



Repetitive questioning behavior in Alzheimer's disease: Relationship to regional cerebral blood flow

Yuki Kishimoto^a, Seishi Terada^{a,*}, Shuhei Sato^b, Hidenori Yoshida^a, Hajime Honda^a, Naoya Takeda^a, Etsuko Oshima^a, Takeshi Ishihara^a, Shigetoshi Kuroda^a

^aDepartment of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan

^bDepartment of Radiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan

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ABSTRACT

Repetitive questioning is among the most common and burdensome of the behavioral and psychological symptoms of Alzheimer's disease (AD). Regardless of the clinical significance of the repetitive questioning, the neural substrates involved remain unclear. Fifty-eight consecutive patients with AD participated in this study. The score of repetitive questioning behavior was evaluated by multiplying the severity by the frequency of the behavior. They underwent brain SPECT with ^{99m}Tc-ethylcysteinate dimer. Scores of repetitive questioning behavior had a significant positive correlation with regional cerebral blood flow (rCBF) in the bilateral pericallosal regions. After removing the effect of memory test scores, we found a significant positive correlation of scores of repetitive questioning behavior to rCBF in the left pericallosal region. The pericallosal region includes the upper precuneus, cingulate, and posterior cingulate cortices on 3DSRT. Repetitive questioning behavior among AD patients might be a manifestation of mental state associated with a relative increase or preservation of rCBF in the left pericallosal region.

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1. Introduction

Recently, researchers have focused on behavioral disturbances in dementia because they represent a major source of caregiver distress (Marini et al., 1997). Troublesome and disturbing behavior is a very frequent component of dementia (Baumgarten et al., 1990). Repetitive behaviors such as asking the same question many times or doing the same thing all day are observed quite frequently in demented patients (Baumgarten et al., 1990), and the behaviors exhaust and agitate caregivers (Miyamoto et al., 2002).

Repetitive behaviors are among the most common and burdensome behavioral and psychological symptoms of Alzheimer's disease (AD), and repetitive questioning is the most frequent of the repetitive behaviors (Baumgarten et al., 1990; Marini et al., 1997; Miyamoto et al., 2002; Cullen et al., 2005). In both mobile and non-mobile groups, 'repeating the same questions' was predictive of caregiver burden (Miyamoto et al., 2002). Repetitive questioning has been presumed to be a direct result of memory impairment (Ready et al., 2003). However, while memory impairment is present in all AD patients, repetitive questioning behavior is not. This could mean that the overall level of memory impairment is more severe in questioners or that other factors influence the occurrence of the symptom.

Regardless of the clinical significance of repetitive questioning behavior in AD, the neural substrates involved remain unclear because neuroimaging studies investigating the brain regions related to the repetitive questioning behavior in patients with AD have not been performed (Hwang et al., 2000; Cullen et al., 2005). In the present study, we investigated the relationship between repeated questioning behavior and regional cerebral blood flow (rCBF) in order to assess the neural substrates for the behavior.

2. Methods

2.1. Subjects

Fifty-eight consecutive patients with Alzheimer's disease were recruited from the outpatient units of the Memory Clinic of Okayama University Hospital between January 2002 and December 2006 according to the following criteria (Table 1): 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), the frontal assessment battery (FAB) (Dubois et al., 2000; Kugo et al., 2007), and a memory test within 1 week of scanning; (iii) underwent brain single photon emission computed tomography (SPECT) with ^{99m}Tc-ethylcysteinate dimer with analysis by three-dimensional stereotaxic region of interest template (3DSRT) (Takeuchi et al., 2003; Takeuchi et al., 2004) as well as magnetic

* Corresponding author. Tel.: +81 86 235 7242; fax: +81 86 235 7246.

E-mail address: terada@cc.okayama-u.ac.jp (S. Terada).

Table 1
Demographic characteristics and scores of repetitive questioning.

| Variables | N | % |
|----------------------------------|----|----|
| Sex | | |
| Male | 18 | 31 |
| Female | 40 | 69 |
| Age | | |
| – 64 | 4 | 7 |
| 65–69 | 4 | 7 |
| 70–74 | 11 | 19 |
| 75–79 | 17 | 29 |
| 80–84 | 20 | 34 |
| 85– | 2 | 4 |
| Clinical dementia rating | | |
| 0.5 | 15 | 26 |
| 1 | 30 | 52 |
| 2 | 13 | 22 |
| Scores of repetitive questioning | | |
| 0 | 24 | 41 |
| 1 | 1 | 2 |
| 2 | 6 | 10 |
| 3 | 8 | 14 |
| 4 | 3 | 5 |
| 6 | 7 | 12 |
| 8 | 8 | 14 |
| 9 | 1 | 2 |

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) other

Table 2
Scores of Neuropsychiatric Inventory.

| Subscales | N | % |
|-------------------------|----|----|
| Delusion | | |
| ≥ 1 | 13 | 22 |
| ≥ 4 | 8 | 69 |
| Hallucination | | |
| ≥ 1 | 5 | 9 |
| ≥ 4 | 1 | 2 |
| Agitation/aggression | | |
| ≥ 1 | 17 | 29 |
| ≥ 4 | 12 | 21 |
| Depression | | |
| ≥ 1 | 15 | 26 |
| ≥ 4 | 7 | 12 |
| Anxiety | | |
| ≥ 1 | 21 | 36 |
| ≥ 4 | 11 | 19 |
| Euphoria | | |
| ≥ 1 | 9 | 16 |
| ≥ 4 | 6 | 10 |
| Apathy | | |
| ≥ 1 | 35 | 60 |
| ≥ 4 | 25 | 43 |
| Disinhibition | | |
| ≥ 1 | 10 | 17 |
| ≥ 4 | 9 | 16 |
| Irritability | | |
| ≥ 1 | 21 | 36 |
| ≥ 4 | 10 | 17 |
| Aberrant motor behavior | | |
| ≥ 1 | 5 | 9 |
| ≥ 4 | 4 | 7 |

neurological and/or psychiatric diseases, (ii) evidence of focal brain lesions on MRI, and (iii) treatment with cholinesterase inhibitors, antipsychotics, antidepressants or anxiolytic drugs.

The memory test consisted of two items. One item was to recall the names of three things learned earlier (a part of the MMSE, 3 points), and the other was to recall a name and address learned earlier (both about 5 min). The name and address consisted of seven elements (7 points). Therefore, the score of the memory test ranged from 0 to 10. A higher score meant a better performance. This delayed recall test is a part of Addenbrooke's Cognitive Examination (ACE) (Mathuranath et al., 2000; Yoshida et al., 2010). The reliability and validity of the Japanese ACE have been reported (Yoshida et al., 2010).

The profile of each subject (age, sex, years of education, years of disease duration) was recorded, and the CDR score was rated by the chief clinician. Fifty-eight outpatients with Alzheimer's disease were examined. The age range was 59–86 years (mean age, 76.3 ± 6.2 years), the mean scores on the MMSE, FAB, and memory test were 19.3 ± 4.2, 10.0 ± 2.9, and 0.72 ± 1.5, respectively. The mean number of years of education and duration of disease were 10.0 ± 2.5 years and 3.0 ± 2.1 years, respectively.

2.2. 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.

2.3. Repetitive questioning behavior and Neuropsychiatric Inventory (NPI)

Repetitive questioning behavior was defined as asking the same questions repeatedly. Information was gathered from caregivers familiar with the patient's daily behavior. Only caregivers living with the patient served as informants.

A widely used scale for evaluating repetitive or stereotypic behaviors of patients with dementia in Japan is the Stereotypy Rating Inventory (SRI) (Shigenobu et al., 2002). There is an item evaluating repetitive speech in the SRI, but the item does not include repetitive questioning (Shigenobu et al., 2002). Therefore, we evaluated repetitive questioning behavior in the same way that the repetitive behavior is evaluated in the SRI.

The caregiver was asked whether repetitive questioning behavior had been observed during the past month. If the caregiver indicated that repetitive questions were asked, the caregiver was asked to rate the severity (1 = mild, 2 = moderate, or 3 = marked) and frequency (1 = often, approximately once a week; 2 = moderately frequently, several times per week but less than everyday; 3 = frequently, everyday but less than 5 times per day; 4 = extremely frequently, everyday but more than 5 times per day or almost all the time) of the

Table 3
Correlation coefficient of repetitive questioning to patient profiles and test scores.

| | Age | Education | Duration | MMSE | FAB | Memory |
|---------------------|----------|-----------|----------|-------|---------|---------|
| Repeated questions# | 0.006 | 0.090 | 0.187 | 0.067 | 0.114 | −0.292* |
| MMSE | −0.211 | 0.205 | 0.070 | 1 | 0.400** | 0.428** |
| FAB | −0.100 | 0.092 | −0.043 | | 1 | 0.125 |
| Memory test | −0.339** | 0.406** | −0.036 | | | 1 |

*, $P < 0.05$; **, $P < 0.01$; education, years of education; duration; disease duration repeated questions #, scores of repetitive questioning.

MMSE, Mini Mental State Examination; FAB, Frontal Assessment Battery.

Correlation coefficient between scores of repetitive questioning to other scores, Spearman's correlation coefficient.

Other correlation coefficient, Pearson's correlation coefficient.

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