EXTRA Dementia and Geriatric Cognitive Disorders

Dement Geriatr Cogn Disord Extra 2017;7:395–405
DOI: 10.1159/000481854
Received: June 16, 2017
Accepted after revision: September 1, 2017
Published online: November 23, 2017

Original Research Article

Gustatory Dysfunction as an Early Symptom of Semantic Dementia

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Keywords
Semantic dementia · Gustatory function · Taste · Food preference

Abstract
Objective: To investigate the gustatory function in patients with semantic dementia (SD). ***Methods:*** Detection and recognition thresholds of the 4 basic tastes (sweet, salty, sour, and bitter), taste discrimination, and taste identification were evaluated in 18 patients with SD, 18 patients with Alzheimer disease (AD), and 22 healthy controls. ***Results:*** Total detection and recognition threshold values were significantly higher in the SD and AD groups than in the control group. Patients with early-stage SD (Clinical Dementia Rating Scale score 0.5) exhibited significantly higher detection and recognition thresholds relative to controls, while increases in recognition threshold were only noted in patients with AD. Patients with SD exhibited significantly higher thresholds for the detection of sweet and salty tastes and the recognition of salty, sour, and bitter tastes, while patients with AD exhibited significantly higher thresholds only for the recognition of salty and sour tastes. Taste discrimination was preserved, whereas taste identification was disturbed, in both the SD and AD groups. ***Conclusions:*** Gustatory dysfunction at both the sensory and semantic levels may be among the early symptoms of SD. Although patients with SD had difficulty detecting sweet tastes, they more easily recognized these tastes than others, which may explain their strong preference for sweets.

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Introduction

Patients with dementia often exhibit severe eating abnormalities. Previous studies have reported that eating abnormalities of various types are more frequently observed in frontotemporal lobar degeneration than in Alzheimer disease (AD). Concerning changes in food preference, which both patients with frontotemporal lobar degeneration and those with AD tend to exhibit [1–4], patients with semantic dementia (SD) have this symptom more than twice as often as patients with AD [5]. Previous studies have revealed that both olfactory and gustatory functions are disturbed in the early stages of AD [6–11], suggesting that these dysfunctions may be involved in the changes in food preference. However, to date, no studies have directly examined basic gustatory function in SD, though researchers suggest that deficits in identifying odors [12, 13] and flavors [14, 15] occur in this disease.

In the present study, we investigated gustatory thresholds, taste discrimination, and taste identification for the 4 basic tastes (sweet, salty, sour, and bitter) in patients with SD and compared the results to those in patients with AD and healthy controls. We further analyzed the relationship between these functions and dementia severity and dominant side (left or right) atrophy in the temporal lobes.

Methods

Participants

Eighteen patients with SD (11 with left-predominant atrophy and 7 with right-predominant atrophy) were recruited from among the outpatients of the following dementia clinics: Asakayama Hospital, Ehime University Hospital, Osaka University Hospital, Kumamoto University Hospital, Jikei University Hospital, Hyogo Prefectural Rehabilitation Center at Nishi-Harima, and Saiseikai Ibaraki Hospital. Inclusion criteria for participants with SD were: (1) diagnosis of SD according to standard criteria [16, 17], (2) SD diagnosis supported by MRI, i.e., showing knife-edge atrophy in the temporal pole, inferior, and middle temporal gyri [18–20], and SPECT, i.e., showing focal hypoperfusion in the temporal lobe [21], and (3) a Clinical Dementia Rating Scale (CDR) score ≤1 [22]. Patients with CDR scores of 2 and 3 were excluded, as several tasks are too demanding for those patients. For the comparison group, 18 patients with AD were recruited from among the outpatient population of the dementia clinic in the Department of Neuropsychiatry at Osaka University Hospital. Inclusion criteria for participants with AD were as follows: (1) diagnosis of probable AD according to NINCDS-ADRDA criteria [23], (2) diagnosis supported by MRI, i.e., showing atrophy in the medial temporal cortex, and SPECT, i.e., showing hypoperfusion in the posterior cingulate cortex, precuneus, and temporal and parietal areas [24], and (3) CDR score ≤1. Patients with AD age- and sex-matched with those in the SD group were recruited from consecutive outpatients. Exclusion criteria for both the SD and AD groups were as follows: (1) physical and surgical complications that may affect examination and (2) diagnosis compatible with other types of dementia, such as probable vascular dementia according to NINDS-AIREN criteria [25], probable dementia with Lewy bodies [26], or probable corticobasal degeneration [27]. In addition, 22 healthy, age- and sex-matched controls were recruited.

All procedures followed the Clinical Study Guidelines of the Ethics Committee of the Osaka Prefecture University and were approved by the Internal Review Board.

Cognitive Examinations

All patients were evaluated using the Mini-Mental State Examination [28], digit span (forward, backward) test, "information" subtests of the Wechsler Adult Intelligence Scale-III,

and verbal fluency tasks (animal names and nouns with the initial phoneme "Ka" in 1 min). Behavioral and psychiatric symptoms were assessed via a structured interview using the Neuropsychiatric Inventory [29, 30].

Gustatory Threshold

Gustatory thresholds for the 4 basic tastes (sweet, salty, sour, and bitter) were assessed using a Taste Disk® kit (Sanwa Chemical Inc., Nagoya, Japan). This test kit contains 4 kinds of solutions (sucrose, sodium chloride, tartrate, and quinine hydrochloride, corresponding to sweet, salty, sour, and bitter tastes, respectively) of 5 different concentrations ranging from 1 (lowest) to 5 (highest) for each taste solution. One drop of solution was applied to a circular disk of filter paper (5-mm diameter) using a syringe, and placed on the participant's tongue, 2 cm to the left of the lingual apex. Participants were required to choose a taste from the taste index table (6 choices: "sweet," "salty," "sour," "bitter," "undefined taste," and "don't know"). We measured 2 types of thresholds, namely, "detection threshold" and "recognition threshold." Detection threshold was measured as the concentration level at which participants reported any taste, regardless of accuracy. Then, recognition threshold was measured as the concentration level at which participants were able to recognize the taste. When answers were incorrect at the highest concentration, the solution was directly dropped onto the tongue using a pipette. If the answer was correct, participant received a score of 6. To simplify the analysis, incorrect responses were assigned a score of 7, and the scores were treated as components of an ordinal scale of comparisons among the groups. Participants were instructed to rinse their mouths at least once after each measurement, and an interval of at least 1 min was included prior to beginning measurements for a different taste.

To obtain an indicator of overall taste sensitivity for each participant, total gustatory threshold values for detection or recognition, respectively, were calculated by adding the threshold scores for all 4 tastes.

Taste discrimination and taste identification tests were performed using each taste solution with a concentration one grade higher than that for the gustatory recognition threshold.

Taste Discrimination Test (Judgment of the Same or Different Tastes)

Ten pairs of tastes, including 6 pairs of different and 4 pairs of the same tastes, were used for taste discrimination. Tastes in each pair were presented in random order, and participants were asked to state whether the tastes were the same or different. Participants rinsed their mouths with water between stimuli. The maximum number of correct answers was 10.

Identification Test (Taste-Picture Matching Test)

Twelve cards containing pictures of food were prepared. Three pictures were included for each taste: a cake, sweets, and sugar for sweetness; salt, Japanese pickled vegetables, and salty kelp for saltiness; lemon, pickled plum, and mandarin orange for sourness; and medicine, coffee, and bell peppers for bitterness. Participants tasted solutions with the 4 kinds of tastes 3 times each in random order and were then asked to choose the one picture that most appropriately corresponded with each taste. Participants rinsed their mouths with water between each taste exposure. The maximum number of correct answers was 3 for each taste, yielding a total possible score of 12.

Statistical Analysis

Data regarding demographics, cognitive function, gustatory function, and gustatory perception were analyzed using the χ^2 and Kruskal-Wallis tests. A two-way Mann-Whitney U test was used for post hoc analysis. To examine the effects of demographic and clinical factors

Table 1. Demographic data

	SD (n = 18)	AD (n = 18)	Control (n = 22)	p
Age, years	66.7±7.7	69.8±6.8	68.0±8.0	NS[a]
Sex (male:female)	8:10	7:11	9:13	NS[b]
Disease duration, years	3.1±1.4	2.5±1.8	–	NS[a]
CDR (0.5:1)	14:4	11:7	–	NS[b]
Education, years	12.7±2.3	13.2±3.1	13.3±2.8	NS[a]
History of alcohol consumption, n	5	9	6	NS[b]
History of tobacco use, n	2	2	3	NS[b]

Mean ± standard deviation. SD, semantic dementia; AD, Alzheimer disease; CDR, Clinical Dementia Rating. [a] Kruskal-Wallis test. [b] χ^2 test.

on gustatory threshold, ordinal logistic regression analysis was performed with each total threshold value as the dependent variable. Age, sex, disease duration, history of alcohol and tobacco consumption, and the CDR score (with control participants rated at 0) were used as independent variables. When the CDR score was a significant factor, we used two-sided Kruskal-Wallis and Mann-Whitney U post hoc tests to compare total gustatory threshold values among CDR subgroups. Two-way Mann-Whitney U tests were also used to compare SD subgroups according to left-/right-predominant atrophy. Data analysis was performed using SPSS version 23 (IBM Analytics, Chicago, IL, USA).

Standard Protocol Approvals, Registrations, and Patient Consent

This research was approved by the Ethics Committee of the Osaka Prefecture University, and written informed consent was obtained from all patients and their caregivers prior to study participation.

Results

Demographic and Cognitive Data

No significant differences were observed among the SD, AD, and control groups with regard to age, sex, educational history, alcohol consumption, or smoking (Table 1). No significant difference was observed between the SD and AD groups with regard to either disease duration or CDR score. Both the SD and AD groups exhibited significantly lower performance on all cognitive function tests than controls. Significantly lower scores were observed in the SD group than in the AD group on "information" of subtests of the Wechsler Adult Intelligence Scale-III and verbal fluency tasks (Table 2). Patients with left-predominant atrophy exhibited decreased performance relative to those with right-predominant atrophy in the verbal fluency task (nouns with initial phoneme "Ka") (p = 0.044).

Gustatory Threshold

Total Threshold Value

Compared with the control group, the SD and AD groups demonstrated significantly higher total values for both detection and recognition thresholds (Table 3). Patients with CDR scores of 0.5 in the SD group ($CDR0.5_{SD}$) exhibited significantly higher total detection threshold values than controls, while those with CDR scores of 0.5 in the AD group ($CDR0.5_{AD}$) did not

Table 2. Cognitive functions

	SD	AD	Control	Kruskal-Wallis H	Post hoc analyses
MMSE (/30)	21.9±6.2	22.3±2.9	28.1±2.1	28.8**	SD, AD < Control
Digit span					
Forward	4.8±1.1	4.7±1.1	5.9±1.1	12.9**	SD, AD < Control
Backward	3.4±1.1	3.0±0.8	4.0±0.9	12.6**	SD, AD < Control
WAIS-III					
Information	3.8±1.5	7.6±2.0	10.9±3.0	38.8***	SD < AD < Control
Verbal fluency					
Category	6.2±4.3	11.5±4.4	17.3±5.4	30.4***	SD < AD < Control
Initial letter	3.6±2.3	8.8±4.0	11.8±0.4	24.6***	SD < AD, Control

Mean ± standard deviation. *** $p < 0.001$, ** $p < 0.01$. SD, semantic dementia; AD, Alzheimer disease; MMSE, Mini-Mental State Examination; WAIS-III, Wechsler Adult Intelligence Scale-III.

Table 3. Gustatory thresholds

	SD	AD	Control	Kruskal-Wallis H	Post hoc analyses
Detection thresholds					
Total	7.8±2.4	7.2±2.5	5.5±1.6	11.8**	SD, AD > Control
Sweet	2.1±0.8	2.1±1.3	1.4±0.7	8.2*	SD > Control
Salty	1.8±0.7	1.4±0.9	1.1±0.3	12.2**	SD > Control
Sour	1.9±0.8	1.6±0.8	1.4±0.6	NS	NA
Bitter	2.0±1.1	2.1±0.6	1.6±0.8	NS	NA
Recognition thresholds					
Total	14.4±4.5	13.8±3.7	9.9±2.8	16.0***	SD, AD > Control
Sweet	3.0±1.6	2.9±1.2	2.3±0.8	NS	NA
Salty	4.2±2.2	3.3±1.9	2.1±1.0	12.8**	SD, AD > Control
Sour	4.1±1.9	4.3±1.8	2.9±1.0	8.5*	SD, AD > Control
Bitter	3.2±1.0	3.4±1.5	2.5±0.9	(5.881)†	(SD $p = 0.037$)

Mean ± standard deviation. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, † $p = 0.053$ (tendency of difference). SD, semantic dementia; AD, Alzheimer disease.

(Fig. 1a). However, no significant difference relative to controls was observed between the $CDR1_{SD}$ and $CDR1_{AD}$ subgroups.

Total recognition threshold scores were significantly higher in the $CDR0.5_{SD}$ and $CDR0.5_{AD}$ subgroups than in the control group (Fig. 1b). However, only the $CDR1_{AD}$ group exhibited significantly higher total recognition threshold scores than the control group.

Ordinal logistic regression analysis revealed that only the CDR score had a significant effect on both threshold values ($p < 0.05$), while no significant effect was observed for age, sex, alcohol, or tobacco use. Furthermore, CDR score significantly influenced detection and recognition thresholds even when the covariance of all other factors was adjusted.

Thresholds for Respective Tastes

Compared with the control group, detection thresholds for sweet and salty were significantly higher in the SD group, while no significant difference was observed in the AD group

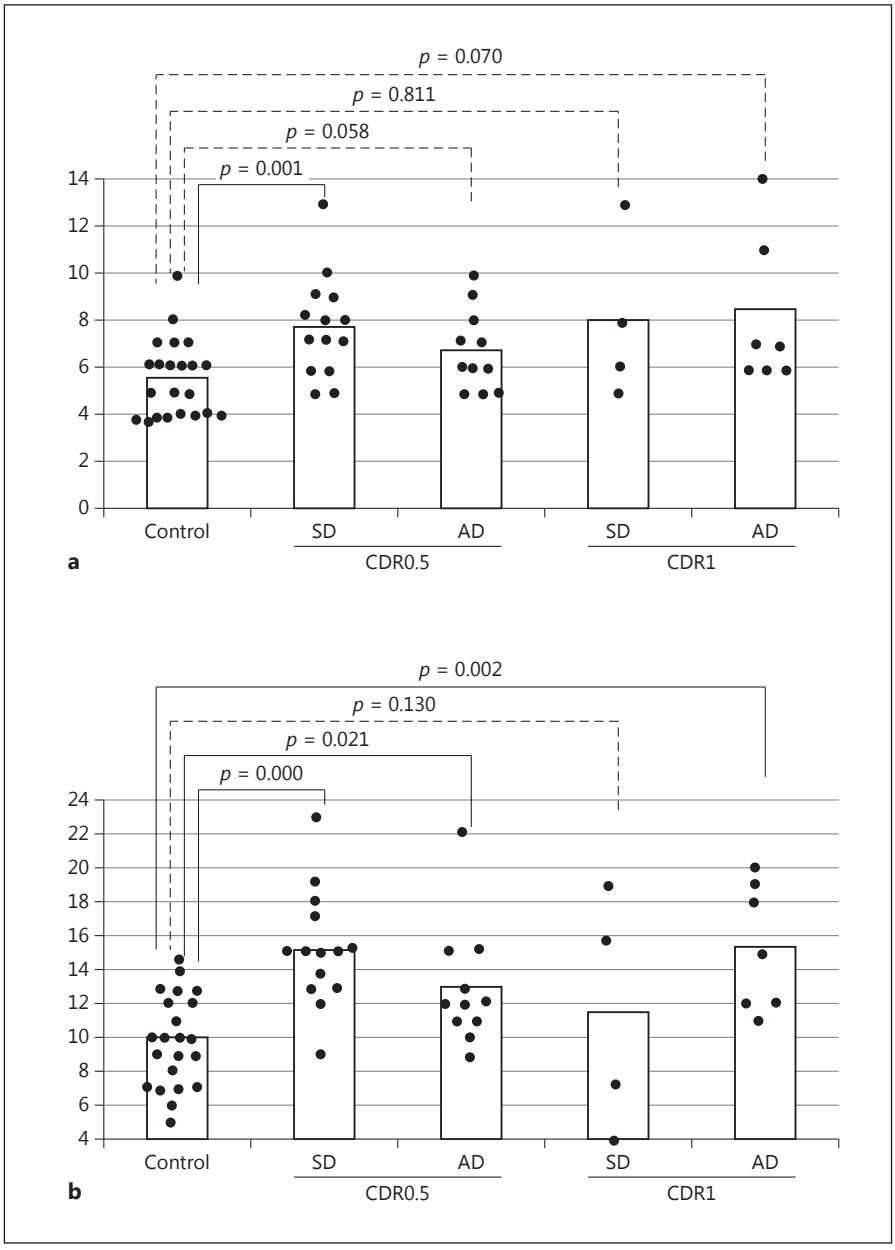

Fig. 1. Total gustatory detection and recognition threshold values according to CDR grade. **a** Total value of gustatory detection thresholds. **b** Total value of gustatory recognition thresholds. SD, semantic dementia; AD, Alzheimer disease.

(Table 3). No significant difference was observed between the SD and AD groups with regard to any taste. No significant difference in either total detection threshold or recognition threshold was observed between patients with left- and right-predominant atrophy in the SD group.

Recognition thresholds (Table 3) were significantly higher for all tastes except sweet in the SD group, and higher for salty and sour in the AD group, than in the control group. No significant differences were observed between the SD and AD groups, nor between the left and right atrophy subgroups, with regard to any taste.

Table 4. Results of the taste discrimination and taste-picture matching tests

	SD	AD	Control	Kruskal-Wallis H	Post hoc analyses
Tate discrimination test (/10)	8.2±1.3	8.4±1.3	8.8±1.2	–	NS[a]
Taste-picture matching test (/12)	5.2±2.1	7.7±1.8	9.9±1.9	30.7***	SD < AD < Control

Mean ± standard deviation. *** $p < 0.001$. SD, semantic dementia; AD, Alzheimer disease. [a] Kruskal-Wallis test.

Taste Discrimination Test

No significant differences in the number of correct responses were observed among the 3 groups (Table 4). Furthermore, no significant differences were observed between the left-predominant and right-predominant atrophy subgroups.

Identification Test

Significant differences in performance on the identification test were observed among the 3 groups (Table 4). The number of correct responses was lowest in the SD group and highest in the control group. No significant difference was observed between the left-predominant and right-predominant atrophy SD subgroups ($p = 0.328$).

Discussion

To our knowledge, this study is the first to investigate gustatory thresholds in patients with SD. We measured two types of threshold in order to clarify the relationship between eating abnormalities (e.g., food preference for sweet) and basic gustatory functions in SD: detection threshold, at which participants reported any taste, and recognition threshold, at which participants were able to identify each specific taste. Furthermore, we examined taste discrimination and identification abilities using tasks that required participants to judge whether pairs of taste stimuli were the same or different and to associate specific taste stimuli with pictured foods, respectively.

Detection threshold results indicated that patients with SD exhibited deficits in basic sensitivity to sweet and salty tastes, whereas sensitivity to sour and bitter tastes was comparatively preserved. Recognition threshold results further revealed that patients with SD exhibited decreased ability to identify salty, sour, and bitter tastes, although the ability to identify sweet tastes was comparatively preserved.

Our results indicated that deficits in gustatory threshold appear in the very early stage of SD. Total detection and recognition threshold values were significantly higher in the $CDR0.5_{SD}$ subgroup than in the control group, whereas only recognition threshold was higher in the $CDR0.5_{AD}$ subgroup. No significant difference relative to controls was observed in either threshold value for the $CDR1_{SD}$ subgroup, most likely because the number of CDR1 participants ($n = 4$) in the present study was rather low. These results align with those of previous studies, which have indicated that deficits in gustatory function become more pronounced in patients with SD as the disease progresses [10, 11]. Our results further highlight that gustatory dysfunction may be one of the early signs of SD.

In humans, the primary gustatory area is located in the frontal operculum and insular cortex [31], where quality and intensity of taste are discriminated. In the present study, although detection threshold results indicated deficits in sensitivity to sweet and salty stimuli

in patients with SD, taste discrimination following detection was preserved, suggesting that the primary gustatory area had not yet sustained fundamental damage in the early stage.

Since no previous study has directly addressed gustatory function in patients with SD, we should refer to the findings in patients with temporal lobectomy. Henkin and Comiter [32] reported that, while taste detection thresholds for 4 kinds of basic tastes remained unchanged after temporal lobectomy, recognition thresholds for sour and bitter tastes were impaired, and that left temporal lobectomy produced deficits in recognition threshold more often than right temporal lobectomy. Small et al. [33] measured the threshold for sour taste in cases of right or left temporal lobectomy, and found that, although the detection threshold was nearly normal, the recognition threshold was increased in patients with right anterior temporal lobectomy. Small et al. [34] further examined the detection and recognition thresholds for sour taste alone, as well as the identification ability for the 4 basic tastes, in a patient with left anterior medial temporal lobectomy. They reported that, although the patient's detection threshold was preserved, the recognition threshold for sour taste was severely impaired, and identification was severely impaired for all tastes. Henkin and Comiter [32] and Small et al. [33] suggested that the anterior temporal lobe (ATL) plays an important role in recognizing taste quality. In a study by Small et al. [33], only 1 patient who had undergone removal of part of the insular cortex, in addition to the ATL, showed deficits in the detection threshold. The authors suggested that the interruption of fibers passing from the primary gustatory area (insula/frontal operculum) to the secondary gustatory area (orbitofrontal cortex) produced such deficits. Since the pathological changes of SD typically involve the ATL, orbitofrontal cortex, and insula [35, 36], deficits in the detection threshold observed in the present study may involve similar disturbances.

These studies have reported conflicting results regarding the functional lateralization of taste recognition. Henkin and Comiter [32] emphasized the role of the left temporal lobe in taste recognition, while Small et al. [33] emphasized the importance of the right temporal lobe. However, our results revealed no significant differences between the right and left atrophy SD subgroups with regard to detection and recognition thresholds for any taste. Although we cannot comment on the discrepancies reported in temporal lobectomy studies, our finding suggests that the degenerative pathology of SD may not be restricted to one hemisphere but may advance bilaterally. Alternatively, our results may indicate that taste recognition is not lateralized to one hemisphere.

Our finding that the degree of change in each threshold varied according to taste type may reflect the differences in the biological significance of each taste. Sweet and salty tastes tend to indicate high nutritional and mineral content, respectively. Sour and bitter tastes, on the other hand, often suggest rotting or the presence of toxins [37], which are typically avoided by primates [38] as well as rodents [39]. In terms of gustatory development, the stage at which tastes that should intrinsically be avoided are appreciated as "sour" and "bitter" may emerge later than the ability to appreciate sweet tastes [40]. The tendency for detection of sour and bitter tastes to be preserved even when recognition is disturbed may therefore represent a collapse of the developmental process in patients with SD, reflective of regression to a previous stage.

A recent study using voxel-based morphometry on patients with frontotemporal lobar degeneration indicated the association between preference for sweet foods and activation in the bilateral orbitofrontal cortex and right anterior insula [4]. The changes in gustatory function observed in the SD and AD groups of the present study may be responsible in part for producing this strong preference for sweet foods in patients with dementia [1–4]. In the present study, the detection threshold for sweet tastes increased in patients with SD, although the recognition threshold was comparatively well preserved for sweet alone. These results suggest that sweetness, if once detected, remains an easy taste for patients with SD to

recognize, even after they have developed difficulty in recognizing other tastes. Human beings may instinctively possess a preference for sweet tastes, and this preference may resurface after the ability to appreciate a variety of other foods, which is acquired later in life, has been lost.

Semantic memory in SD has been investigated from the perspectives of various sensory modalities, including chemosensory function. Studies on olfactory and flavor perception have found that, while discrimination is possible, identification remains impaired [12–15]. In the present study, we also observed that patients with SD were capable of discrimination but not identification. Patients with SD performed significantly worse than both controls and patients with AD on the taste-to-picture-matching task, suggesting that semantic memory for taste may be impaired in ways similar to those observed for other modalities of semantic memory. Researchers have reported that the temporal poles may be associated with deficits in flavor identification [15]. The ATL, in particular, is involved in semantic processing of amodal sensory information [41, 42], suggesting that semantic memory of taste may be impaired as well.

Limitations

One limitation of the present study was that the effect of language dysfunction, which is particularly evident in patients with SD, could not be excluded. Due to the nature of the disease, this may be a difficult problem to fully overcome. However, as our measurement of detection thresholds included any verbal responses regardless of accuracy, and as the discrimination task required only judgments of "same" or "different," precise linguistic abilities were not required. Moreover, we exclude patients with CDR2 and 3 from this study. While patients with SD exhibited higher detection thresholds than controls, they were not significantly different from those of patients with AD. If the threshold had been measured using a more precise method (i.e., measuring ratios of correct responses), some differences may have been detected between the SD and AD groups. However, it is often necessary to limit the number of trials for patients with dementia due to the cognitive demands of certain tasks.

Acknowledgements

The authors would like to thank all study participants as well as Dr. Shunichiro Shinagawa (The Jikei University School of Medicine) and Dr. Tetsuo Kashibayashi (Hyogo Prefectural Rehabilitation Hospital at Nishi-Harima) for their help with collecting and recording data used in this study. This study was supported by grants provided to M.S. by the Research Foundation for Dementia of Osaka 2014. The present study was also undertaken with the support of grants provided by the Ministry of Health, Labour and Welfare (Research on Dementia; H27-29 Longevity-General-004) for M.I.

Disclosure Statement

All of the authors declare no conflicts of interest associated with the manuscript.

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