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ORIGINAL RESEARCH

Early prediction of donepezil cognitive response in Alzheimer's disease by brain perfusion single photon emission tomography

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Abstract

Currently, there is no effective means to evaluate donepezil response. We evaluated brain perfusion change at 4 h after donepezil administration (4 h DNPZ) to predict cognitive responses after 6 months of medication. CERAD neuropsychological assessment battery was used to define cognitive response at 6 months. We compared 4 h DNPZ to baseline single photon emission tomography (SPECT) by statistical parametric mapping to identify perfusion changes in responders ($N = 16$) and non-responders ($N = 7$). In responders, there were significant relatively increase in perfusion in left parietal lobe (BA39, 7, 1), right superior frontal gyrus (BA6) and right middle occipital gyrus (BA39). In the non-responders, perfusion was relatively increase in the left parietal lobe (BA39) only. In an explorative analysis, we found a significant correlation between perfusion changes in right BA6 and CERAD score changes at 6 months. Different SPECT perfusion changes at 4 h after donepezil administration were demonstrated in the group of responders and non-responders with potential correlation with CERAD score change. Thus, 4 h DNPZ brain perfusion SPECT can be used to predict donepezil response at 6 months.

Keywords Cholinesterase inhibitor · dementia · SPECT · SPM · voxel-based analysis · CERAD · response

Introduction

Alzheimer's disease (AD) is the most common cause of dementia in the elderly (Barker et al. 2002). It causes substantial burdens to the patient's family and caregivers, as well as the society as a whole. Currently, there are 5 drugs approved by the U.S. Food and Drug Administration (FDA) to treat AD symptoms including donepezil, galantamine, memantine, rivastigmine, and a combination of donepezil and memantine (Alzheimer's association 2016). Donepezil is a cholinesterase inhibitor, which was approved to treat all stages of AD, however only 15–30% of patients benefit from the treatment (Miranda et al. 2015; Raschetti et al. 2005), and many suffer from unwanted, known side-effects (Boada-Rovira et al. 2004). Brain perfusion single photon emission tomography (SPECT) has been used to predict cognitive response after donepezil administration by various means (Yoshida et al. 2007; Tateno et al. 2008; Nobili et al. 2002). Some studies used SPECT at dual time points to follow the changes in perfusion after donepezil treatment. The earliest follow-up

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SPECT time point was 1 month after donepezil administration (Yoshida et al. 2007), which may be too long for a patient struggling with the common side effects. Since the donepezil peak plasma level is approximately 4 h after administration, SPECT at this time point may reveal observable brain perfusion changes due to the treatment. We thus aimed to examine SPECT 4 h after donepezil administration to study early perfusion changes and to relate these changes to cognitive response after 6 months of treatment with donepezil.

Methods

Patients with cognitive impairment aged 50 and above were recruited after being diagnosed with probable AD by the National Institute of Neurological and Communicative Disorders, and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria (McKhann et al. 2011). Only mild to moderate AD patients (scores between 10 and 23 points) were recruited, classified by mini-mental state examination (MMSE) 2002 (Thai version).

We excluded patients with a history of severe head trauma, chronic obstructive pulmonary disease, sick sinus syndrome, peptic ulcer or upper gastrointestinal bleeding, type I diabetes mellitus, as well as those who had been receiving cholinesterase inhibitors, nicergoline, or other medications affecting the central nervous system within 1 month before this study. MRI was used for excluding suspected vascular lesion or other lesion that may explain the cause of cognitive problem. Patients who had alcohol or substance use disorder, or those receiving NSAIDs, anticholinergic, carbamazepine, dexamethasone, phenobarbital or ketoconazole were also excluded. However, patients on a stable dose of antidepressants for at least 1 month before entering the study were included. Patients who received short-acting psychotropic drugs or drugs affecting the CNS were asked to withhold drugs for more than 6 half-lives prior to brain perfusion SPECT.

After entering the study, baseline characteristic data including age, sex, years of education, years of regular work, downtime, duration from the onset of AD, cerebral or vascular disease, diabetes mellitus, dyslipidemia, smoking and neurological as well as psychological clinical history were collected. Hypothyroidism, B12 deficiency and syphilis were excluded by blood examinations for FT3, FT4, TSH, B12 level, and TPHA. Physical and neurological examinations were performed.

Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological assessment battery (J-module) were performed by clinical psychologists, which consists of 8 subtests namely verbal fluency test, modified Boston naming test, MMSE 2002 Thai version, word list memory, constructional praxis, word list recall, word list recognition, and recall of constructional praxis. Scores in each subtest were summed into a total score of 100 points. A higher score reflected better cognitive performance. The CERAD neuropsychological assessment battery was previously translated into the Thai language and validated in the Thai population, which included 63 normal elderly subjects, 60 subjects with mild cognitive impairment (MCI) and 60 patients with mild to moderate AD (Tangwongchai et al. 2018; Tunvirachaisakul et al. 2018). Clinician's interview-based impression of cognitive change plus caregiver's input (CIBIC-plus) for cognitive function, neuropsychiatric inventory questionnaire (NPI-Q) for behavioral and psychological symptoms, Barthel index (Thai version) for basic activity of daily living, and the Chula activities of daily living index for instrumental activities of daily living (IADL) were also performed.

Score changes, between baseline and after 6 months, in the CERAD J-module were used as the primary outcome to assess any changes in cognitive function. Those who scored better than or equal to the baseline were defined as responders, while those who scored worse than the baseline were defined as non-responders.

Brain perfusion SPECT procedure

Brain perfusion SPECT was scheduled within 15 days of neuropsychological examinations. Ten minutes before the examination, the intravenous catheter rinsed with heparin was inserted, and patients were instructed to lay still with eyes closed in a quiet, dimly-lit room. After 10 min, Tc-99 m ethyl cisteinate dimer (ECD), with an activity of 555 MBq, was injected. The baseline brain SPECT was acquired at 30 min after injection, for 30 min using a dual-headed Siemens Symbia T6 (Erlangen, Germany) SPECT machine equipped with high resolution, parallel hole collimators. The zoom factor was set at 1.78. Images were acquired in 32 views, 30 s per view, with 6 degrees/steps. Reconstruction was done using filtered back projection with Chang's attenuation correction and a Butterworth filter (0.35 Nyquist frequency and order 5). Donepezil 5 mg was administered orally immediately after finishing the baseline SPECT. After a 4-h period, a dose of 925 MBq Tc-99 m ECD was administered. Patients waited, in similar controlled conditions as the baseline study, for another 30 min. The second SPECT study was then performed for another 30 min.

Donepezil treatment

A day after the SPECT study, 5 mg/day dose of donepezil was prescribed for 1 month. The dose was then increased, depending on patient's tolerability, to a maximum dose of 10 mg/day towards the end of the study in 6 months. Treatment adherence was inspected by pill count, and patients who missed a dose were encouraged to discuss the problem and continue treatment.

Data analysis

Statistical parametric mapping (SPM12) (Wellcome Trust Centre for Neuroimaging, UCL, UK) running under MATLAB 7.10.0 was used to compare baseline brain SPECT with 4 h SPECT in 16 responders and 7 non-responders. To see obvious change, we also did a subgroup analysis for change of perfusion in the 7 patients those showed highest CERAD score change of the responder group. For each patient, brain perfusion SPECT images were co-registered and a mean image was calculated. This mean image was only used to calculate the spatial normalization to MNI space using the old normalize procedure in SPM12. The same transformation was then applied to the coregistered baseline and 4 h SPECT images followed by a smoothing using an isotropic 3D-Gaussian kernel of 16 mm FWHM to increase signal to noise and to compensate for any residual differences in spatial warping among subjects. All images were corrected for dose by equating global counts. For the comparison of baseline and 4 h brain perfusion SPECT in each group, we used a paired t-test. Regression between perfusion change and CERAD score change for the whole group were analysed. Statistical significance was defined as the combination of uncorrected $p < 0.001$ at the voxel level and family-wise error (FWE) corrected $p < 0.05$ at the cluster level. Significant clusters of positive (4 h-baseline) and negative contrasts (baseline-4 h) between 4 h SPECT and baseline SPECT were determined. The anatomical location from the resulting MNI coordinates were identified by neuromorphometric function in SPM12. Brodmann areas of the anatomical locations were defined using Yale's BioImage Suite application (https://bioimagesuiteweb.github.io/webapp/mni2tal.html).

Differences in neuropsychological test score change from baseline to 6 months follow-up between responders and non-responders were assessed using a two-sample t-test. The threshold for significance was defined at $p < 0.05$.

This study was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the ethics committee of the Faculty of Medicine, Chulalongkorn University (IRB No 425/55). Informed consent was obtained from all individual participants included in the study. It was registered in the Thai Clinical Trial Registry (TCTR20140901001).

Results

A total of 25 AD patients were recruited. Two patients dropped out due to intolerable donepezil side effects. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. Based on the CERAD neuropsychological test battery, 16 patients were categorized as responders and 7 patients as non-responders. Demographic data of both groups are shown in Table 1. There was no significant difference in demographic data between both groups.

In responders (Fig. 1, Table 2), we found relatively increased perfusion at 4 h as compared to baseline in both cerebral hemispheres in the left parietal lobe (angular gyrus-BA39, superior parietal lobule-BA7, post central gyrus-BA1) and right frontal lobe (superior frontal gyrus-BA6). Areas in the right hemisphere were widespread with less changes involving superior frontal gyrus-BA6 and superior parietal lobule-BA1. The areas of relatively decreased perfusion from baseline were located at right subcallosal gyrus-BA 25 and right orbital gyrus-BA11. However, these areas had less changes of perfusion.

In the subgroup analysis of 7 responders with the highest CERAD score change (CERAD score change of 9 to 22), the significant relatively increased perfusion voxels were located mostly on the right cerebral hemisphere (Fig. 2, Table 3) with the maximum peak located at the right middle occipital gyrus.

Table 1 Demographic data of responders and non-responders ($N = 23$)

Characteristics	Responders ($N = 16$)	Non-responders ($N = 7$)	p value
Age (years) (Mean ± SD)	74.94 ± 7.93	77.86 ± 9.70	0.5
Sex (Male/Female, %Male)	5/16 (31.25%)	3/7 (42.86%)	–
Baseline CERAD (Mean ± SD)	37.25 ± 10.56	38.14 ± 6.39	0.8
Baseline MMSE score (Mean ± SD)	16.19 ± 4.18	18.14 ± 4.28	0.4
% right handedness	16/16 (100%)	7/7 (100%)	–
Years of education (Mean ± SD)	5.38 ± 5.14	4.14 ± 5.14	0.6
Active activity (N, %)	5/16 (31.25%)	2/7 (28.57%)	–
Donepezil dose at 6 months (mg, Mean ± SD)	7.50 ± 2.74	8.57 ± 2.53	0.3
Duration from dementia onset (years, Mean ± SD)	2.83 ± 1.95	1.75 ± 0.96	0.2

CERAD, Consortium to Establish a Registry for Alzheimer's Disease; *MMSE*, mini-mental state examination; *mg*, milligrams

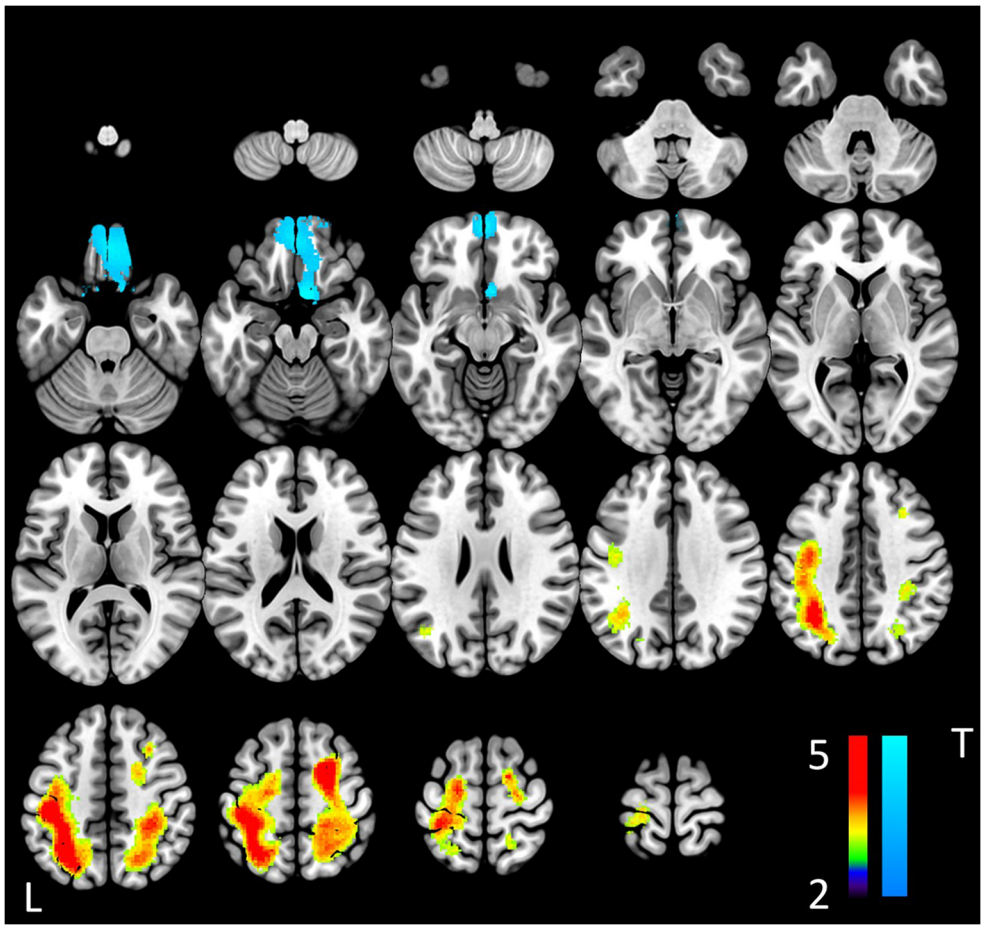

Fig. 1 Areas of significant relatively increased perfusion (yellow/red) at bilateral parietal and right frontal lobes and relatively decreased perfusion (blue) at subcallosal and orbitofrontal gyri at 4 h compared to baseline in all responders overlaid on mni152_2009bet.nii (available in MRIcroGL; http://www.mccauslandcenter.sc.edu/mricrogl/)

The positive perfusion changes extended to the right superior parietal lobule-BA7 and right precentral gyrus-BA4 with lesser changes. Another cluster of positive perfusion change was smaller, located at the left parietal lobe-BA 7 and BA39 with non-significant peaks. There was no significant relatively decreased perfusion with peak voxel exceeding the predefined threshold ($p = 0.05$).

In non-responders (CERAD score change of −2 to −11) (Fig. 3, Table 4), the areas of relatively increased perfusion were located in the left superior parietal lobule/left angular

Table 2 Areas of relatively increased and relatively decreased perfusion at 4 h compared to baseline in all responders ($N = 16$)

Cluster *p* (FWE-corrected)	Number of voxels	Peak *p* (FWE-corrected)	T	x	y	z	Anatomical location
Increases							
6.74E-11	**6180**	**0.006**	**7.32**	**−32**	**−56**	**49**	left superior parietal lobule/left angular gyrus, BA39
		0.007	**7.19**	**−32**	**−48**	**51**	left superior parietal lobule, BA7
		0.04	**6.22**	**−44**	**−28**	**51**	left postcentral gyrus, BA1
1.93E-07	**3472**	**0.02**	**6.56**	**20**	**4**	**57**	right superior frontal gyrus, BA6
		0.07	*5.89*	*20*	*−6*	*59*	right superior frontal gyrus, BA6
		0.2	5.38	32	−36	51	right superior parietal lobule, BA1
Decreases							
5.89E-07	**3136**	0.1	5.61	6	8	−21	right subcalloscallosal gyrus, BA25
		0.2	5.20	12	12	−25	right medial orbital gyrus, BA11
		0.2	5.18	6	12	−13	right subcalloscallosal gyrus, BA25

p, *p* value; *NS*, not significant; *FWE*, family-wise error; *BA*, Brodmann area; *Bold number*, cluster with significant *p* value; *Italic number*, cluster with nearly significant *p* value

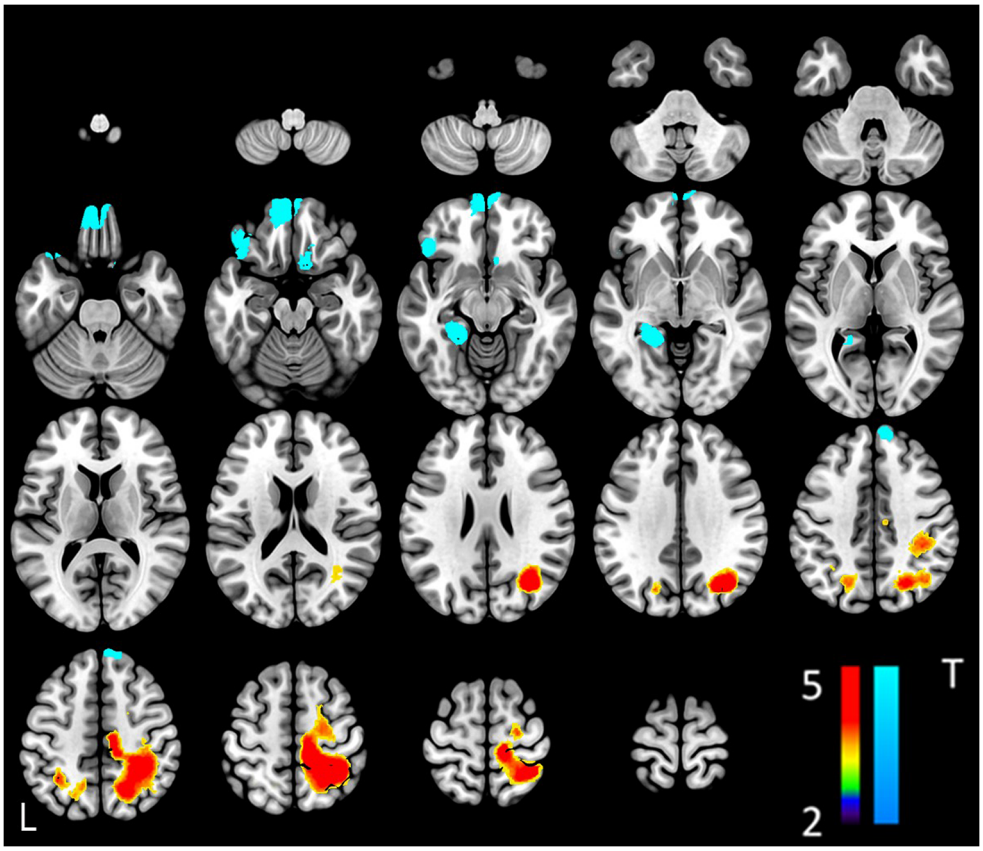

Fig. 2 Areas of significant relatively increased perfusion (yellow/red) at right fronto-parieto-occipital lobes and left parietal lobe and relatively decreased perfusion (blue) at lingual and orbital gyri at 4 h compared to baseline in 7 highest CERAD score change responders overlaid on mni152_2009bet.nii (available in MRIcroGL; http://www.mccauslandcenter.sc.edu/mricrogl/)

Table 3 Areas of relatively increased and relatively decreased perfusion at 4 h compared to baseline in 7 highest CERAD score change responders

Cluster *p* (FWE-corrected)	Number of voxels	Peak *p* (FWE-corrected)	T	x	y	z	anatomical location
Increases							
4.01E-11	**4776**	**0.03**	**9.27**	**32**	**−68**	**29**	right middle occipital gyrus, BA39
		0.07	*8.15*	*12*	*−30*	*57*	*right precentral gyrus, BA4*
		0.1	7.60	30	−44	55	right superior parietal lobule, BA7
0.026805	**460**	0.8	5.18	−34	−52	47	left superior parietal lobule, BA39
		0.9	4.90	−14	−58	53	left superior parietal lobule, BA7
		0.9	4.84	−20	−72	33	left superior parietal lobule, BA7
Decreases							
0.323857	166	*0.05*	*8.44*	*8*	*52*	*47*	*right superior frontal gyrus, BA9*
		0.7	5.39	12	50	39	right superior frontal gyrus, BA9
0.019598	**501**	0.2	6.87	−26	−40	−9	left lingual gyrus, BA36
		0.3	6.64	−22	−44	1	left lingual gyrus, BA19
0.028521	**452**	0.3	6.60	−42	26	−21	left posterior orbital gyrus, BA47
		0.5	5.96	−40	38	−21	left lateral orbital gyrus, BA47
		0.8	5.10	−48	36	−19	left lateral orbital gyrus, BA47
0.000196	**1216**	0.6	5.70	−10	52	−21	left medial orbital gyrus, BA11
		0.7	5.48	−6	60	−21	left gyrus rectus, BA11
		0.7	5.38	−2	64	−15	left frontal pole, BA10

p, *p* value; *NS*, not significant; *FWE*, family-wise error; *BA*, Brodmann area; *Bold number*, cluster with significant *p* value; *Italic number*, cluster with nearly significant *p* value

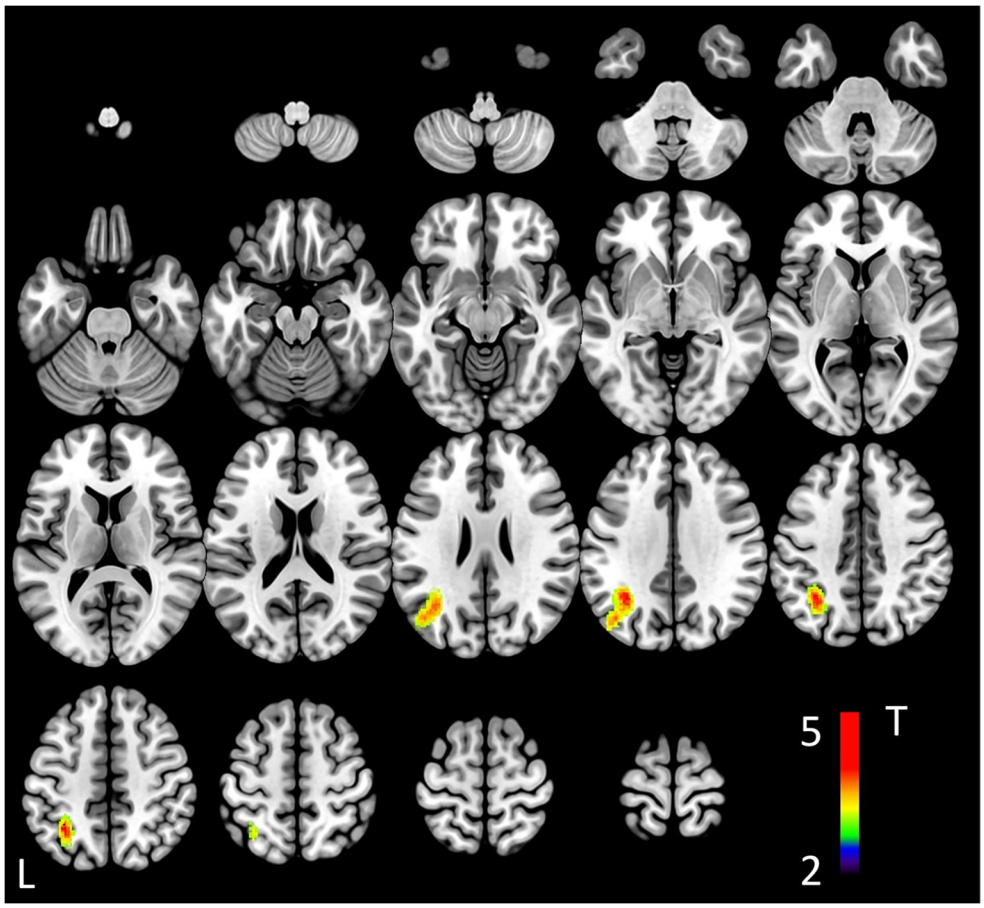

Fig. 3 Areas of significant relatively increased perfusion (yellow/red) at left parietal lobe at 4 h compared to baseline in non-responders overlaid on mni152_2009bet.nii (available in MRIcroGL; http://www.mccauslandcenter.sc.edu/mricrogl/)

gyrus-BA39, which were subsets of perfusion changes in responders. No area of relatively decreased perfusion was found.

There were no significant areas that showed a correlation between early perfusion changes and changes in CERAD scores after 6 months. Therefore, we investigated the data on a more explorative basis using the same statistical threshold at the voxel level but combined with a cluster size of 100 voxels to see if some candidate regions for further studies could be found. We found only one region in the right precentral gyrus, BA6 (cluster size = 248 voxels; x = 54, y = 4, z = 13) showing a correlation between perfusion changes (4 h – baseline) and changes in CERAD score after 6 months of therapy. In Fig. 4, one can see that there is a clear relation ($r = 0.7$, $p = 0.0002$) between an early change in perfusion and change in CERAD score after 6 months. However, since these results were explorative, future studies are required to confirm these results before it can be used to classify patients.

When comparing tests between responders and non-responders at 6 months, only CERAD J-module score change showed a significant difference ($p = 4.221E-07$). Score changes in some subtests of CERAD J-module showed a significant difference between the two groups: J4 word list memory ($p = 0.002$), J5 constructional praxis ($p = 0.007$) and J7 word list

Table 4 Areas of relatively increased and relatively decreased perfusion at 4 h compared to baseline in non-responders ($N = 7$)

Cluster p (FWE-corrected)	Number of voxels	Peak p (FWE-corrected)	T	x	y	z	anatomical location
Increase							
0.001	**1153**	0.15	5.46	−34	−54	41	Left superior parietal lobule/left angular gyrus, BA39
		0.41	4.78	−44	−68	27	Left angular gyrus, BA39
Decrease							
NS							

p, *p* value; *NS*, not significant; *FWE*, family-wise error; *Bold number*, cluster with significant *p* value

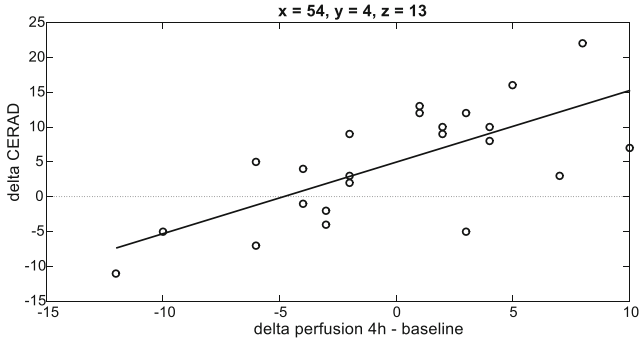

Fig. 4 The relation between early perfusion changes (4 h – baseline) and the change in CERAD score after 6 months in the right precentral gyrus in the local maxima found in the explorative analysis ($r = 0.7$, $p = 0.0002$)

recognition ($p = 0.039$). Other tests including CIBIC plus, NPI-Q, Barthel index and Chula-ADL did not show a significant difference between the two groups.

Discussion

To date, response to donepezil in AD cannot be predicted with confident by clinical or pharmacogenetic aspects including apolipoprotein E (APOE) genotype and cytochrome P450 2D6 (CYP2D6) polymorphisms (Miranda et al. 2015; Waring et al. 2015). Previous studies have used brain perfusion SPECT either only at baseline or with the second-time point months after donepezil administration, to predict the patient's response to the drug.

Mega et al. (2000) and Hongo et al. (2008) used pretreatment perfusion to predict behavioral and cognitive responses at 8 and 24 weeks, respectively. For behavioral response, there were more hypoperfusion in the lateral orbitofrontal and the dorsolateral frontal bilaterally. Cognitive responders also showed hypoperfusion at the right orbitofrontal area. In our study, we found that frontal lobe especially at orbitofrontal areas showed relative reduction of perfusion at 4 h as compared to baseline in both the full 16 responders analysis (Table 2) and the 7 highest CERAD score change responders analysis (Table 3). However, the changes were diffuse and were not significant at peak level. Thus, other than showing hypoperfusion at baseline in other studies, these areas also showed diffuse reduction 4 h after giving donepezil, which might be a predictor for cognitive response at 6 months because these areas did not show reduction in non-responder group.

Other studies used SPECT perfusion change at 2 points of time, at baseline and 1 month (Yoshida et al. 2007) to 12 months (Tateno et al. 2008; Nobili et al. 2002) to evaluate response. Tateno et al. (2008) showed that there were areas of perfusion change in the callosomarginal, pericallosal and lenticular nucleus. Patients in their study were mostly non-responders, which was defined by the decrease in MMSE scores. Nobili et al. (Nobili et al. 2002) compared patients who were treated and not treated with donepezil. They found that the untreated group showed relatively decreased perfusion in the left temporal and temporo-occipital lobes, while there was no significant perfusion change in the treatment group. However, both groups showed comparable reduction in MMSE scores. Thus, perfusion reduction in the left temporal and temporo-occipital lobes may not reflect cognitive response. Yoshida et al. (2007) evaluated response using ADAS-cog at 12 months, and found that brain perfusion SPECT at 1 month showed an increase in perfusion in the anterior frontal and parietal lobes in responders, while there was a reduction in blood flow in all regions of the cortical and subcortical regions in non-responders. The areas of perfusion change in their study are similar to this study, but in their study, no laterality was defined because they used the mean value of both sides for each region.

This study showed that there were some changes in perfusion after 4 h of donepezil administration, which is the time point when plasma level of donepezil peaks (Seltzer 2005). Hypoperfusion has been known to occur in AD patients in the bilateral superior parietal cortex (BA 7), which is more extensive on the left side; inferior parietal (BA 40); and temporo-occipital regions (BA 37, 39, 19) (Varrone et al. 2002; Tranfaglia et al. 2009). These features have been used to distinguish AD from other dementia subtypes. In our study, the areas of relatively increased perfusion at 4 h in responders were mainly located at bilateral parietal lobes (BA 39 and BA 7) and right frontal lobe (BA 6). BA 39 is connected to BA 7 via the occipito-frontal fasciculus (Makris et al. 2007). So, the change in perfusion at BA 39 may be a secondary effect from BA 7 via the interconnections of nerve fibers. BA 7 and BA 39 are among the areas known to be the very first hypometabolic areas in pre-dementia state (Kljajevic et al. 2014). When we focused on the 7 highest CERAD score change responder group, positive perfusion changes were more pronounced on the right posterior part of the brain (right middle occipital gyrus, BA 39). This area was much larger and had higher significant peak voxel than the left side. While in the non-responders, a positive perfusion change was seen only in a small area at the left parietal lobe (BA 39). The relative increase in perfusion after donepezil administration at BA 39 in both groups and BA 7 in responders suggests that perfusion and/or function of these areas are not permanently damaged and can be restored after donepezil treatment, as early as 4 h. Having perfusion restoration on the left parietal lobe is not enough to maintain brain cognitive function. Restoration of brain perfusion and function on the right parieto-occipital lobe (BA39) is essential to do so. This may imply that to be a good responder, positive perfusion needs to be evidenced on the right posterior part of the brain, while positive perfusion only on the left posterior part of the brain does not indicate a good response. The more extensive areas of perfusion improvement

in responders means that there is more functional reserve of the brain in responders.

Another area that showed relatively increased perfusion in responders was the posterior part of the right superior frontal gyrus at BA 6. Right superior frontal gyrus was known to be the area involved in auditory attention to words (Wegrzyn et al. 2017) and effortful retrieval of memory (Wiggs et al. 1999). It has anatomical connection with precentral gyrus (Li et al. 2013). A part of right precentral gyrus, which is also located at BA 6, was the area of positive correlation between the perfusion change and CERAD score change in the explorative part of our study. Significantly better scores in CERAD subtests (word list memory, constructional praxis and word list recognition) of responders when compared to non-responders may relate to the capability for perfusion improvement at this area. Furthermore, preserved perfusion at this area could be related to a "resilience" system as it may compensate impairment of functionally connected temporo-parietal areas. The mechanism could explain the potential correlation between right frontal area and cognitive performance at 6-months follow-up.

In this study, we used CERAD J-module instead of merely MMSE (Tateno et al. 2008; Nobili et al. 2002), which was different from other studies, because CERAD provides more details and presents a wider range of cognitive profile that may be more sensitive to subtle changes in cognition.

The areas that showed relatively decreased perfusion after donepezil administration in responders involved the bilateral orbitofrontal, left rectal, right superior frontal and right subcallosal gyri. These areas were known as part of the anterior hub of the default mode network (DMN) (Mak et al. 2017), which has been known to be disturbed in AD. Significant hypoconnectivity within the DMN, which consists of precuneus, posterior cingulate cortex and medial prefrontal cortex, have been shown by functional MRI studies (Badhwar et al. 2017). The areas in DMN also showed hypometabolism on F-18 FDG PET study, which correlates with an increased cerebrospinal fluid (CSF) lactate level reflecting altered metabolism in these areas (Liguori et al. 2016). The decrement of perfusion in our study may explain that the increment of lactate level is probably due to the poor reserve of blood or oxygen supply to the DMN. Futhermore, the relative decrease of perfusion at these areas after donepezil administration might cause future deleterious effect on the brain. Further correlation study of drug effect on these areas is needed to confirm this finding.

There was no robust explanation for non-response to donepezil in patients with acetylcholine deficit. However, studies suggested that pharmacokinetic linked to genetic variations might play some parts. Patients with normal functioning of cytochrome P450 subtype 2D6 had a better response to donepezil than those with increased function (hence lower active drug in the body) (Xiao et al. 2016), however with a small effect size. Further, the response to treatment might be mediated by individual variation in the subtype of acetylcholine esterase (e.g. acetylcholine esterase and butyrylcholinesterase) (Bartorelli et al. 2005) or the change in acetylcholine esterase level in cerebrospinal fluid (Davidsson et al. 2001). These might suggest the possibility of predicting response to treatment in patient with Alzheimer's disease using wider range of demographic, clinical, genetic and imaging data (Gallucci et al. 2016).

This study is considered as preliminary data which have to be confirmed in a larger cohort and by means of more advanced techniques such as FDG-PET or functional MRI.

In conclusion, different SPECT perfusion patterns at 4 h after donepezil administration were demonstrated in responders and non-responders. This can be used as an early marker for predicting response to donepezil at 6 months before starting treatment. This may lead to personalizing treatment, resulting in cost-saving measures in Alzheimer's care in the future.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments.

Conflict of interest The authors declare that they have no conflict of interest.

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