Galantamine Response Associates with Agitation and the Prefrontal Cortex in Patients with Alzheimer's Disease

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Running title: Galantamine Associates with Agitation

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Abstract

Behavioral and psychological symptoms of dementia (BPSD) occur in up to 80% of AD patients and represent one of the largest factors contributed to caregiver burden. To analyze the effect of galantamine on BPSD and caregiver burden, we treated a total of 50 patients with mild AD for 12 weeks and evaluated them using the Neuropsychiatric Inventory (NPI) and Japanese version of the Zarit Caregiver Burden Interview (ZBI). We also performed regional cerebral blood flow Single Photon Emission Computed Tomography (rCBF SPECT) at baseline using three-dimensional sterotatic surface projections. Total NPI and ZBI scores did not significantly change after 12-week galantamine treatment. To identify the characteristics of patients who show improvement after galantamine treatment, we divided patients into two groups, with and without sub-items of NPI. Patients with aggression showed improvement of ZBI scores ($p < 0.05$). A comparison of rCBF SPECT between these two groups indicated that patients with aggression exhibited increased rCBF in the right prefrontal cortex compared with those without aggression. In a patient with aggression, 20-month treatment of galantamine inhibited increases in the rCBF area in the right prefrontal lobe. These results suggest that galantamine response may be related to aggression and dysfunction of

the prefrontal cortex.

Introduction

Alzheimer's disease (AD) is a progressive dementia characterized by cognitive dysfunction, and behavioral and psychological symptoms of dementia (BPSD). As the disease progresses, diverse behavioral changes including depression, delusion, hallucination, agitation, and other symptoms, manifest themselves with increasing severity of AD [1]. The cholinergic systems has been implicated in AD for over twenty-years [2] and studies of autopsied brain samples demonstrated a relationship between BPSD and cholinacetyltransferase activity [3] or muscarinic M2 receptors in AD [4]. Cholinergic pathways innervate all cortical areas, and cholinergic abnormalities in AD are most marked in the temporal and superior frontal gyri which would be associated with psychosis of AD[5].

Acetylcholineesterase inhibitors (ChEIs) are the most established medication for the treatment of mild to moderate of AD. Three types of ChEIs (donepezil, rivastigmine and galantamine) have been shown to be effective in treating behavioral abnormality in patients with AD. [5, 6] [7] Galantamine has allosteric modulating activity at the nicotinic acetylcholine receptors in addition to acting as an acetylcholinesterase inhibitor [8]. The behavioral effects of galantamine have been assessed using the Neuropsychiatric Inventory (NPI) [7, 9] [10] [11]. Two double blind, placebo-controlled studies showed significant reduction in the total NPI

score form baseline after administrating galantamine [7] [11]. One study showed reduction of emergence of behavioral disturbance among the AD patients who were not symptomatic at baseline[11].

BPSD of patients with dementia has been shown to be one of the largest factors contributed to caregiver burden [12] [13]. The stress of caregivers has negative effects on the quality of care for patients with dementia and early institutional placement. However, to the best of our knowledge, clinical trials of galantamine were not fully focused on caregiver burden. Only two studies evaluated caregiver burden using NPI caregiver burden [10] and the time spent supervising patients [14]. The Zarit Caregiver Burden Interview (ZBI) is based on the caregiver-based interviews to evaluate caregiver burden [15]. Since ZBI is consisted of 22 brief questionnaires and it takes only 10minute, numerous studies have used this scale to assess the caregiver burden in various disease[16-19] as well as Alzheimer's disease [20, 21] .

In the present study, we used Japanese version of the Zarit Caregiver Burden Interview (ZBI) [22] and NPI, and investigated the change of both scales before and after treatment with galantamine. To identify the characteristics of patients who show improvement with galantamine treatment, we divided patients into two group

with and without subitems of NPI. We identified patients with aggression showed more improvement than those without aggression. Patients with aggression exhibited increased cerebral blood flow in the prefrontal cortex compared with those without aggression.

Methods

Patients

This is a prospective trial in patients with clinical diagnosis of probable AD according to the Diagnostic and Statistical Manual of Mental Disorders,4th edition(DSM-Ⅳ), carried out from February 2012 to September 2013 at the department neurology of Juntendo university. Further inclusion criteria were 60 to 90 years of age with mild to moderate AD patients (MMSE score was more than 11) and no cholinesterase inhibitors use prior to trial start. In this 12-week study, patients started galantamine at 4mg twice daily, and doses were titrated up after intervals of 4 weeks, until individual achieved dose up 8mg twice a day, if there was no effect, 12mg twice a day. At baseline and at 12-week interval, patients were evaluated by MMSE, NPI and ZBI. NPI evaluates both frequency and severity of 10 neuropsychiatric symptoms by asking caregivers [23]. ZBI is also based on the caregiver-based

interviews, consists of 22 questionnaires to measure feelings of burden of caregivers [22].

All patients provided informed consent, and the study protocol was approved by the committee for ethics in clinical research of the University of Juntendo, Japan.

SPECT analysis

One month before treatment, each patient underwent Single Photon Emission Computed Tomography (SPECT) scan to evaluate regional cerebral blood flow (rCBF). The patients were imaged with a triple-head, rotating gamma camera (Toshiba GCA9300A, Toshiba, Tokyo, Japan) with a fan-beam collimator, which permits a spatial resolution of 6.4-mm full width at half maximum. Our hospital buildings were reconstructed in 2014 and the gamma camera changed to a dual-head variable-angle gamma camera (Symbia E, Siemens, The Hague, The Netherlands) .The imaging was started 20 minutes after intravenous injection of 222-MBq ^{123}I-IMP.Reconstruction of images was performed by filtered backprojection using Butterworth and Ramp filters with attenuation correction (Chang μ=0.07/cm). Matrix size and slice thickness of SPECT images were retrospectively.

To determine the regions demonstrating a significant alteration in rCBF, group analysis by three-dimensional stereotactic surface projection (3D-SSP) was used [24]. 3D-SSP images that represent the distribution of rCBF calculated in each pixel as a Z-score map were collected using the computer software iSSP4 (Nihon MediPhysics, Japan). Pixel-by-pixel two-sample t-test was made using iSSP35_2tZ (Nihon MediPhysics, Japan) to compare brain perfusion in iSSP4 set between the patients with and without agitation at baseline. To examine the effect of galantamine on rCBF, we searched patient records in our hospital. We found that a 67-year-old female patient has undergone SPECT images at baseline, 20 months, and 40 months after commencement of galantamine treatment. Since the SPECT camera was changed before and after starting galantamine, we were not able to directly compare the images. We performed 3D-SSP analysis using age-matched controls for each camera. For the triple-head, rotating gamma camera (Toshiba GCA9300A, Toshiba), a normal database (N = 57, female:male = 28:29, age 60.9±11.7 years old) was used. For the dual-head variable-angle gamma camera (Symbia E, Siemens), another normal database (N = 29, female:male = 10:19, age (64.2 ± 8.2 years old) was used.

Statistics

Statistical analyses were performed using JMP11 software (SAS Institute Japan). We used the Wilcoxon Signed-Rank Test for comparison between two groups. Pearson's correlation coefficient was calculated to examine the relationship between two groups.

Results

Of the 86 patients recruited, 50 patients completed the study as planned (Fig. 1). The 13 patients withdrew for its adverse events: digestive symptoms (n = 8), irritability (n = 3), pallid face (n = 1) and tremor (n=1) and the 23 patients were discontinued of the treatment. Table 1 showed the sociodemographic features of included patients. Of the 50 patients, the mean age was 76.9 ± 5.8 years and 20 were women (40%). The mean MMSE sore at baseline was 20.0 ± 3.7. The relationship of caregiver to the patient was spouse in 54%, and child in 46%.

No significant differences were found in the scores of MMSE, NPI, and ZBI between baseline and at 12 weeks (Supplementary Fig. 1 and 3). There was no significant correlation between the change of MMSE and NPI, and MMSE and ZBI scores; however, the change of ZBI was weakly correlated with that of NPI total (r = 0.26) (Supplementary Fig. 2). To reveal characteristics of patients who show

improvement of ZBI or NPI total scores after galantamine treatment, we divided the patients into two groups according to whether each subscale of NPI was present (≥ 1) or not (< 1) (Fig. 2). Of note, in the patients with agitation at baseline, galantamine treatment decreased the scores of total ZBI ($p = 0.0234$), although there was no significant difference of total NPI scores (Supplementary Fig. 4). To investigate the relationship between agitation and brain regional function, we compared SPECT images between groups with or without agitation at baseline. The group with agitation exhibited an increase in rCBF in the right lateral prefrontal cortex compared with that without agitation (Fig. 3). The change in rCBF SPECT in the patient with agitation is shown in Figure 3b. This patient is a 67-year-old female. At baseline, she scored 19 points on MMSE, 13 points on ZBI, and 2 points on agitation of NPI. After 12 weeks of galantamine treatment, she improved by 6 points on ZBI and 2 points on agitation of NPI. Of note, the increased area in rCBF in the right lateral frontal lobe (single arrow) disappeared after 24 mg galantamine treatment for 20 months. However, after 36 months, the increased area in the right lateral frontal lobe reappeared (double arrow).

Discussion

We analyzed the change in cognition, behavior symptoms and caregiver burden of patients in patients with mild to moderate AD after receiving 12 weeks galantamine treatment. The result showed was that the level of ZBI score decreased in the patients with agitation at baseline. SPECT study comparing the groups with and without agitation, suggests that the magnitude of rCBF increase in the right prefrontal cortex may affects the patient's response to treatment with galantamine. The fact that 20-month treatment of galantamine inhibited increases in the area of rCBF in the right prefrotal cortex of a patient with aggression supports this view.

Several studies suggest that agitation and aggressive behavior may be associated with the prefrontal cortex in AD. It was showed that the onset of agitation in dementia patients were predicted by frontally mediated behaviors including irritability, delusions and disinhibition [25]. Fluorodeoxyglucose positron emission tomography (PET) study showed a significant relationship between the agitation factor scores of NPI and hypometabolism in the frontal and temporal lobe in AD patients [26]. Hirano et al. demonstrated the relationship between the aggression factor of NPI and hypoperfusion of SPECT at bilateral dorsofrontal, left anterior and right parietal cortex in AD patients [27].

Our study suggested that agitation could be correlated with increased but not decreased perfusion in the prefrontal cortex. A recent study of patients with mild cognitive impairment (MCI) revealed that cortical hyperglucose metabolism area was consistent with [^{11}C] Pittsburgh compound B (PiB) negative area possibly indicating amyloid ß oligomer accumulation and it was postulated that hypermetabolism might be indicative of greater adaptive plasticity as a compensatory mechanism before sufficient amyloid deposition[28]. Taken together, the accumulation of oligomeric Aß species in the prefrontal lobe may play a role to develop agitation in mild AD patients. The mechanism that the administration of galantamine to the transgenic mice model of AD reduced soluble Aβ via microglial Aβ phagocytosis may contribute to galantamine response [29].

In patients with mild and moderate AD, switching from donepezil to galantamine decreased the agitation score assessed by the Cohen-Mansfield Agitation Inventory (CMAI) [30] .Patients with amnestic mild cognitive impairment (MCI) and mild AD were switched from donepezil to galantamine however, only mild AD patients showed the significant benefical effect on the score of NPI, especially the subscale of agitation, delusion and aberrant motor activity [31]. Taken together, galantemine treatment may be more effective to alleviate agitation than donepezil.

Since galantemine is a rather weak acetylcholinesterase inhibitor, but is a potent allosteric potentiating ligand (APL) of nicotinic acetylcholine receptors, it alters other neurotransmitters such as monoamine, dopamine and glutamate [32] [8]. Galantamine treatment to the rodent model affected the level of acetylcholine, dopamine, and glutamate in the prefrontal cortex [32]. Therefore, galantamine may be effective for the AD patients with aggression via the APL mechanism.

The limitations of our study are small and open-label, single-arm design. A blind comparative study is necessary to confirm our findings. Although the results indicated that AD patients with aggression reduced the score of ZBI, we were not able to show that galantamine treatment reduced aggression. Post hoc analysis of pooled large data from three large trials of 3-,5-,and 6-month galantamine treatment in AD patients showed a slightly benefit of galantamine against the placebo and the agitation was also included one of the significantly improved domains [33]. Since this study is exprolatory, we only analyzed rCBF SPECT data at baseline to look at the association with aggression. To understand the precise mechanism of aggression in AD patients, further study will be needed to examine the change of rCBF SPECT after galantamine treatment using more aggression -directed scale such as CMAI.

In conclusion, we showed that 12-week galantamine treatment reduced caregiver burden in mild AD patients with agitation. It was shown that cognitive impairment cases with agitation was associated with the greater number of additional hours of caregiver help [34] and the agitation subscale scores of NPI was associated with degree of caregiver burden and impact on caregivers on the Caregiver Appraisal scale[25]. These findings may indicate that physicians should consider galantamine treatment to mild AD patients with agitation. SPECT measurement of right prefrontal hyperperfusion at baseline may be helpful to predict response to galantamine treatment.

Supplementary Fig. 1. Mini-Mental State Examination (MMSE), the Neuropsychiatric Inventory (NPI) total score and the Zarit Caregiver Burden Interview (ZBI) at the start (0w) and study end (12w). Data correspond to the mean value and 95% confidence limits for 50 patients. There were not siginificant differences.

Supplementary Fig. 2. The correlation disgrams between the changes of Mini-Mental State Examination (MMSE) and the Neuropsychiatric Inventory (NPI), the Zarit Caregiver Burden Interview (ZBI) and NPI, MMSE and ZBI.

There was no significant correlation found between NPI and MMSE (R=0.12), MMSE and ZBI (R=0.09). There was a weak correlation between ZBI and NPI(R=0.26).

Supplementary Fig. 3. The change of the Neuropsychiatric Inventory (NPI) subscales score at the start (0W) and the end (12W). There was no diffarence between before and after galantamine therapy in the each NPI subscales.

The score of anxiety decreased and aberrant motor increased significantly($P<0.05$).

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Conflict of Interest

Dr. Yumiko Motoi received a speaker honorarium from Janssen Pharmaceutical K.K. She has received a speaker honorarium and research grants from Takeda Pharmaceutical company limited. Dr. Nobutaka Hattori received a speaker honorarium and research grants from Takeda Pharmaceutical company limited.

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Sociodemographic Features of Included Patients	
Age (n=50)	
Mean (SD)	76.9 (5.80)
Sex (n=50)	
Female	20 (40%)
Male	30 (60%)
Duration of Dementia (yr)	
Mean (SD)	2.75 (2.62)
MMSE	
Mean (SD)	20.0 (3.7)
Caregivers (n=50)	
Spouse	27 (54%)
Child	23 (46%)

Table 1. Patient baseline characteristics

SD = standard deviation, MMSE = mini mental state examination

Figure Legends:

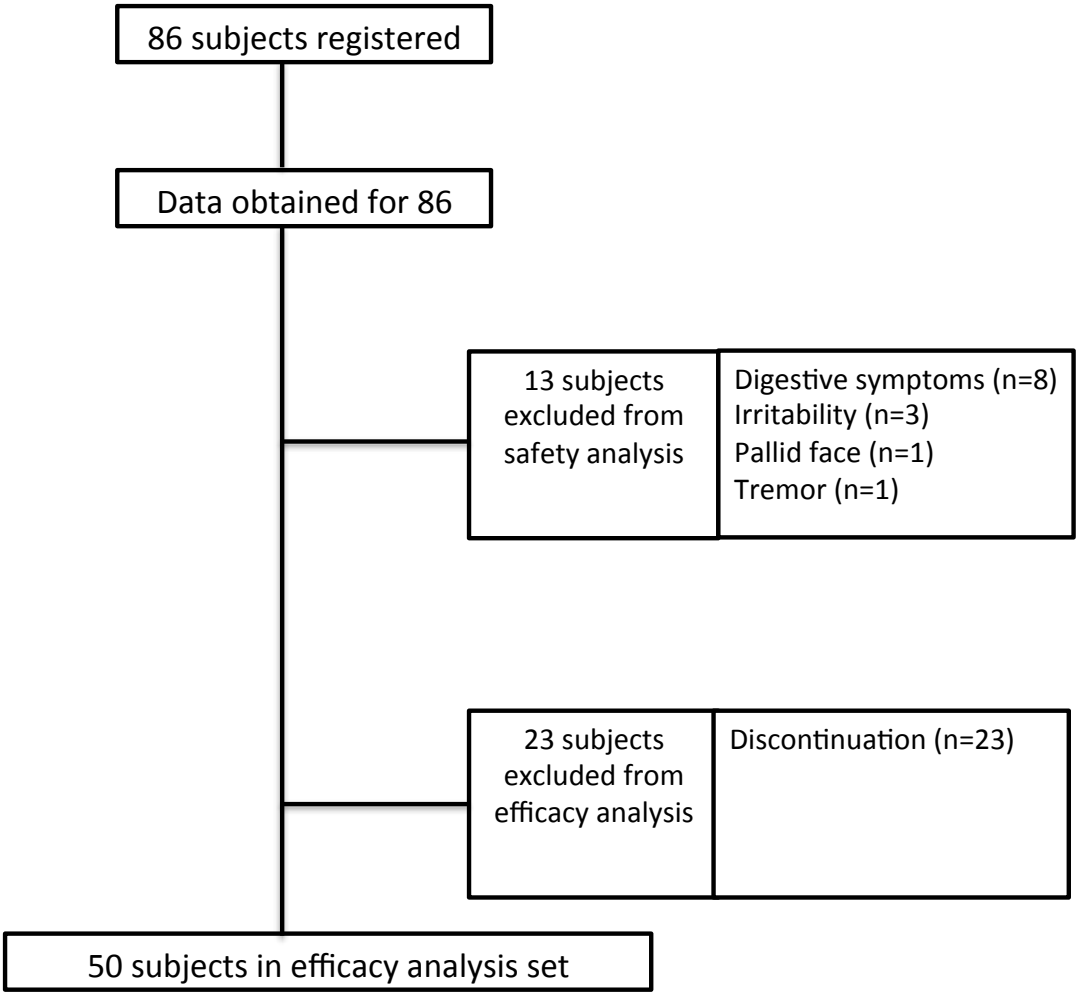
Fig. 1. Distribution of subjects throughout of study. Reasons for withdrawal are also shown.

Fig. 2. The change of the total scores of the Zarit Caregiver Burden Interview (ZBI) after taking galantamine between the groups with or without each symptom of NPI at baseline.

The patients with agitation at baseline decreased the scores of total ZBI significantly(P=0.02). We defined the agitation positive cases as the agitation subscale in NPI was more than 1 point.

Fig. 3. Statistical parametric map on a surface standard anatomical image of rCBF SPECT. a). The map reflects regions with significantly higher blood flow in the group with agitation at baseline than without. The differences were found in the right lateral prefrontal cortex. b) The maps show the changes of rCBF in a 67-year-old female patient. The maps reflect regions with significantly high blood flow compared with normal controls. The increased region in the right lateral prefrontal cortex at baseline decreased 20 months after commencement of galantamine treatment, but had reappeared by 36 months.

Fig. 1.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Irritability (n=3)
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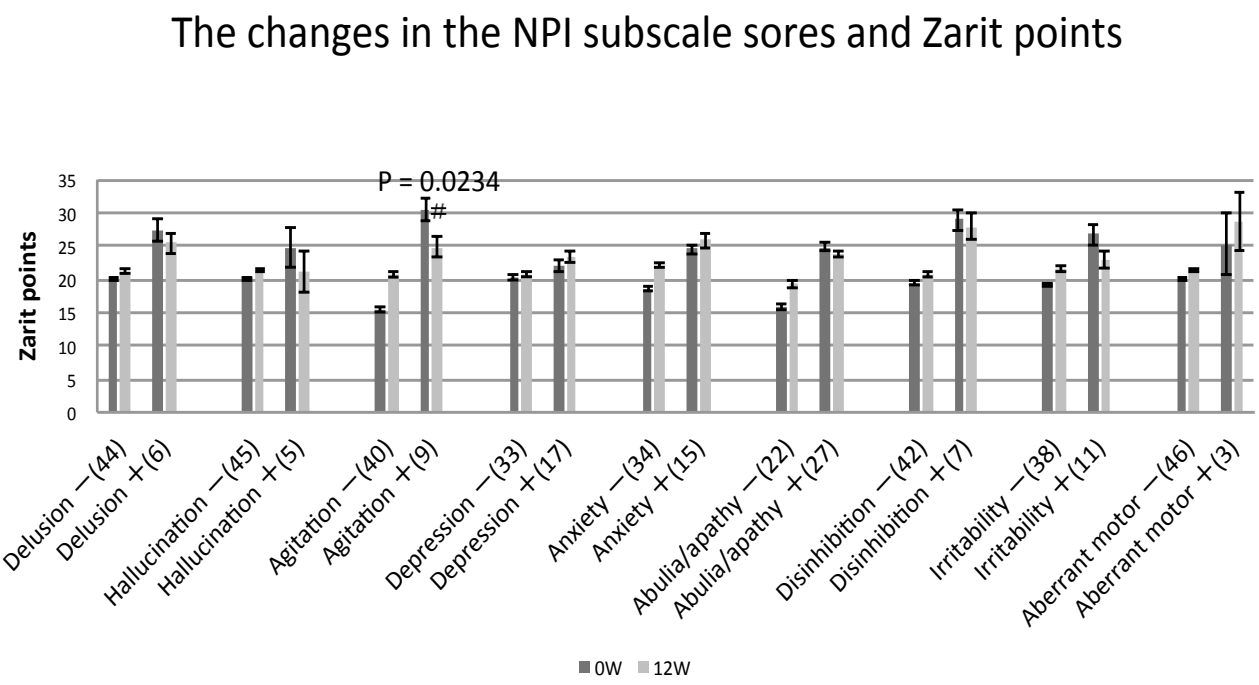
23 subjects excluded from efficacy analysis
Discontinuation (n=23)
50 subjects in efficacy analysis set

Fig. 2.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Agitation +(9)
Depression −(33)
Depression +(17)
Anxiety −(34)
Anxiety +(15)
Abulia/apathy −(22)
Abulia/apathy +(27)
Disinhibition −(42)
Disinhibition +(7)
Irritability −(38)
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Aberrant motor −(46)
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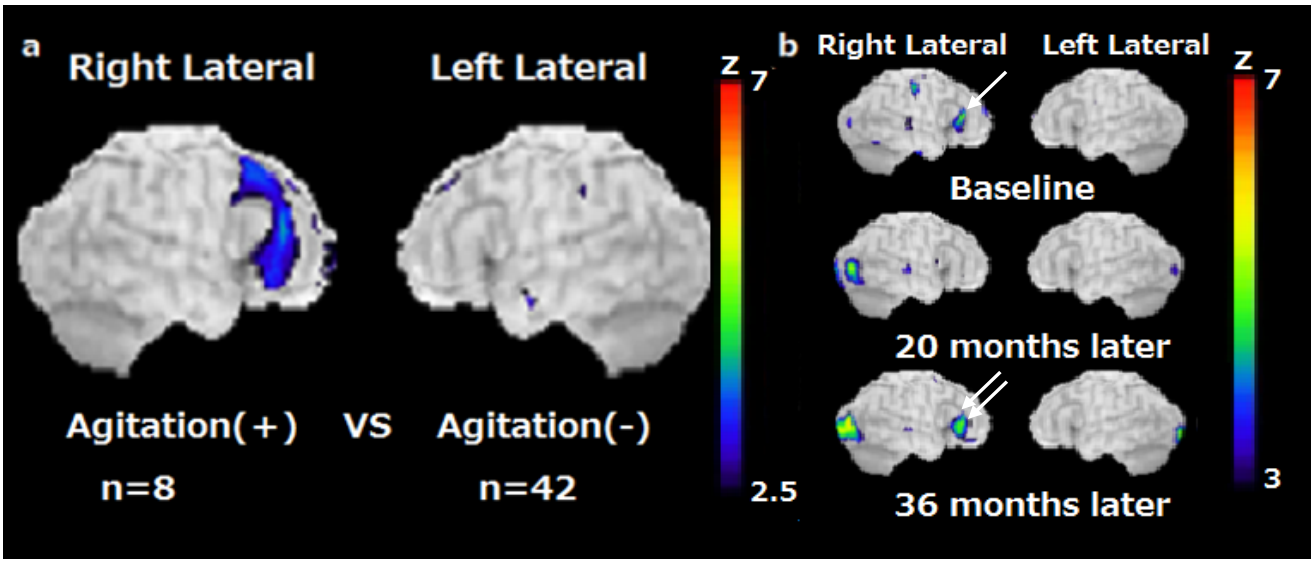
Fig. 3.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Baseline
20 months later
36 months later

Supplementary Figure Legends:

Supplementary Fig. 1. Mini-Mental State Examination (MMSE), the Neuropsychiatric Inventory (NPI) total score and the Zarit Caregiver Burden Interview (ZBI) at the start (0w) and study end (12w). Data correspond to the mean value and 95% confidence limits for 50 patients. There were not significant differences.

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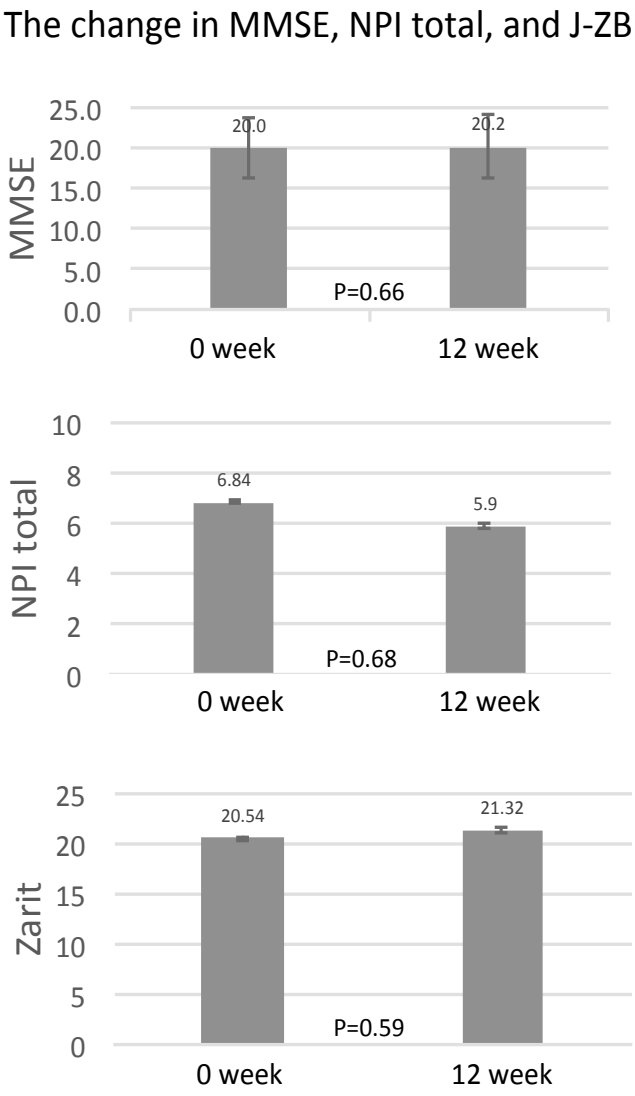
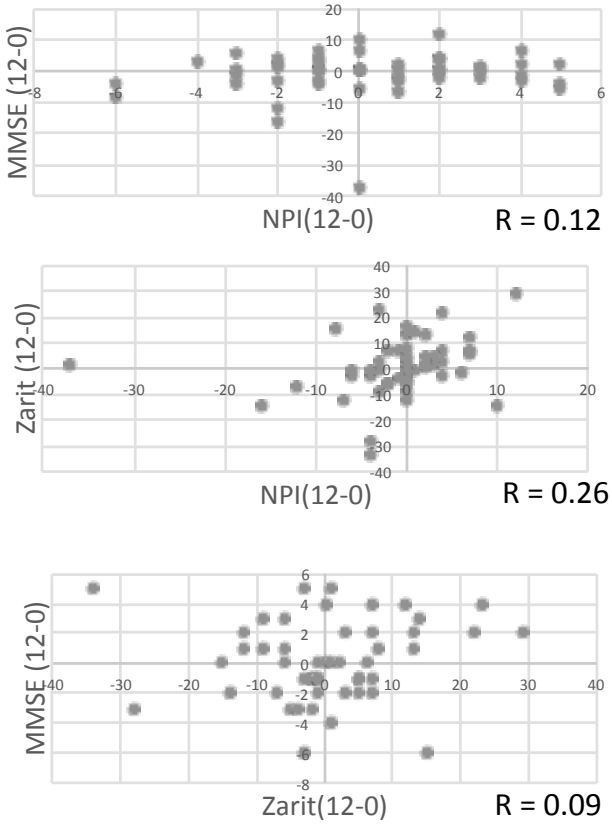
Supplementary Fig. 3. The change of the Neuropsychiatric Inventory (NPI) subscales score at the start (0W) and the end (12W). There was no difference between before and after galantamine therapy in the each NPI subscales.

Supplementary Fig. 1.



Supplementary Fig. 2.

The relationship between the change in MMSE, NPI total, and ZBI score



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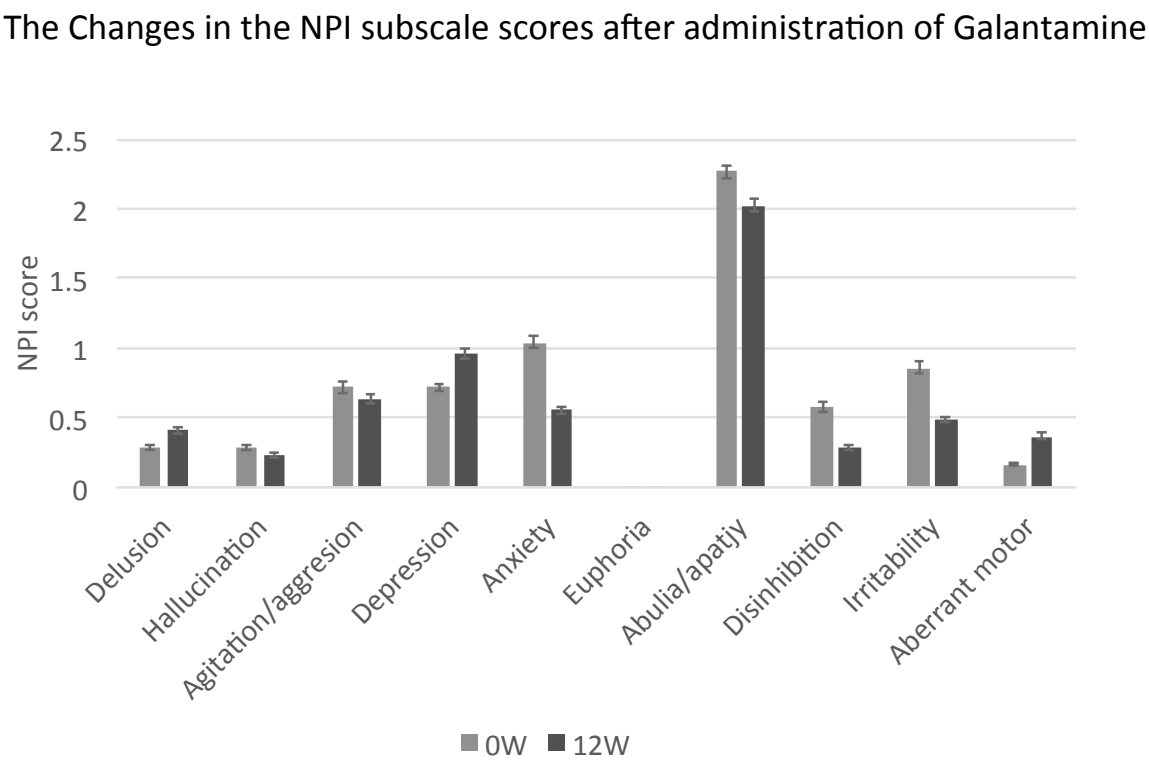

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Supplementary Fig. 4.