



# Functional connectivity change between posterior cingulate cortex and ventral attention network relates to the impairment of orientation for time in Alzheimer's disease patients

Ken-ichiro Yamashita<sup>1</sup> · Taira Uehara<sup>1</sup> · Pukovisa Prawiroharjo<sup>1</sup> · Koji Yamashita<sup>2</sup> · Osamu Togao<sup>2</sup> · Akio Hiwatashi<sup>2</sup> · Yoshihide Taniwaki<sup>3</sup> · Hidetsuna Utsunomiya<sup>4</sup> · Takuya Matsushita<sup>1</sup> · Ryo Yamasaki<sup>1</sup> · Jun-ichi Kira<sup>1</sup>

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## Abstract

Alzheimer's disease (AD) patients exhibit various cognitive dysfunctions, including impairment of orientation for time (OT). The brain regions underlying OT impairment remain to be elucidated. A previous single-photon emission computed tomography study has indicated hypoperfusion of the posterior cingulate cortex (PCC) in relation to deterioration of OT. In this study, we investigated whole brain functional connectivity changes of PCC using resting-state functional magnetic resonance imaging. Voxel-based functional connectivity with PCC was analyzed in OT-poor or OT-good AD patients, classified according to the mean OT scores of the Mini-Mental State Examination subscale. The connectivities of dorsal frontal lobe, and lateral parietal and lateral temporal lobes with PCC in the right hemisphere were reduced in the OT-poor AD group compared with the OT-good AD group. A subtraction connectivity map of OT score differences (OT-good minus OT-poor) revealed the right middle temporal gyrus near the temporo-parietal junction as a significantly connected region with PCC. These results suggest that the right posterior part of the middle temporal gyrus may play an important role in OT in conjunction with PCC, and that disconnection between PCC and the right ventral attention network may cause OT disturbance in AD patients.

**Keywords** Alzheimer's disease · Orientation for time · Resting-state fMRI · Posterior cingulate cortex · Middle temporal gyrus · Attention network

## Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease (Alzheimer's association 2016). Recent memory loss is the most prominent feature of AD (Spinnler and Della Sala 1988), though numerous cognitive dysfunctions have been

reported during the disease course (Hebert et al. 1995), including impairments of orientation for time (OT) and orientation for place (OP) (Ashford et al. 1989). OT impairment has been documented in the early stage of AD (Galasko et al. 1990), and deterioration of OT parallels AD progression (Ryan et al. 2009). Previous studies of human pathology and animal models have revealed that the medial temporal lobe, including the hippocampus, is associated with OP (Breese et al. 1989; Giannakopoulos et al. 2000). However, the brain regions associated with OT impairment remain to be elucidated.

Functional neuroimaging techniques have revealed that AD patients exhibit hypoperfusion in the temporal lobe, and the medial [posterior cingulate cortex (PCC) and precuneus] and lateral regions [superior parietal lobule (SPL) and inferior parietal lobule (IPL)] of the parietal lobe (Burns et al. 1989; Neary et al. 1987; Nitrini et al. 2000), which are compatible with the  $\beta$ -amyloid deposition sites (Terry et al. 1991). In addition, a positron emission tomography study in AD patients has shown an association of hypometabolism in the bilateral PCC with disturbance of OP and OT (Hirono et al.

✉ Ken-ichiro Yamashita  
keniciro@neuro.med.kyushu-u.ac.jp

<sup>1</sup> Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

<sup>2</sup> Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan

<sup>3</sup> Department of Neurology, Fukuoka Sanno Hospital, 3-6-45 Momochihama, Sawara-ku, Fukuoka 814-0001, Japan

<sup>4</sup> Department of Radiology, Fukuoka Sanno Hospital, 3-6-45 Momochihama, Sawara-ku, Fukuoka 814-0001, Japan

1998). Single positron emission tomography (SPECT) studies using 3D-SSP analysis have revealed hypoperfusion in the bilateral SPL, IPL, PCC, and precuneus (Honda et al. 2003). Among these areas, ROI analysis has found significantly higher numbers of hypoperfused pixels in the left PCC of patients with poor OT compared with those with good OT (Yamashita et al. 2014).

Although it remains to be established whether OT impairment relates to the single PCC lesion, functional magnetic resonance imaging (fMRI) studies executed during resting-state have detected several functionally connected large-scale distributed networks named resting-state networks (RSNs) (Yeo et al. 2011; Lee et al. 2012). Recently, some resting-state fMRI studies have reported alterations of RSNs associated with performance of cognitive tasks (Ranasinghe et al. 2014; Giessing et al. 2013). For example, functional connectivity from the bilateral dorsolateral prefrontal cortex, which belongs to the central executive network, to the anterior corpus callosum significantly correlates with the performance of a working memory task (Hampson et al. 2010).

In this study, we aimed to clarify the functional connectivity changes associated with OT impairment using resting-state fMRI and seed-based analysis. The correlations between OT scores and connectivity changes in the OT-specific regions were also examined.

## Materials and methods

### Subjects

Twenty-five AD patients (9 males and 16 females; mean age  $\pm$  SD,  $76.4 \pm 10.5$  years), who were studied from 2012 to 2015 at Kyushu University Hospital and Fukuoka Sanno Hospital, were enrolled in the study. Ten age-matched normal controls (2 males and 8 females;  $71.5 \pm 10.5$  years) were also examined. Diagnosis of AD was made by two neurologists based on the National Institute on Aging and Alzheimer's Association criteria (McKhann et al. 2011). Brain MRI of all subjects showed no abnormalities except brain atrophy. Subjects were all right-handed and had no past neurological disorders. None of the subjects were taking psychiatric medications, including acetylcholine esterase inhibitors or memantine. Mini-Mental State Examination (MMSE) (Folstein et al. 1975) was performed on all subjects, and its subscore of the OT scale (0–5) was used for analyses. AD patients were classified into two groups according to the OT scores, as previously reported in our SPECT study (Yamashita et al. 2014). Briefly, the OT-good group consisted of subjects with an OT score of integral number higher than the mean score of the total AD patients ( $3.3 \pm 1.4$ ), and the OT-poor group consisted of subjects with a score of integral number lower than the mean. The MMSE and OT scores were

evaluated with a Kruskal–Wallis test with post-hoc Scheffé test to compare the significance of differences between each AD patient group and the normal control group.

### Image acquisition

Three Tesla MRI (Achieva TX, Philips Medical Systems) scanning was conducted in this study. Scout images were first collected to align the field of view to be centered on the subject's brain. Three dimensional T1-weighted turbo field echo were obtained for anatomical reference [repetition time (TR) = 8.1 ms; echo time (TE) = 3.8 ms; FOV = 240 mm; matrix size =  $240 \times 240$ ; slice thickness = 1.0 mm]. For functional imaging, a gradient echo echo-planar sequence was used (TR = 2800 ms; TE = 30 ms; flip angle = 90 degrees;  $40 \times 3$  mm slices; in-plane resolution of  $3 \times 3$  mm). One functional run was collected, and the total scanning time was 7 min.

### Image analysis

Preprocessing of imaging data was performed using SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm/>). Functional images were slice timing, realigned, normalized to the baseline template, and spatially smoothed (full width at half maximum = 8 mm). The first five functional volumes were excluded from the analysis to take into account of the equilibrium of longitudinal magnetization.

To reduce motion-related effects during resting-state fMRI scanning, we calculated framewise displacement (FD), which represents a six-dimensional timeseries across frames (Power et al. 2012), in each subject. Subjects who had more than 90% of time points with an FD below 0.5 mm were included in this study (Power et al. 2014).

PCC is one of the main hubs of the default mode network (DMN) and connects with various brain regions. Hypometabolism of PCC (Minoshima et al. 1997) and disruption of functional connectivity with PCC (Zhang et al. 2010) have been reported in the early stage of AD. Dysfunction of PCC in AD patients is responsible for cognitive impairment, including memory loss (Sperling et al. 2010). Furthermore, previous studies have indicated OT impairment-associated PCC hypoperfusion using PET (Hirono et al. 1998) or SPECT (Yamashita et al. 2014). Based on these previous findings, PCC was selected as the seed for the seed-voxel analysis in this study. The Pearson linear correlation coefficient between the time course of signal in each voxel and the average signal of the PCC was calculated using CONN software (<https://www.nitrc.org/projects/conn/>) (Whitfield-Gabrieli and Nieto-Castanon 2012). The gray matter signal was filtered with a bandpass filter (0.01–0.1 Hz) to reduce the effect of low-frequency physiologic noise. Voxel-by-voxel one-sample *t*-tests were used for elucidating significantly connected voxels with the PCC in each group. Then we made a

subtraction map of the disease differences (Normal vs OT-good and Normal vs OT-poor) and OT score differences (OT-good vs OT-poor) to identify disease- or OT-specific connectivity changes with PCC. A  $p$ -value less than 0.05 corrected with a peak-level family-wise error rate was considered to indicate a statistically significant difference. In cases where the seed-voxel analysis revealed significantly connected voxels with PCC, we executed ROI analysis including the significant voxels, which were defined anatomically from the FSL Harvard-Oxford Atlas maximum probability cortical atlas, with bilateral areas divided into left and right hemispheres (91 ROIs). Spearman rank-order correlation analysis was performed for verifying the relation of the OT score and the Z transformed  $r$ -value of that ROI in the AD group. One-way ANOVA with the post-hoc Bonferroni test was performed for comparing the differences of Z transformed  $r$ -values of the significantly connected ROIs with PCC between the three groups (OT-poor, OT-good and normal controls). Data were presented as mean  $\pm$  SD. In the subtraction map of OT score differences, we performed ROI-based partial correlation analysis to regress out the influence of MMSE that reflects AD progression on the functional connectivity. The degree of association of MMSE scores was used as a variable of the functional connectivity to the ROI, which included significantly connected voxels with PCC.

## Results

### Behavior data

Three subjects (two OT-poor AD patients and one normal subject) were excluded based on the FD criteria. Finally, 32 subjects (12 OT-good AD patients, 11 OT-poor AD patients and nine normal subjects) were entered into the analysis.

The mean OT score of all AD participants was  $3.3 \pm 1.4$ . Based on this mean OT score, AD patients were classified into the OT-good group (12 patients) or OT-poor group (11 patients). There was no significant difference in the age at examination between the three groups, including the normal control group. The MMSE/OT scores of the OT-good, OT-poor, and normal control groups were  $23.9 \pm 1.7/4.4 \pm 0.5$ ,  $17.2 \pm 4.3/2.0 \pm 0.9$ , and  $28.5 \pm 1.5/4.6 \pm 0.7$ , respectively. Compared with the normal controls, the OT-poor AD patients had significantly lower MMSE ( $p < 0.01$ ) and OT ( $p < 0.01$ ) scores. OT-good patients also showed significantly decreased MMSE ( $p < 0.05$ ), however, there was no significant difference in OT scores compared with normal controls. OT-poor patients showed a significant reduction in MMSE ( $p < 0.05$ ) and OT ( $p < 0.01$ ) compared with OT-good patients. There were no differences in other cognitive functions including OP, delayed recall and calculation between the OT-good and OT-poor AD groups (Table 1).

**Table 1** Demographic features of the normal controls, and OT-good and OT-poor AD patients

	AD		Normal
	OT-good	OT-poor	
Number	12	11	9
M:F	5:7	3:8	1:8
Age	$74.6 \pm 8.1$	$77.0 \pm 13.3$	$71.5 \pm 10.4$
MMSE	$23.9 \pm 1.7^\dagger$	$17.2 \pm 4.3^{* \dagger \dagger}$	$28.5 \pm 1.5$
OP (0–5)	$4.3 \pm 0.8$	$3.4 \pm 1.0^{\dagger \dagger}$	$5.0 \pm 0.0$
OT (0–5)	$4.4 \pm 0.5$	$2.0 \pm 0.9^{* \dagger \dagger}$	$4.6 \pm 0.7$
DR (0–3)	$1.4 \pm 1.2$	$0.5 \pm 0.7^{\dagger \dagger}$	$2.4 \pm 0.7$
Calculation (0–5)	$2.8 \pm 1.1^\dagger$	$1.6 \pm 1.5^{\dagger \dagger}$	$4.6 \pm 0.7$

Data are shown as mean  $\pm$  SD

DR, delayed recall; MMSE, mini-mental state examination; OP, orientation for place; OT, orientation for time

$^\dagger p < 0.05$  compared with Normal subjects

$^{\dagger \dagger} p < 0.01$  compared with Normal subjects

$^* p < 0.05$  compared with OT-good patients

$^{* \dagger \dagger} p < 0.01$  compared with OT-good patients

### Imaging data

Functional seed-voxel connectivity maps with PCC in each group were analyzed separately. Normal subjects showed significantly connected voxels between PCC and precuneus, right medial frontal gyrus which belong to the DMN (Buckner et al. 2008). In addition to these regions, bilateral temporal gyri were also significantly connected with PCC in normal subjects (Table 2). The connection between PCC and other DMN regions (precuneus and lateral temporal gyri) were also significant in OT-good AD patients, although the number of areas was reduced, compared with normal subjects. OT-poor patients showed significant connectivity in the medial part of DMN with PCC, similar to OT-good and normal subjects. However, connectivity in the dorsal frontal lobe, lateral parietal and lateral temporal lobes was decreased, especially in the right hemisphere (Fig. 1). A gradual decrease of connectivity in the DMN according to the deterioration of OT was similar to the impairment of the DMN in parallel with AD severity (Damoiseaux et al. 2012).

Although normal subjects showed significant connectivity in the right middle frontal gyrus with PCC compared with total AD patients in the subtraction Z-score map, no region was significantly associated with disease differences (Normal vs OT-good, Normal vs OT-poor; data not shown). The contrast of the OT score differences (OT-good minus OT-poor) in AD patients revealed significant connectivity between PCC and the posterior part of right middle temporal gyrus [MTG;

**Table 2** Regions significantly connected with posterior cingulate cortex in each group

		X	Y	Z	Voxel	T
Normal	Precuneus	-2	-52	42	6265	72.49
	medial frontal gyrus	-6	44	28	5790	13.48
	Medulla	-4	-46	-44	782	12.40
	superior temporal gyrus	-48	-56	28	1936	11.35
	inferior temporal gyrus	58	-26	-20	588	10.51
	Cuneus	50	-72	26	1523	7.74
	middle temporal gyrus	-52	-4	-28	149	6.58
	Cerebellum	50	-78	-40	142	6.10
OT-good	Precuneus	-8	-54	40	8401	29.92
	middle frontal gyrus	26	34	38	768	10.59
	middle temporal gyrus	-60	-30	-16	658	10.56
	middle temporal gyrus	58	-6	-30	550	10.45
	angular gyrus	40	-58	12	2013	10.36
	superior frontal gyrus	6	56	2	2793	9.68
	angular gyrus	-42	-56	12	2282	9.04
OT-poor	Precuneus	-8	-50	42	6510	37.34
	superior frontal gyrus	-20	34	40	3817	8.99
	angular gyrus	46	-54	16	784	7.77
	Cuneus	-44	-78	24	1584	7.72
OT-good > OT-poor	middle temporal gyrus	64	-56	-2	138	7.01

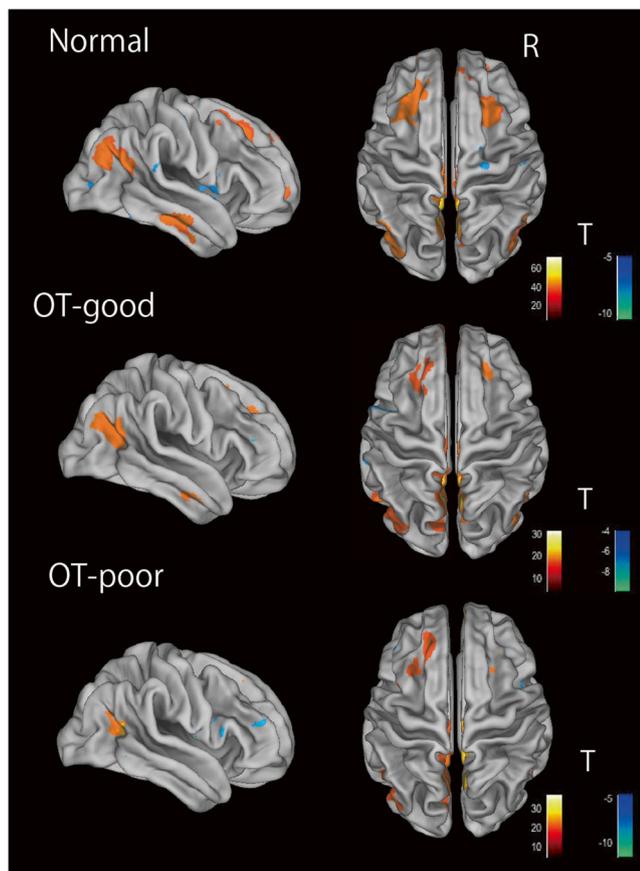
OT, orientation for time

$t(21) = 7.0$ ,  $p < 0.05$ , FWE corrected; Table 2, Fig. 2]. This area was close to the right temporo-parietal junction (TPJ), where connectivity with PCC was diminished in the OT-poor AD group. Furthermore, we performed seed-voxel analysis with the medial prefrontal ROI that composes part of the anterior hub of the DMN (Buckner et al. 2008). There were no significantly connected regions with the medial prefrontal ROI in the contrast of OT score differences. Partial correlation analysis revealed MMSE scores had no significant correlation ( $p = 0.77$ ) with functional connectivity between PCC and the right MTG ROI. To elucidate the association between the right MTG and OT, we performed spearman's correlation analysis between OT scores and Z transformed r-value of the right MTG ROI connected with PCC and found a significant positive correlation [ $r = 0.66$ ,  $p < 0.01$ ; Fig. 3]. This suggests that AD patients with higher OT scores have a functionally tight connection with PCC to the right MTG compared with lower OT score AD patients. Finally, we analyzed the Z transformed r-value difference between right MTG and PCC ROIs among OT-good, OT-poor and normal subject groups using one-way ANOVA. Although there was no significant difference between OT-good AD patients and normal subjects, OT-poor AD patients showed significantly lower Z transformed r-values compared with the other two groups in the post-hoc Bonferroni test (Fig. 4).

## Discussion

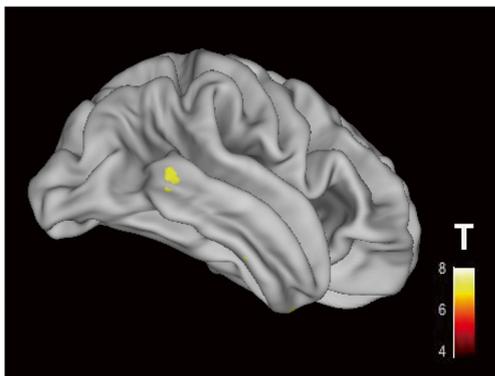
In the present study, we found that OT-poor AD patients exhibited decreased connectivity with PCC in the right hemisphere compared with OT-good AD patients and normal subjects, suggesting that dysfunction of the ventral attention network (VAN) may be associated with OT impairment in AD patients. Moreover, OT-good patients showed a significant connection between PCC and the posterior part of the MTG compared with OT-poor patients, and a significant OT-related increment of r-values was also found in this area.

Previous fMRI studies have reported that the right dorsal fronto-parietal network is associated with search and detection tasks (Corbetta et al. 2000; Corbetta and Shulman 2002; Vossel et al. 2014). These search and detection systems consist of two attention systems in the human brain: the dorsal attention network (DAN), concerned with the top-down control of visual processing (Liu et al. 2011), and the ventral VAN, including TPJ associated with stimulus-driven control (Corbetta et al. 2008). Decreased functional connectivity in both DAN and VAN of AD patients has been demonstrated in comparison with mild cognitive impairment and normal subjects (Zhang et al. 2015; Brier et al. 2012), which may be the basis of attentional deficits in AD (Perry and Hodges 1999). Right-lateralized reduction of connectivity with PCC, especially in

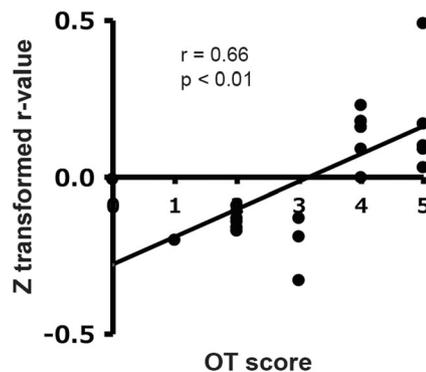


**Fig. 1** Statistical activation t-map of normal controls, and orientation for time (OT)-good and OT-poor Alzheimer’s disease (AD) patients from top to bottom. The activation map is displayed as the right lateral and top view on the template anatomical image. The color bar indicates the T-value

the OT-poor AD patients, suggests that dysfunction of the attention network may cause OT impairment. This result is compatible with our previous SPECT study showing hypoperfusion in the lateral parietal lobe of OT-poor AD patients (Yamashita et al. 2014).

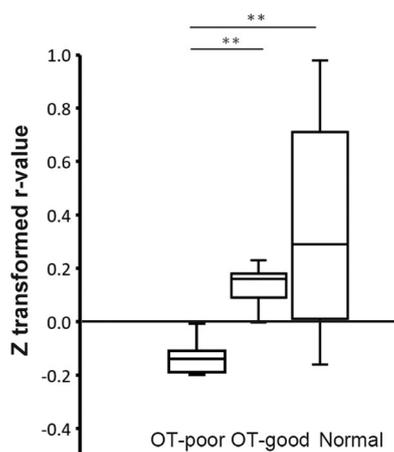


**Fig. 2** Subtraction map of OT-good minus OT-poor AD patients. The activation map is displayed as the right lateral view and overlaid on the template anatomical image. The color bar indicates the T-value



**Fig. 3** Correlation map between OT scores and Z transformed r-values in the right medial temporal gyrus with posterior cingulate cortex, analyzed using Spearman’s rank correlation test. One plot indicates data from one subject

OT-good AD patients showed significantly increased connectivity between PCC and the posterior part of the MTG compared with OT-poor AD patients. The similar Z transformed r-values from PCC to this area between OT-good AD patients and the normal group suggests that disconnection of the right MTG and PCC is specific to the OT-poor AD group. A recent high-resolution 7 T fMRI study investigating activation during a mental-orientation task elucidated time-domain related activity in the bilateral IPL, close to the right MTG in our study (Peer et al. 2015). A diffusion-weighted imaging tractography study indicated the posterior part of TPJ that belongs to the VAN is connected with the right posterior MTG (Mars et al. 2012). Therefore, it appears that not only a functional connection, but also structural connection exists between PCC and the right MTG. Consequently, disconnection between PCC and the right MTG may secondarily affect the right TPJ involved in VAN.



**Fig. 4** The bar graph indicating the Z transformed r-values of normal, OT-good and OT-poor AD patients. End stopped lines in the graph bars show the standard error. Analysis was performed using one-way ANOVA with post-hoc Bonferroni test. \*\*:  $p < .01$

Various neurodegenerative diseases have been shown to have a change in the structural and functional link of several large-scale functional RSNs (Pievani et al. 2011; Dipasquale and Cercignanani 2016). For example, Parkinson's disease patients show reduced functional connectivity in the basal ganglia network, and anti-parkinsonian drugs significantly improve that connectivity (Szewczyk-Krolikowski et al. 2014). Reduced functional connectivity of the left frontal cortex is associated with dysexecutive function, whereas visuospatial impairment significantly correlates with reduced functional connectivity of the left inferior parietal cortex in AD patients (Ranasinghe et al. 2014). Intra-network dysfunction and loss of correlation between networks have both been reported in severe AD patients (Brier et al. 2012). Therefore, disconnections between RSNs may cause various kinds of cognitive impairment in AD patients (Grothe and Teipel 2016; Qian et al. 2015).

OP disturbance can be caused by lesions in the parahippocampal gyrus containing neurons specific for spatial orientation called place cells (O'Keefe and Burgess 1996). Only a few studies have investigated the brain areas associated with OT. Giannakopoulos et al. (2000) found a significant correlation between neurofibrillary tangle densities in Brodmann's area 23, located in the ventral area of PCC, and impairment of OT. Deterioration of OT in AD patients may be induced by the disconnection between VAN and PCC resulting from the pathological transition in PCC, which belongs to the memory system called the Papez circuit (Papez 1995).

A limitation of this study is the relatively small sample size, which limited the statistical power. Therefore, our results should be confirmed by large sample size studies. Although the circular ROI analysis using the same data set for selection and analysis may be affected by noise because of the ROI selection bias (Kriegeskorte et al. 2009), we performed the ROI analysis defined by the seed-voxel activation map because of the sample size. Therefore, an independent data set should be used for the ROI analysis in a future study. In addition, more detailed investigation using independent component analysis should be done in the OT-poor AD patients to elucidate the impairment of RSNs pattern that is independent of the hypothesis of disconnection with PCC. Despite these limitations, this study revealed that disconnection between PCC and the right MTG is associated with OT impairment. If the network dysfunction is proven to be caused by  $\beta$  amyloid deposition, it may be possible to use this functional disconnection as a diagnostic and therapeutic biomarker for AD in the future.

## Conclusions

Severity of OT impairment in AD patients is paralleled by the functional disconnection between DMN and VAN, mediated by the right MTG. Functional connectivity between these areas is likely to play an important role for maintaining OT.

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## Compliance with ethical standards

**Conflict of interest** Ken-ichiro Yamashita, Taira Uehara, Pukovia Prawiroharjo, Koji Yamashita, Osamu Togao, Akio Hiwatashi, Yoshihide Taniwaki, Hidetsuna Utsunomiya, Takuya Matsushita, Ryo Yamasaki and Jun-ichi Kira report no conflicts of interest.

**Informed consent** All procedures performed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975. Informed consent was obtained from all patients included in the study.

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