are related to positive affect or identifying a neural substrate of the decrease in positive affect among AD patients. In this study, we tried to clarify the clinical characteristics of decreased positive affect and the cerebral blood flow (CBF) correlates of positive affect in AD. In previous studies, positive affect was evaluated objectively to avoid the effect of memory disturbance (Kolanowski et al., 2014; Schreiner et al., 2005; Materne et al., 2014; Casey et al., 2014; Beck et al., 2002; Williams and Tappen, 2007). Therefore, objective scaling of positive affect was also adopted in this study. As a hypothesis, we predicted that positive affect is inversely related to apathy and depression.

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2. Methods

2.1. Subjects

One hundred sixteen consecutive patients with AD were recruited from outpatient units of the Memory Clinic of Okayama University Hospital between September 2008 and April 2012 according to the following criteria. They all (i) underwent general physical and neurological examinations and extensive laboratory testing, including thyroid function tests, serum vitamin B12, and syphilis serology; (ii) had taken the Mini Mental State Examination (MMSE) (Folstein et al., 1975), the Frontal Assessment Battery (FAB) (Kugo et al., 2007), and Geriatric Depression Scale (GDS) (Muraoka et al., 1996); (iii) underwent brain single photon emission computed tomography (SPECT) with 99mTc-ethylcysteinate dimer as well as magnetic resonance imaging (MRI) of the head; and (iv) were diagnosed with probable AD according to the criteria formulated by the NINCDS-ADRDA (McKhann et al., 1984). The exclusion criteria were (i) complications from other neurological diseases or illnesses; (ii) history of mental illness or substance abuse prior to the onset of dementia; (iii) any evidence of focal brain lesions on head MRI; (iv) treatment with cholinesterase inhibitors, memantine, antipsychotics, antidepressants, or anxiolytic drugs; and (v) left handedness or ambidexterity.

The profile of each subject (age, sex, months of disease duration, years of education) was recorded. The Neuropsychiatric Inventory (NPI), Physical Self-Maintenance Scale (PSMS), and the Instrumental Activities of Daily Living Scale (IADL) were rated by a trained clinical psychologist based on the information from family caregivers. The Clinical Dementia Rating (CDR) (Hughes et al., 1982) score was rated by chief clinician.

2.2. Instruments

The QOL-D is an objective QOL scale and comprises 31 items encompassing six domains: positive affect, negative affect and actions, communication, restlessness, attachment to others, and spontaneity (Terada et al., 2002). Each item is ranked on a four-point scale (from 1 to 4). In this study, total scores of the positive affect domain, which includes seven items, were used as the positive affect score (from 7 to 28). In the positive affect domain, a high score means a higher level of positive affect.

The MMSE is a cognition screening test used widely in many parts of the world. The MMSE has a maximum score of 30 points. It assesses aspects of orientation, recall, language, and visual construction (Folstein et al., 1975). The MMSE was evaluated by a trained clinical psychologist.

The FAB consists of six items, and the score on each item ranges from 0 to 3. A lower score indicates a greater degree of executive dysfunction. The six subtests of the FAB explore (1) similarities (conceptualization), (2) lexical fluency (mental flexibility), (3) Luria motor sequences (programming), (4) conflicting instructions (sensitivity to interference), (5) a go/no-go test (inhibitory control), and (6) prehension behavior (environmental autonomy). For this study, we used the Japanese version of the FAB described elsewhere (Dubois et al., 2000; Kugo et al., 2007).

NPI is a valid and reliable instrument for measuring non-cognitive symptoms in dementia. (Cummings et al., 1994; Hirono et al., 1997). The original NPI comprises 12 domains, but the Japanese version of NPI (Hirono et al., 1997) consists of ten domains because it excludes appetite and eating abnormalities. It is a caregiver-based tool. The NPI gives a composite score for each domain, which is the product of frequency by severity subscores: scores from 1 to 4 (with 4 being the most severe) for the frequency and from 1 to 3 (with 3 being the most severe) for the severity of each behavior (Akiyama et al., 2008). The maximum attainable score was 12.

The Geriatric Depression Scale (GDS) has been extensively used in the fields of psychiatry and public health to assess depression in the elderly (Yesavage and Blink, 1983). The GDS has two different versions: a standard version with 30 items and a shortened version with 15 items. For the present study, the shortened 15-item version of the GDS was administered (Burke et al., 1991; Muraoka et al., 1996). A higher score means higher subjective depressive signs.

The Physical Self-Maintenance Scale (PSMS) and the Instrumental Activities of Daily Living Scale (IADL) are validated scales for the assessment of activities of daily living (ADL) (Lawton and Brody, 1969; Hokoishi et al., 2001). The PSMS is a six-item scale that rates self-care ability in toileting, feeding, dressing, personal hygiene and grooming, locomotion (physical ambulation), and bathing. The IADL Scale assesses the patients' ability to perform the following eight complex daily tasks: ability to use the telephone, shopping, food preparation, household tasks, laundering, mode of transportation, responsibility for medications, and ability to manage finances.

2.3. Ethics

This study was approved by the Internal Ethical Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences. After a complete description of the study to the subjects and their relatives, written informed consent was obtained.

2.4. Brain perfusion SPECT imaging

All subjects were examined by brain perfusion SPECT. Patients were examined in a comfortable supine position with their eyes closed in quiet surroundings. First, the passage from the heart to the brain was monitored after intravenous administration of 99mTc-ethylcysteinate dimer (ECD, 600 MBq, FUJIFILM RI Pharma Co. Ltd., Tokyo, Japan). Ten minutes after the angiography, SPECT images were obtained using a triple-head, rotating gamma camera interfaced to a minicomputer (GCA9300A/DI; Toshiba, Tokyo, Japan) equipped with a fan beam, low-energy, high-resolution collimator. Sixty projection images over a 360° angle in a 128×128 matrix were acquired. All images were reconstructed using ramp-filtered back-projection and then three-dimensionally smoothed with a Butterworth filter (order 8, cutoff 0.12 cycles/cm). The reconstructed images were corrected for gamma ray attenuation using the Chang method ($\mu = 0.09$).

2.5. Data analysis

Spatial reprocessing and statistical analysis of images was performed on a voxel by voxel basis using Statistical Parametric Mapping 8 (SPM8, Wellcome Department of Imaging Neuroscience, UK) running on MATLAB (The Mathworks, Inc., Natick, MA, USA). All SPECT images of each subject were normalized to the standard brain of the Montreal Neurological Institute (MNI), and spatial normalization was performed with 12-parameter affine and non-linear transformations (Friston et al., 1995). The voxel sizes of the reslice option were 2 mm × 2 mm × 2 mm. The non-linear parameter was set at 25 mm cut-off basis functions and 16 iterations. All the normalized SPECT images were then smoothed with an isotropic Gaussian kernel filter (12-mm full-width at half-maximum).

To show areas where the correlation between rCBF and positive affect scores was significant among the 116 CE subjects, multiple regression analysis was performed using SPM8. The analysis used a threshold of $p < 0.005$ (uncorrected) at the voxel level, and