Decreased activation along the dorsal visual pathway after 3 month treatment with Galantamine in mild Alzheimer's Disease: an fMRI study

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Abstract

Visual perception has been shown to be altered in Alzheimer's disease (AD) patients and it is associated with decreased cognitive function. Galantamine is an active cholinergic agent, which has been shown to lead to improved cognition in mild to moderate AD patients. This study examined brain activation in a group of mild AD patients after a 3 month open-label treatment with galantamine. The objective was to examine the changes in brain activation due to treatment. There were two tasks to visual perception. The first task was a face matching task to test the activation along the ventral visual pathway and the second task was a location matching task, to test neuronal function along the dorsal pathway. Brain activation was measured using functional magnetic resonance imaging. There were 5 mild AD patients in the study. There were no differences in task performance and in the cognitive scores of the CERAD battery before and after treatment. In the location matching task, we found a statistically significant decrease in activation along the dorsal visual pathway after galantamine treatment. A previous study found that AD patients had higher activation in the location matching task compared to healthy controls. There were no differences in activation for the face matching task after treatment. Our data indicate that treatment with galantamine leads to more efficient visual processing of stimuli or changes the compensatory mechanism in the AD patients. A visual perception task recruiting the dorsal visual system may be useful as a biomarker of treatment effects.

Introduction

Alzheimer's disease (AD) is the most common primary neurodegenerative illness in older adults. In the early clinical stages, the first symptoms can be observed are primarily related to memory decline, but there are also progressive impairments in other cognitive domains such as visual function [1]. Vision problems were part of Alois Alzheimer's original case report [2]. Accurate perception, both visual and auditory, facilitates higher cognitive function (such as navigation and orientation), and perceptual dysfunction contributes significantly to the severity of cognitive dysfunction [3-5].

Various studies that have examined the effect of cholinergic enhancement using physostigmine have found selective increases in activation in the perceptual areas during the encoding phase in working memory [6] and activation in the visual cortex was modulated across a range of attentional and memory tasks [7]. During periods of high attentional demand, acetylcholine is released diffusely throughout the neocortex [8] to modulate processing in the visual cortices, parietal and frontal lobes [9]. Cholinergic input to visual cortex has been shown to sharpen stimulus representations through a combination of signal amplification and noise suppression [10].

Consistently, independent large-scale randomized-controlled clinical trials suggest that enhancement of cholinergic function with cholinesterase inhibitors (ChE-I) such as galantamine may attenuate symptomatic progression and cognitive decline in mild to moderate AD [11] and similar effects have been found with donepezil and rivastigmine

[12]. Previous pharmacological studies using functional magnetic resonance imaging (fMRI), single photon emission computed tomography (SPECT) or positron emission tomography (PET) to investigate functional brain changes in AD patients due to galantamine [13-17], donepezil (see for example [18-21]) and rivastigmine (for example [22, 23] examined resting metabolism or blood flow changes, or changes due to cognitive stimulation using attention and memory paradigms. There is evidence that perception has effects on cognition [3-5] and our previous studies using fMRI found that perception is altered in AD patients [24]and mild cognitive impaired (MCI) subjects [25].

We asked the question whether brain activation changes in visual perception tasks were produced by treatment with galantamine in mild AD patients. We focused on visual function with two tasks: (a) face and (b) location matching tasks. These tasks have been shown to selectively activate the ventral and dorsal visual pathways in HC [25]. The study was an open-label study where each patient received 3 months treatment with galantamine and there were two functional magnetic resonance imaging (fMRI) sessions to measure brain activation. The fMRI sessions were before and after treatment. This was a small scale study to demonstrate the utility of fMRI and this paradigm for investigating the effects of cholinergic treatment in AD patients.

Methods

Subjects

There were 8 AD patients enrolled in the study. The analysis was performed with the data from 5 patients. The fMRI data from one patient had scanner-related artifacts and two patients did not complete the study. The average age of the 5 patients at entry was 74

years (standard deviation = 1.9 years) (neuropsychological profiles and task performance results in Table 1). The AD patients were recruited from an experienced and specialized expert memory clinic at a university hospital. The diagnosis was made according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD [26]. The clinical assessment included detailed medical history, neurological and neuropsychological examinations, and laboratory tests. Subjects were excluded if they had cortical infarction, excessive subcortical vascular disease, space-occupying lesions, depression, and any other psychiatric or neurological disease. The cognitive deficits were measured using the Consortium to establish a Registry for Alzheimer's Disease battery (CERAD) [27].

Subjects were excluded on MRI criteria such as pacemaker implant, recent metallic implants and claustrophobia. All subjects had normal vision or corrected by use of MR-compatible eyeglasses. All subjects gave written informed consent to participate in the study after the study was fully explained to them. The study was performed in accordance with the Declaration of Helsinki and the Ethics Committee of the Faculty of Medicine at Ludwig-Maximilian University approved the study.

The study was 3 months in length, with a scanning session a few days before start of treatment. The treatment was 4 mg twice a day for the 1st month, the second month the patients received twice per day 8 mg doses, and the last month the patients received 12

mg doses twice a day. At the end of the 3 months the patients had a second fMRI imaging session.

Stimuli and tasks

The two tasks were a face and location matching task. The face matching task consisted of two faces presented simultaneously and participants were asked to decide on each trial if a pair of faces was identical or not. If they were, the subject would respond by pressing a button in the right hand. No response was required if the faces were dissimilar. The faces were grey scale stimuli where only the face was visible (Figure 1). Each trial was 2.8 sec long with an interval between pairs of faces of 0.318 sec. There were 8 trials per block and there were 3 blocks of the task in each scan. The faces were obtained from the Max Planck Institute for Biological Cybernetics (Tübingen, Germany) database [28].

The location matching task, as shown in Figure 1(b), consisted of two abstract images located within a smaller square. The smaller square was located within the large square. The subject had to decide if the relative location of the small square relative to the larger one was the same. The subject would press a button if the relative locations were identical.

In the control task, the subject had to press the button every time an abstract image appeared. The images were identical to the images in the location matching task with the images always located in the center. There were 4 blocks of the control task and the parameters for the presentation of the images were identical to the task of interest.

The order of the face and location matching tasks were randomized across subjects in each group. At the beginning of each block there was a 7.2 sec task instruction. Performance was monitored and the percentage correct and reaction times measured.

Scanning

The imaging sequence was an interleaved T2* weighted echoplanar (EPI) sequence with 28 axial slices (4 mm slice thickness and slice gap = 1 mm, repetition time (TR) = 3.60 s, echo time (TE) = 60 ms, flip angle = 90º, field of view = 240 mm. Matrix = 64 x 64) and 69 volumes acquired per run (each volume was measured in 2.8 sec with 0.8 sec gap between volumes) on a 1.5 Tesla Siemens Magneton Vision scanner (Erlangen, Germany). For anatomical reference in each subject, a T-1 weighted sequence with 28 slices was acquired in the same orientation as the EPI sequence (TR = 620 ms, TE = 12 ms, flip angle = 90º, FOV = 240 mm, matrix = 224 x 256, Rect. FOV = 7/8, Effective Thickness = 1.25 mm), and a high resolution T1-weighted 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) structural image was acquired (TR = 11.4 ms, TE = 4.4 ms, flip angle = 8º, FOV = 270 mm, matrix = 224 x 256, Rect. FOV = 7/8, Effective Thickness = 1.25 mm).

Data Analysis

The data was analyzed on an Intel Pentium III computer (San Jose, California, USA) running Linux (Red Hat version 7.0, Red Hat Inc, Raleigh, North Carolina, USA) using

AFNI [29] (http://afni.nimh.nih.gov/afni/) and FSL (FMRIB Software Library – http://www.fmrib.ox.ac.uk/fsl).

The initial step was to delete the first 4 volumes of each scan to remove the initial T1 magnetic transients. The remaining data were corrected for the timing differences between each slice using Fourier interpolation and then corrected for motion effects (6-parameter rigid body).

Each run for each subject was analyzed using a fixed effects general linear model using FSL. Each model was composed of the regressor modeling the task of interest, the instructions, the time derivatives of the two previous regressors, and regressors for motion during the run. The task and instruction models were square wave-forms (on-off). The regressors for the task of interest and instructions were convolved with a standard double gamma hemodynamic response function. The data were smoothed (Gaussian filter at full width at half maximum = 8 x 8 x 8 mm) and high pass filtered with a cutoff at (1/100) Hz. The statistical results were normalized to the Montreal Neurological Institute/International Consortium for Brain Mapping 152 standard (MNI/ICBM). The location of the activation in the brain was done with reference to the Talairach and Tournoux template [30]. To convert the MNI/ICBM coordinates to the Talairach and Tournoux coordinates, we utilized a non-linear transformation developed by M. Brett for transforming coordinate location between both stereotaxic spaces (see online at http://www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html).

The group statistical analyses were based on a mixed effects model with a voxel wise threshold of $p < 0.05$ and was corrected for multiple comparisons at the $p < 0.05$ level using Monte Carlo simulations to set the cluster size to obtain the $p< 0.05$ significance level. The Monte Carlo simulation, using program AlphaSim from AFNI, simulated the image generation, the spatial correlation of voxels within the images, the voxel-level statistical thresholding, brain size, and cluster size identification. Based upon a predetermined p-value at the voxel level and cluster sizes, the algorithm determined the minimum cluster size to the probability of a false positive detection. The minimum cluster size was 800 mm^3 for a corrected $p <0.05$ value The model for obtaining the activation maps of the functional tasks compared to the control task was the one sample t-test, and the model for the contrast pre- and post-treatment was the paired t-test. The contrast for treatment effect was (activation post-treatment) – (activation pre-treatment).

The structural images were first edited of the non-brain tissue using BET [31]. The EPI images were co-registered to the 28-slice T1 weighted image (7-parameter rigid body), the 28-slice T1 weighted image was registered to the MPRAGE image, and the MPRAGE image was registered to the MNI/ICBM template (12 parameter). The statistical results from each subject were transformed into the MNI/ICBM space for group analysis.

Results

Neuropsychological and Behavioral Performance

There were no statistically significant differences in the mean scores between both pre- and post-treatment in the subtests of the CERAD battery (see Table 1, paired t –test, $p < 0.05$ uncorrected for multiple comparisons).

The correct response rate and response time in the face and location matching tasks were not statistically different between pre- and post-treatment (see Table 1, paired t-test, $p < 0.05$ level uncorrected for multiple comparisons).

Baseline Group Activation for Face Matching

The baseline activation peaks in the brain of the AD group during the face matching task were detailed in Table 2 and presented in Figure 2. The activation peaks included a wide network of regions in the occipital, temporal lobes, the dorsolateral prefrontal cortex (DLPFC) and medial frontal areas and cerebellum.

Baseline Group Activation for Location Matching

The activation peaks during the location matching task were detailed in Table 3 and Figure 3. In the location matching task, the activation pattern was dominated by a network of activation peaks along the dorsal visual pathway, with strong activation peaks along the parietal and frontal lobes.

Differences in Activation Between Pre- and Post- Treatment

There were statistically significant brain activation differences in the location matching task between pre- and post-treatment. The differences were decreases in activation after

treatment (Table 4 and Figure 4) and there were no increases in activation after treatment. The peaks of decreased activation were primarily located along the dorsal visual pathway, from the occipital lobes to parietal lobes and to the frontal lobes.

In the face matching task there were no areas that were statistically significant different between pre- and post- treatment.

Discussion

In the present study we investigated visual processing in mild AD patients after receiving open-label treatment with galantamine. We have demonstrated decreased activation during the location matching task after a 3 month treatment with galantamine in the dorsal visual pathway. The face matching task, which activated the ventral visual pathway, did not have statistically significant activation changes post-treatment compared to pre-treatment. Treatment with galantamine led to decreased activation only for the location task, a task in which it was previously demonstrated activation differences in both MCI subjects [25] and in AD patients [24] compared to age-matched HC. There were no significant changes in cognitive performance, as measured using the CERAD battery, and in task performance pre- and post- treatment. Performance differences cannot account for the changes in activation during the location matching task. The present results are very promising but need to be replicated in a larger cohort of subjects as the present results are based on 5 MCI subjects.

The visual system is organized in two visual pathways, the ventral and dorsal visual pathways. In healthy subjects the ventral visual pathway is recruited during tasks of object or color recognition while the dorsal visual pathway is recruited for tasks related to motion or object localization [32, 33]. The ventral pathway includes early visual processing areas in the occipital cortex, then higher processing regions in temporal lobes and with activation in ventral- and dorsal- lateral prefrontal cortices in the frontal lobes. The dorsal visual pathway includes early visual areas, areas in the parietal cortex, particularly inferior parietal lobes and precuneus/posterior cingulate and also ventral- and dorsal- lateral prefrontal cortices. In patient populations, there may be compensatory mechanisms that lead to increased activation along either pathway. The compensatory mechanism may involve recruitment of regions in the complementary visual pathway compared [34], or lead to increased activation in the frontal lobes or along the respective visual pathway [25]. The changes in activation due to treatment are primarily in early visual areas of the cortex, in visual processing areas in the ventral visual pathway, in the dorsal pathway (parietal cortex). In a previous study we found that MCI subjects activated the ventral visual pathway for the location matching task whereas the HC did not [25]. The decreased activation due to treatment occur within the visual system and are in areas that were previously demonstrated to be increased compared to the HC [25].

In previous studies with MCI and AD subjects it has been demonstrated that the changes in activation between both groups were only along the dorsal visual pathway. One possible explanation for the changes along the dorsal pathway is that the magnocellular neurons, which are the primary neuronal type along the dorsal visual pathway, may be

more susceptible to AD neuropathology than the parvocellular neurons, which dominate the ventral visual system. Using PET Mentis and colleagues [35, 36] found that in bilateral middle temporal association areas, an area limited only to input from magnocellular neurons, AD patients showed a significant decrease in activation response to a patterned flash stimulus compared to HC. This effect occurred at the particular patterned flash stimulation frequency at which the greatest apparent motion was produced. The studies of Mentis and colleagues [35, 36] showed that there was increased vulnerability of the magnocellular cells in AD patients demonstrated by utilizing a flashing visual stimulus to activate the visual system.

In the previous studies using the same cognitive paradigms it was found that there was increased activation in MCI subjects [25] along the dorsal pathway compared to the HC groups. The increased activation was interpreted as a compensatory process that may have included two different mechanisms, namely (a) the subjects perform the task utilizing the same strategy but require additional activation or (b) perform the task utilizing a different strategy. Given the previous findings, the decreased activation changes in the present AD group after 3 month treatment with galantamine would indicate that treatment may have led to a reduced compensatory process in the AD patients. It may also be that the treatment has changed the compensatory process in the patients thus altering the activation. In the face matching task, there were no changes between pre- and post-treatment. In the face matching task there were no differences in activation between MCI and HC [25]. It is further evidence that the effects for the location matching task are unlikely to be non-specific effects.

The present group is composed of mild AD patients only, thus the results may be applicable to this severity range. We focused on mild AD patients as there is a focus in the field to provide treatment to AD patients as early as possible. In addition, mild AD patients would have been likely to perform the task well within the scanner. Further studies could be performed in moderately demented patients, but it may require other cognitive paradigms or a modified one from the present one.

In another study examining encoding of faces after treatment with rivastigmine [20], it was found that the patients had greater activation in the middle fusiform gyrus after treatment, a key area of face processing [37]. Similarly, a study with rivastigmine found increased activation in frontal areas and the fusiform gyrus after treatment compared to before treatment in a face encoding task [38]. In an open-label study with donepezil, there was increased activation in the right fusiform gyrus after a 10 week treatment in the AD patients in a face encoding task [20]. The activation pattern was similar as in the HC subjects and it was suggested that the increased activation in the fusiform gyrus indicates increased reliance upon perceptual processes compared to before treatment in the encoding task. The differences may be due to differences in paradigm, with the current study we have a face matching task while the other studies were memory-encoding tasks with faces.

There have been a few studies that have investigated the changes in brain function produced by galantamine with neuroimaging [16, 15]. Goekoop and colleagues [16]

found, using a face recognition task, that after a single dose of galantamine there was increased activation bilaterally in the parahippocampal area and left hippocampus compared to the activation level before the galantamine dose. In addition, they found no decreased activation after single galantamine dose compared to pre-treatment. After a 5 day exposure to galantamine there were decreases in activation in the right parahippocampal area while there was no increased activation in any areas of the brain. Shanks and colleagues [15] found in a study examining the changes in brain activation in a group of mild AD patients during a semantic association task and a target detection task that after a 5 month treatment with galantamine the activation pattern in AD patients after treatment were not statistically different from the healthy controls (HC), whereas at baseline there were statistically significant differences between the AD and HC groups. In these studies it was found that treatment led to decreased activation when measured over a longer period of time (more than a week) whereas after a single dose the changes in brain activation were generally included increased activation compared to before treatment. Our results after 3 month galantamine treatment are consistent with these studies, where one finds decreased activation within the network initially activated in the task.

There have no changes in the mean values of the neuropsychological data pre- and post-treatment. Over a 3 month period we did not expect changes in the neuropsychological profiles as large scale clinical studies have demonstrated statistically significant neuropsychological changes only after at least a 6 month period [12]. In the group of 5 patients, there was an increase in the MMSE in one patient (3 points), a decrease in 2

patients (2 points each) and stable in another patient. A similar pattern of improved/stable/decreased cognitive scores was obtained in the sub-tests of the CERAD. A greater number of patients is required to make more definite statements about cognitive changes using neuropsychological scores or to investigate the neural correlates underpinning these changes. The data from clinical studies can also be examined using individual profiles for the various participants so that not only neuropsychological and imaging related results are examined but also symptoms are investigated [39-41]. This approach can be used because individualized measures may be clinically important as changes in specific symptoms may be important for the patient and caregiver [42]. In this study, we did not find any correlation between symptomatic changes and changes in neuropsychological scores or task performance, which may have been due, in part, to the small sample and the short follow-up time frame.

Studies that have included a placebo group the results compared to placebo were more complex than the general decrease in activation after treatment as described in the already-cited studies. In a study with donepezil and placebo in mild to moderate AD patients (double-blind cross over design) there was an increase in the hippocampus after treatment compared to placebo during a cognitive stimulation while the resting scan indicated decreased glucose metabolism in frontal areas and right hippocampus [21]. A double-blind, placebo controlled study with parallel design with donepezil found a decrease of 10% in resting glucose metabolism in the placebo group while in the patients under treatment there was no evidence of a decrease in resting metabolism over a 24 week time period [43]. Another study that examined the effects of a cholinesterase

inhibitors in a double blind study, where the patients were grouped into responders and non-responders, found a significant decrease in resting glucose metabolism, as measured using PET, in the non-responders [22]. In the study, there was no decrease in glucose metabolism in the responders.

There was no placebo phase in the study. The differences in activation post-treatment compared to pre-treatment may have been due to practice effects. Increasing practice will lead to changes in activation within the neural network activated in the first scan of the task (among the many studies see [44-47]. One result that points against practice effects being a primary cause of the changes in brain activation in the location matching task, are the lack of brain activation changes in the face matching task. A counter argument may be that practice effects may be more evident in areas that are more vulnerable, such as the dorsal visual pathway. In the present study, this issue cannot be resolved but one possible way to address this issue in a future study is to include a placebo-controlled group. An additional issue is that the compensation process in AD is inferred to be demonstrated by increased activation in the AD group along the network activated in a HC group or in distal regions related to the visual system. Thus it is assumed that the network changes related to treatment are related to changes in the compensatory process. In the present work, as well as in other studies referred to this report, there was a focus on a specific network, in the present case the visual system. Other networks may have also been altered, such as attention or memory. These cognitive domains were not investigated in this study with a specific fMRI paradigm.

A limitation of neuroimaging tools such as fMRI, may be that the decreased activation is not due to treatment effects may be due to the increased severity of the disease state in the subjects. In AD patients, one would expect increased activation in early stages but the increased activation at later stages would be blunted due to neuronal death. Thus decreased activation may not necessarily reflect normalization to a normal state but increased neuronal death. It is unknown at what time frame the impact of increased neuronal death would have greater impact than a possible effect of treatment. In the present study we found changes only in the task where a previous study found increased activation compared to HC and no changes in the other task. The pre-and post-treatment scanning sessions were 3 months apart, a time frame that would minimize these effects. Including a placebo arm would also help to address this issue in a future study.

In general, the interpretation of the fMRI signal (the blood oxygenated level dependent – BOLD) with respect to neuronal function should be interpreted with some caution. The BOLD signal is dependent upon a combination of different factors, such as blood flow changes, blood volume and oxygenation changes in the blood that are secondary to neuronal and synaptic function. It may be advantageous in future pharmacological trials to include electrophysiological measurements in parallel to fMRI measurements as pharmacological studies may affect both neuronal function and vascular response of the brain.

A limitation of the current study is the small number of patients in the study. There may not be sufficient power to detect all the changes in activation, and particularly to detect changes in the face matching task. In the location matching task, the effects are quite

robust given the statistically significant changes found. This study is a small scale study to show the feasibility of the design and the initial results should be followed up with a larger scale study.

In conclusion, we may have found a specific effect of galantamine on the dorsal visual pathway during the location matching task. The effects of the treatment were located in areas where there are differences between AD patients and HC. The present study shows that measurement of the effects of cholinergic treatment with fMRI is a practical and a powerful method for investigating the effects of pharmacological agents on brain function and on behavior. Further studies are warranted to elucidate potential neurobiological effects of currently approved anti-dementia drugs beyond symptomatic effects assessed using clinical evaluation and psychometric testing.

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Table 1. Neuropsychological characteristics of the AD group pre- and post-treatment.

	Pre-treatment	Post-treatment
MMSE [30]	25.6 (1.5)	25.4 (2.6)
Word List Memory [30]	14.0 (5.6)	12.2 (6.9)
Word List Recall [10]	2.0 (2.4)	2.0 (2.9)
Word List Recognition [10]	8.0 (3.4)	6.6 (2.3)
Verbal Fluency	13.0 (6.0)	12.4 (5.5)
Modified Boston Naming Test [15]	12.4 (4.8)	12.0 (4.0)
Constructional Praxis [11]	10.8 (0.5)	9.6 (1.3)
Object Matching – % correct	86.7 (6.8)	88.3 (5.44)
Object Matching – RT	1.51 (0.15)	1.60 (0.22)
Location Matching – % correct	89.2 (6.9)	89.9 (4.74)
Location Matching – RT	1.46 (0.18)	1.47 (0.22)

Values in brackets [ ] indicate maximum possible score for each specified test except Verbal Fluency for which a maximum score does not exist.
Values are mean (standard deviation)
RT = response time in seconds

Table 2. Activation peaks during the face matching task pre-treatment. The coordinates are in mm from the anterior commisure point (in the x and y directions) and from the anterior commisure – posterior commisure plane in the z direction.

LEFT HEMISPHERE

Region	Brodmann Area	x	y	z	t-value
Occipital Lobe					
Fusiform Gyrus	18	-24	-96	-19	11.0
Temporal Lobe					
Inferior Temporal Gyrus	20	-67	-32	-19	10.1
Parietal Lobe					
Inferior Parietal Lobulus	40	-30	-54	43	4.36
Frontal Lobe					
Inferior Frontal Gyrus	44	-41	7	22	8.0
Middle Frontal Gyrus	8	-32	33	43	9.3
	6	-30	20	52	6.6
Medial Frontal Gyrus	32	-10	23	38	16.7
Anterior Cingulate Gyrus	32	-14	32	28	8.2
Cerebellum					
		-14	-87	-39	8.5
		-12	-97	-32	9.5

RIGHT HEMISPHERE

Region	Brodmann Area	x	y	z	t-value
Occipital Lobe					
Inferior Occipital Gyrus	18	28	-103	-2	9.0
		42	-87	-2	11.3
	19	44	-82	-11	11.4
Frontal Lobe					
Medial Frontal Gyrus	8	0	33	44	10.0
		8	5	55	8.8

		9		8	49	16	15.5
				10	52	32	12.4
Superior Frontal Gyrus		6		4	15	60	7.8
				6	-5	65	7.5
Anterior Cingulate Gyrus		32		2	36	24	7.9
Inferior Frontal Gyrus	45		46	19	21	22.9	
				54	26	17	14.3
		44		50	17	31	9.0
Precentral Gyrus		6		46	-8	43	30.5
				54	26	17	14.3
Cerebellum							
				40	-55	-23	7.2
				44	-64	-31	7.6

Table 3. Activation peaks during the location matching task pre-treatment. . The coordinates are in mm from the anterior commisure point (in the x and y directions) and from the anterior commisure – posterior commisure plane in the z direction.

LEFT HEMISPHERE

Region	Brodmann Area	x	y	z	t-value
Occipital Lobe					
Fusiform Gyrus	18	-24	-96	-19	11.0
	20	-40	-32	-17	8.2
Middle Occipital Gyrus	19	-42	-97	5	10.8
		-38	-70	-10	10.5
		-36	-75	26	10.5
Cuneus	18	-34	-89	3	10.1
		-24	-87	-4	14.4
	19	-20	-66	33	27.2
Temporal Lobe					
Middle Temporal Gyrus	21	-52	3	-15	18.7
Superior Temporal Gyrus	38	-54	19	-14	14.4
		-44	21	-18	10.4
Hippocampal Gyrus	36	-24	-30	-20	7.2
Parietal Lobe					
Precuneus	19	-22	-78	39	17.5
	7	-16	-71	2	10.2
Inferior Parietal Lobulus	40	-44	-32	26	14.6
		-36	-46	45	9.9
Frontal Lobe					
Inferior Frontal Gyrus	47	-52	29	-5	10.7
	45	-40	26	23	8.7
Middle Frontal Gyrus	46	-50	43	5	9.7
Superior Frontal Gyrus	8	-16	18	53	13.3
Anterior Cingulate	24	-6	12	44	10.8
	32	-2	36	28	17.3

Medial Frontal Gyrus	6	-6	9	53	12.4
	9	-4	52	27	9.3
	8	-4	31	37	17.8
Precentral Gyrus	4	-34	-4	46	40.1
		-24	-24	56	10.6
		-22	-20	62	27.4
Cerebellum					
		-50	-61	-24	16.5
		-36	-37	-35	7.9
		-34	-36	-27	10.5
		-28	-45	-18	24.3
		-10	-45	-6	9.1

RIGHT HEMISPHERE

Region	Brodmann Area	x	y	z	t-value
Occipital Lobe					
Lingual Gyrus	17	18	-97	-10	8.2
Middle Occipital Gyrus	19	22	-84	17	23.7
		38	-71	0	13.7
		42	-65	-9	20.9
Superior Occipital Gyrus	19	30	-72	38	14.5
Temporal Lobe					
Fusiform Gyrus	37	28	-53	-11	12.4
	19	44	-70	-13	17.9
Inferior Temporal Gyrus	20	48	-40	-15	8.4
		68	-40	-15	10.7
	37	60	-54	-9	12.3
Middle Temporal Gyrus	21	38	5	-17	8.3
	37	44	-56	6	14.7
	20	54	-28	-12	7.9
Superior Temporal Gyrus	39	48	-61	27	12.9
	22	56	4	5	14.6
		56	-44	15	8.8

Amygdala		32	-6	-12	41.1
Parietal Lobe					
Inferior Parietal Lobulus	40	40	-42	52	8.9
		44	-50	41	11.6
		56	-34	25	21.5
Precuneus	7	10	-47	39	10.7
		14	-67	51	11.1
Postcentral Gyrus	3	36	-30	59	17.0
Angular Gyrus	39	38	-54	30	25.4
Supramarginal Gyrus	40	42	-45	32	38.2
		52	-45	30	23.1
Frontal Lobe					
Anterior Cingulate	24	0	0	43	17.8
	32	18	21	36	9.9
Inferior Frontal Gyrus	46	46	33	7	9.1
	44	54	15	16	8.4
Middle Frontal Gyrus	9	36	28	28	15.9
		39	15	38	15.0
	46	38	34	19	13.7
		38	26	23	11.3
Superior Frontal Gyrus	9	32	36	31	22.8
Medial Frontal Gyrus	10	2	47	11	7.9
	6	10	10	49	17.5
		12	18	47	9.7
	8	12	35	41	10.3
Precentral Gyrus	4	8	-28	64	12.7
	6	42	-10	35	14.4
Basal Ganglia					
Thalamus		10	-8	0	12.1
		14	-17	12	12.1
Putamen		12	-2	6	42.6
		30	-9	3	8.8

Cerebellum				
	4	-30	-22	9.9
	24	-61	-14	9.3
	16	-81	-25	14.4
	48	-67	-25	8.4
	60	-34	-24	10.2

Table 4. Decreases in Activation Post-treatment compared to Pre-treatment Activation Pattern during the Location matching task. The coordinates are in mm from the anterior commisure point (in the x and y directions) and from the anterior commisure – posterior commisure plane in the z direction.

LEFT HEMISPHERE

Region	Brodmann Area	x	y	z	t-value
Occipital Lobe					
Cuneus	19	-20	-98	27	17.3
	18	-12	-73	26	8.2
Occipital Gyrus	19	-32	-77	22	8.7
Superior Occipital Gyrus	19	-40	-80	34	16.8
		-28	-74	35	11.5
Parietal Lobe					
Precuneus	7	-20	-71	52	8.6
		-16	-77	43	16.7
Temporal Lobe					
Fusiform Gyrus	37	-50	-59	-14	19.7
		-40	-53	-16	21.7
Parahippocampal Gyrus	36	-26	-28	-21	8.5
Middle Temporal Gyrus	39	-38	-71	11	8.4
Frontal Lobe					
Inferior Frontal Gyrus	47	-38	33	-10	8.6
		-38	23	-13	8.4
Precentral Gyrus	4	-18	-26	60	18.2
Medial Frontal Gyrus	9	-4	38	26	21.6
Cerebellum					
		-52	-67	-27	14.9
		-42	-42	-25	9.4
		-4	-43	-35	15.5

RIGHT HEMISPHERE

Region	Brodmann Area	x	y	z	t-value
Occipital Lobe					
Lingual Gyrus	18	6	-76	-5	15.3
Inferior Occipital Gyrus	18	28	-68	-5	16.4
Middle Occipital Gyrus	19	28	-78	18	8.4
		60	-56	-12	12.7
Temporal Lobe					
Fusiform Gyrus	36	42	-44	-20	25.9
	37	52	-51	-18	11.9
Hippocampus		18	-12	-8	9.3
Inferior Temporal Gyrus	19	42	-66	-2	10.1
Middle Temporal Gyrus	39	40	-63	29	22.9
Parietal Lobe					
Precuneus	7	6	-81	46	17.4
		12	-74	37	11.0
Angular Gyrus	39	38	-54	32	10.7
Frontal Lobe					
Inferior Frontal Gyrus	47	32	27	-11	12.8
		34	33	-7	13.1
	44	32	14	12	11.0
		45	12	12	8.9
Basal Ganglia					
Putamen		16	-2	2	13.3
Cerebellum					
		8	-44	-35	9.3
		24	-61	-12	13.2
		36	-40	-28	34.6

Figure 1. Illustration of the cognitive task (a) face matching and (b) location matching. There are two examples of each task, a matching and non-matching pair.

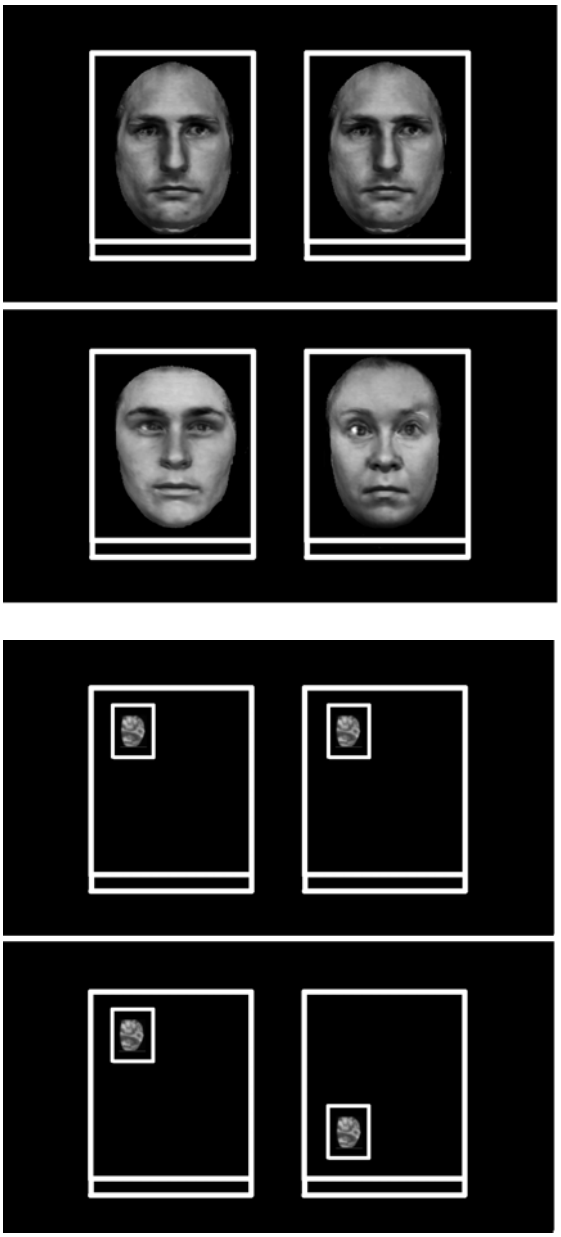

Figure 2. Activation pattern of the AD group at baseline during the face matching task compared to the control task.

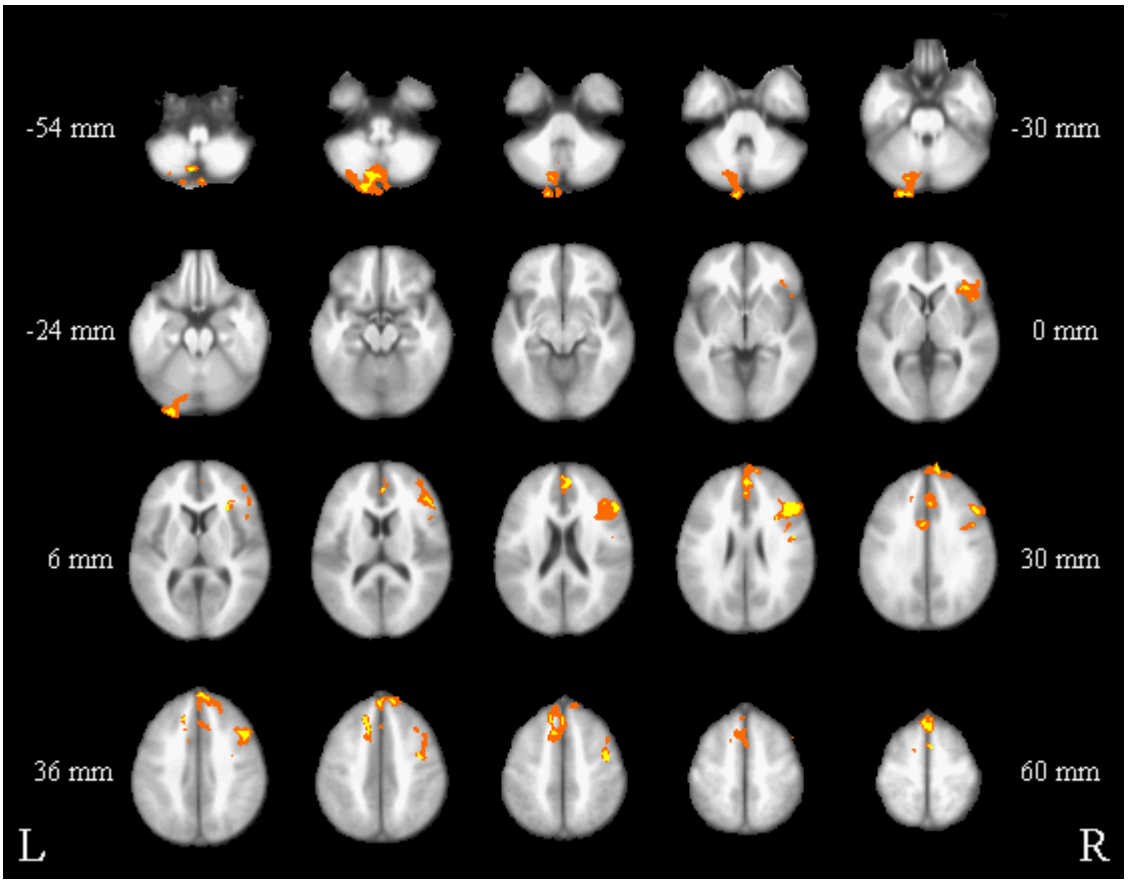

Figure 3. Activation pattern of the AD group at baseline during the location matching task compared to the control task.

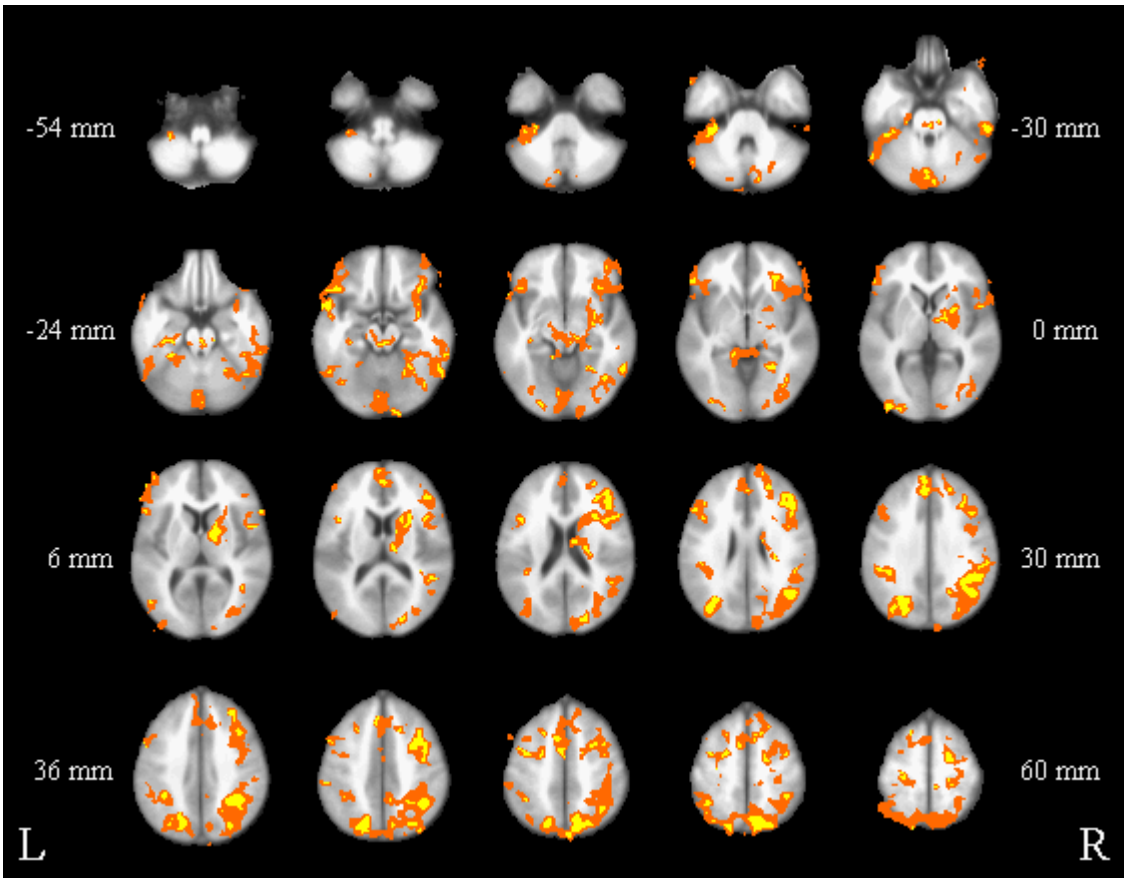

Figure 4. Decreased activation during the location matching task after 3 month open-label treatment with galantamine.