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Distinctive Resting State Network Disruptions Among Alzheimer's Disease, Subcortical Vascular Dementia, and Mixed Dementia Patients

Hee Jin Kim[a,b,1], Jungho Cha[c,1], Jong-Min Lee[c,*], Ji Soo Shin[d], Na-Yeon Jung[a,b,e], Yeo Jin Kim[a,b], Yearn Seong Choe[c], Kyung Han Lee[e], Sung Tae Kim[f], Jae Seung Kim[g], Jae Hong Lee[h], Duk L. Na[a,b,i] and Sang Won Seo[a,b,j,*]

[a]*Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*
[b]*Neuroscience Center, Samsung Medical Center, Seoul, Korea*
[c]*Department of Biomedical Engineering, Hanyang University, Seoul, Korea*
[d]*Pfizer Pharmaceuticals Korea Ltd., Seoul, Republic of Korea*
[e]*Department of Neurology, Pusan National University Hospital, Pusan National University, Department of Nuclear Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*
[f]*Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*
[g]*Department of Nuclear Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea*
[h]*Department of Neurology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea*
[i]*Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, Seoul, Korea*
[j]*Department of Clinical Research Design and Evaluation, SAIHST, Sungkyunkwan University, Seoul, Korea*

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Abstract.
Background: Recent advances in resting-state functional MRI have revealed altered functional networks in Alzheimer's disease (AD), especially those of the default mode network (DMN) and central executive network (CEN). However, few studies have evaluated whether small vessel disease (SVD) or combined amyloid and SVD burdens affect the DMN or CEN.
Objective: The aim of this study was to evaluate whether SVD or combined amyloid and SVD burdens affect the DMN or CEN.
Methods: In this cross-sectional study, we investigated the resting-state functional connectivity within DMN and CEN in 37 Pittsburgh compound-B (PiB)(+) AD, 37 PiB(–) subcortical vascular dementia (SVaD), 13 mixed dementia patients, and 65 normal controls.
Results: When the resting-state DMN of PiB(+) AD and PiB(–) SVaD patients were compared, the PiB(+) AD patients displayed lower functional connectivity in the inferior parietal lobule while the PiB(–) SVaD patients displayed lower functional connectivity in the medial frontal and superior frontal gyri. Compared to the PiB(–) SVaD or PiB(+) AD, the mixed dementia patients displayed

[1]These authors contributed equally to this work.

*Correspondence to: Sang Won Seo, MD, PhD, Department of Neurology, Samsung Medical Center, Sungkyunkwan University, School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, South Korea. Tel.: +82 2 3410 1233; Fax: +82 2 3410 0052; E-mail: sangwonseo@empal.com and Jong-Min Lee, PhD, Department of Biomedical Engineering, Hanyang University, Sanhakgisulkwan 319, Wangsimni-ro Seongdong-gu, Seoul 133-791, Korea. Tel.: +82 2 2220 0685; Fax: +82 2 2296 5943; E-mail: ljm@hanyang.ac.kr.

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lower functional connectivity within the DMN in the posterior cingulate gyrus. When the resting-state CEN connectivity of PiB(+) AD and PiB(–) SVaD patients were compared, the PiB(–) SVaD patients displayed lower functional connectivity in the anterior insular region. Compared to the PiB(–) SVaD or PiB(+) AD, the mixed dementia patients displayed lower functional connectivity within the CEN in the inferior frontal gyrus.

Conclusions: Our findings suggest that in PiB(+) AD and PiB(–) SVaD, there is divergent disruptions in resting-state DMN and CEN. Furthermore, patients with combined amyloid and SVD burdens exhibited more disrupted resting-state DMN and CEN than patients with only amyloid or SVD burden.

Keywords: Alzheimer's disease, amyloid, central executive network, default mode network, resting-state functional MRI, small vessel disease, subcortical vascular dementia

INTRODUCTION

Alzheimer's disease (AD) results from an imbalance in the production and clearance of amyloid, which leads to synaptic and neuronal losses [1]. Subcortical vascular dementia (SVaD) is characterized by extensive small vessel disease (SVD) such as white matter hyperintensities (WMH) and multiple lacunes [2]. Using Pittsburgh compound-B (PiB)-PET, a sensitive method that detects amyloid [3], about 30% of clinically diagnosed SVaD patients have a significant amyloid burden and show more severe cognitive dysfunction and brain atrophy compared to patients with only amyloid or SVD burden [4].

Resting-state functional MRI (rs-fMRI) reveals the correlated spontaneous activity within cortical and subcortical regions that are functionally related [5]. With recent advances in rs-fMRI, many researchers have become interested in intrinsic network connectivity such as default mode network (DMN) and central-executive network (CEN) of aging and degenerative dementia [6, 7]. The DMN, which consists of the ventromedial prefrontal cortex and posterior cingulate cortex, contributes to both episodic memory and visual imagery [8]. On the contrary, the CEN, which consists of dorsolateral prefrontal cortex and lateral posterior parietal cortex, plays an important role in attention, working memory, planning, problem solving, and decision making [9].

Previous studies have reported that both the DMN and CEN are disrupted in AD patients [6, 7, 10] and that SVD is associated with disruption in resting-state networks [11–15]. However, to our knowledge, there were few studies comparing the patterns of DMN or CEN disruption between PiB(+) AD and PiB(–) SVaD patients. It is possible that resting-state DMN is more disrupted in PiB(+) AD, while resting-state CEN is more disrupted in PiB(–) SVaD because memory dysfunction is predominant in AD patients while attention and executive dysfunctions are predominant in SVaD patients [16].

The clinical implication of amyloid burden in patients with SVD burden is an important issue. Pathological studies suggested that AD pathologies and SVD pathologies are independently associated with cognitive impairment in specific domains [17]. Furthermore, more recent studies revealed that amyloid and SVD synergistically affected cognitive dysfunction or structural abnormalities [18, 19]. It might be, therefore, reasonable to determine whether mixed dementia with combined AD and SVD pathologies may have more disrupted DMN and CEN than PiB(+) AD or PiB(–) SVaD.

We investigated clinically diagnosed AD and SVaD patients who underwent PiB-PET and rs-fMRI. First, we aimed to determine whether PiB(–) SVaD patients had distinctive patterns of resting-state DMN or CEN disruptions compared to those of PiB(+) AD patients. We also investigated whether patients with combined amyloid and SVD burdens (mixed dementia) displayed more severe resting-state network disruptions than patients with only amyloid (PiB(+) AD) or SVD burdens (PiB(–) SVaD).

METHODS

Participants

In this cross-sectional study, 65 normal controls (NCs), 37 patients with PiB(+) AD, 37 patients with PiB(–) SVaD, and 13 patients with PiB(+) SVaD (mixed dementia) were recruited from the memory clinic at Samsung Medical Center.

We selected patients with PiB(+) AD, PiB(–) SVaD, or mixed dementia according to clinical diagnosis and PiB-PET status (see the below methods for PiB-PET). PiB(+) AD patients were those who (1) met probable AD dementia criteria proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association [20]; (2) had minimal WMH (periventricular WMH <5 mm and deep WMH <5 mm); (3) and

had significant amyloid burden (PiB SUVR $\geq$1.5) as measured by PiB-PET. SVaD patients were those who (1) met the diagnostic criteria for vascular dementia as determined by the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition; (2) had focal neurological symptoms and signs; (3) had severe WMH, defined as periventricular WMH $\geq$10 mm and deep WMH $\geq$25 mm, as modified from the Fazekas ischemia criteria [21]. Then according to amyloid burden status, SVaD patients were divided into PiB(–) SVaD (PiB SUVR <1.5) and mixed dementia (PiB SUVR $\geq$1.5).

Patients were excluded if they had territorial infarctions, WMH due to radiation injury, multiple sclerosis, vasculitis, or leukodystrophy. Blood tests included complete blood count, blood chemistry test, vitamin B_{12}/folate measurement, syphilis serology, thyroid function test, and APOE genotyping. The detailed diagnostic process and neuropsychological test are provided in Supplementary Material 1.

The NC subjects were recruited from the community. Volunteers were screened using brain MRI and detailed neuropsychological tests including Korean version of Mini-Mental State Examination (K-MMSE) and Clinical Dementia Rating-sum of boxes (CDR-SOB). Those who had minimal WMH and whose neuropsychological test results were within normal range (above 16th percentile of age and education matched norms) were enrolled as NC subjects.

We obtained written consent from each participant. This study protocol was approved by the Institutional Review Board of Samsung Medical Center.

[^{11}C] PiB-PET

All patients completed the [^{11}C] PiB-PET scan. The methods of PiB-PET acquisition and analysis are described in detail in Supplementary Material 2. PiB standardized uptake value ratio (SUVR) $\geq$1.5 was considered as PiB-positive [4].

MR imaging techniques

All imaging was carried out at Samsung Medical Center with a Philips Intera Achieva 3.0 Tesla scanner equipped with an 8-channel SENSE head coil (Philips Healthcare, the Netherlands). Whole-brain Echo planar imaging (EPI) time series scans (TR = 3 s; TE = 35 ms; flip angle = 90°; 1.7 × 1.7 × 4 mm^3 voxel resolution) consisted of 100 volumes and lasted for approximately five minutes, which is known to be sufficient to evaluate resting-state functional connectivity [22]. During each scan, participants were instructed to rest with their eyes open and fixated on a centrally placed, white crosshair against a black background. A high-resolution T1-weighted anatomical image was also acquired using a magnetization-prepared gradient echo (MPRAGE) sequence (TR = 9.9 ms; TE = 4.6 ms; flip angle = 8°; 0.5 × 0.5 × 0.5 mm^3 voxel resolution).

Preprocessing of fMRI data

Analysis of Functional NeuroImages (AFNI) software (http://afni.nimh.nih.gov/afni) was used to preprocess the fMRI data [23]. The first three volumes of each functional image were discarded to allow for stabilization of the magnetic field. The residual images were de-spiked, and were then corrected for slice-time acquisition differences and head motion [24]. To exclude the possibility that differences in motion can introduce artifactual group differences in functional connectivity [25, 26], we screened for head motion artifacts using estimated displacement through the motion correction parameters of x, y, z translation and three rotation axes at the motion correction stage. The estimated displacement was less than 0.3 mm for the Euclidean L2 norm of motion displacement between successive time-series and also less than 2 mm translations in any of the three directions or 2° rotations around any of the axes. The Local Pearson Correlation cost function was used to co-register the functional images of each subject to the structural brain [27]. Next, images were normalized to the Montreal Neurological Institute (MNI) 152 template space [28]. Subsequently, a 6 mm full-width-at-half-maximum (FWHM) Gaussian kernel was used for spatial smoothing.

Independent component analysis

The resting-state DMN and CEN were assessed by group spatial independent component analysis (sICA). The group sICA was carried out using Group ICA for the fMRI toolbox (GIFT) (http://mialab.mrn.org/software/gift/) software [29]. GIFT software includes group data reduction using principal component analysis, ICA calculation and back-reconstruction for each subject. Minimum description length criteria were used to determine the optimal number of components [30]. Forty-four estimated independent components were identified. An independent component estimation was carried out using the Infomax algorithm [31]. For each component, the z-value reflected the degree to which the time series of

each voxel was associated with one of the specific components. The functional connectivity levels were determined using the spatial differences across the z-values of each component. A combination of manual and template-matching procedures was used to choose a component of the DMN and CEN [32]. The component that included the ventromedial prefrontal cortex and posterior cingulate cortex was selected as DMN component and the component that included the dorsolateral prefrontal cortex and posterior parietal cortex was selected as CEN component.

W-score maps

To obtain measurements of functional alteration in patient groups compared with NCs, W-score maps were computed for each patient using the NCs as reference [33]. To obtain the W-score maps, multiple regressions were performed using age, gender, and education as covariates in the NCs. Then, W-score maps were computed as follow: W-score = [(patient's functional connectivity value) - (value predicted in the NCs for the patient's age, gender, education)]/standard deviation of residuals in control groups. The W-scores were reversed so that positive W-scores represent fewer functional connections compared with NCs. Then, individual W-score maps were averaged in the each patient group.

Neuropsychological tests

All patients underwent neuropsychological tests [34, 35]. Memory was assessed using delayed recall scores of the Seoul Verbal Learning Test (SVLT) and Rey-Osterrieth Complex Figure Test (RCFT). Frontal-executive function was assessed using the phonemic Controlled Oral Word Association Test (COWAT) and Stroop color reading test. General cognition and disease severity were assessed using the K-MMSE and CDR-SOB, respectively. The presence of depression was assessed by geriatric depression scale (GDS) $\geq$18 [36].

Statistical analysis

One-way analysis of variance and Bonferroni's *post hoc* analyses were performed to evaluate the differences in demographics and cognitive test results among the four groups.

To determine the differences in the DMN and CEN connectivity among the four groups, an analysis of covariance was performed using age, gender and education as covariates. Monte Carlo simulations were performed using the AFNI's 3dClustSim program to control for Type I errors (parameters: individual voxel p-value = 0.02, simulated 10,000 times iteratively, 6 mm FWHM Gaussian filter width with a whole-brain mask). The 3dClustSim program estimates the overall significance level achieved with various combinations of individual voxel probability thresholds and cluster size thresholds [37]. We obtained a corrected significance level of $P\alpha < 0.05$ (uncorrected individual voxel height threshold of $p < 0.02$ ($F > 3.38$)). Subsequently, to examine the inter-group differences, *post hoc* two-sample t tests were performed between pairs of groups for voxel-wise statistics (corrected significant level of $P\alpha < 0.05$), after adjusting for age, gender, and education. The significant regions between the groups that have >120 voxel size were clinically interpreted.

To evaluate the correlation between resting state DMN/CEN connectivity and neuropsychological test results among patients, we performed multiple linear regression analyses after adjusting for age, gender, and education.

RESULTS

Demographics of subjects

As shown in Table 1, there were age differences between NCs, PiB(–) SVaD, PiB(+) AD, and mixed dementia patients. The education level was lower in PiB(–) SVaD patients compared to NCs.

Comparisons of functional connectivity within the resting-state default mode network

Compared to the NCs, the PiB(+) AD patients displayed lower functional connectivity within the DMN in the left supramarginal gyrus (Table 2, Fig. 1A) and the PiB(–) SVaD patients displayed lower functional connectivity within the DMN in the left superior frontal gyrus (Table 2, Fig. 1B). There were no differences in functional connectivity within the DMN between the NCs and mixed dementia patients. However, when we used W-scores, mixed dementia patients displayed higher W-scores in widespread areas, representing lower functional connectivity within the DMN compared to the NCs (Supplementary Figure 1). Further analyses without depressed patients (GDS <18) showed similar results (Supplementary Figure 2).

In the direct comparison between the PiB(+) AD and PiB(–) SVaD patients, the PiB(+) AD patients displayed lower functional connectivity within the DMN

Table 1
Demographics and clinical findings of the NCs, PiB(+) AD, PiB(–) SVaD, and mixed dementia patients

	NCs	PiB(+) AD	PiB(–) SVaD	mixed dementia
n	65	37	37	13
Age	69.9 ± 3.9	66.8 ± 8.7†‡	72.8 ± 6.5	78.0 ± 4.6*
Gender (M:F)	22 : 43	14 : 23	16 : 21	2 : 11
Education	12.8 ± 4.7	10.6 ± 5.5	8.3 ± 5.0*	9.7 ± 5.0
Neuropsychological test				
Memory				
SVLT delayed	7.5 ± 2.0	0.7 ± 1.6*	1.6 ± 1.9*	0.3 ± 0.6*
RCFT delayed	17.6 ± 6.2	2.0 ± 2.5*	3.6 ± 3.9*	1.4 ± 1.9*
Frontal-executive function				
COWAT phonemic	31.9 ± 12.8	12.2 ± 7.9*	6.8 ± 5.7*	8.7 ± 6.6*
Stroop color	90.2 ± 18.8	38.7 ± 29.2*	28.1 ± 27.7*	26.9 ± 25.3*
MMSE score	28.9 ± 1.2	18.1 ± 4.2*†‡	21.5 ± 4.3*‡	17.9 ± 4.9*
CDR-SOB		4.8 ± 2.4	6.1 ± 4.0	6.8 ± 4.1
Depression (GDS ≥18)		8 (21.6%)	13 (35.1%)	5 (38.5%)

NCs, Normal Controls; AD, Alzheimer's disease; SVaD, subcortical vascular dementia; SVLT, Seoul Verbal Learning Test; RCFT, Rey-Osterrieth Complex Figure Test; COWAT, Controlled Oral Word Association Test; MMSE, Mini-Mental State Examination; CDR-SOB, Clinical Dementia Rating sum of boxes; GDS, Geriatric Depression Scale. *$p < 0.05$ difference between NC and dementia groups. †$p < 0.05$ difference between PiB(+) AD and PiB(–) SvaD. ‡$p < 0.05$ difference between PiB(+) AD and mixed dementia or between PiB(–) SVaD and mixed dementia.

Table 2
Brain regions with significant differences in resting-state functional connectivity within the default mode network among the groups

Brain regions	R/L	MNI coordinates (mm)			Maximum	Number of Voxels
		x	*y*	*z*	*t*	
NC > PiB(+) AD						
Supramarginal Gyrus	L	–44	–52	32	4.62	409
NC > PiB(–) SVaD						
Superior Frontal Gyrus	L	–20	32	58	3.43	124
PiB(–) SVaD > PiB(+) AD						
Inferior Parietal Lobule	L	–46	–46	42	4.41	267
PiB(+) AD > PiB(–) SVaD						
Medial Frontal Gyrus	R	8	64	12	4.36	252
Superior Frontal Gyrus	L	–10	26	56	4.16	186
PiB(–) SVaD > Mixed dementia						
Cingulate Gyrus, posterior	R	2	–26	32	4.03	152
PiB(+) AD > Mixed dementia						
Cingulate Gyrus, posterior	L	–4	–30	34	4.25	183
Superior Frontal Gyrus	L	–8	24	58	3.81	141

NC, normal control; AD, Alzheimer's disease; SVaD, subcortical vascular dementia; R, right; L, left; MNI, Montreal Neurological Institute.

in the left inferior parietal lobule while the PiB(–) SVaD patients displayed lower functional connectivity in the right medial frontal and left superior frontal gyri (Table 2, Fig. 1C). Compared to the PiB(–) SVaD patients, the mixed dementia patients displayed lower functional connectivity within the DMN in the right posterior cingulate gyrus while there was no region where the PiB(–) SVaD patients displayed lower functional connectivity compared to the mixed dementia patients (Table 2, Fig. 1D). Compared to the PiB(+) AD patients, the mixed dementia patients displayed lower functional connectivity within the DMN in the left posterior cingulate gyrus and left superior frontal gyrus while there was no region where the PiB(+) AD patients displayed lower functional connectivity compared to the mixed dementia patients (Table 2, Fig. 1E).

There was no correlation between resting-state DMN connectivity and neuropsychological test results (Supplementary Table 1).

Comparisons of functional connectivity within the resting-state central executive network

Compared to the NCs, the PiB(–) SVaD patients displayed lower functional connectivity within the CEN in the left insular area (Table 3, Fig. 2A). There were

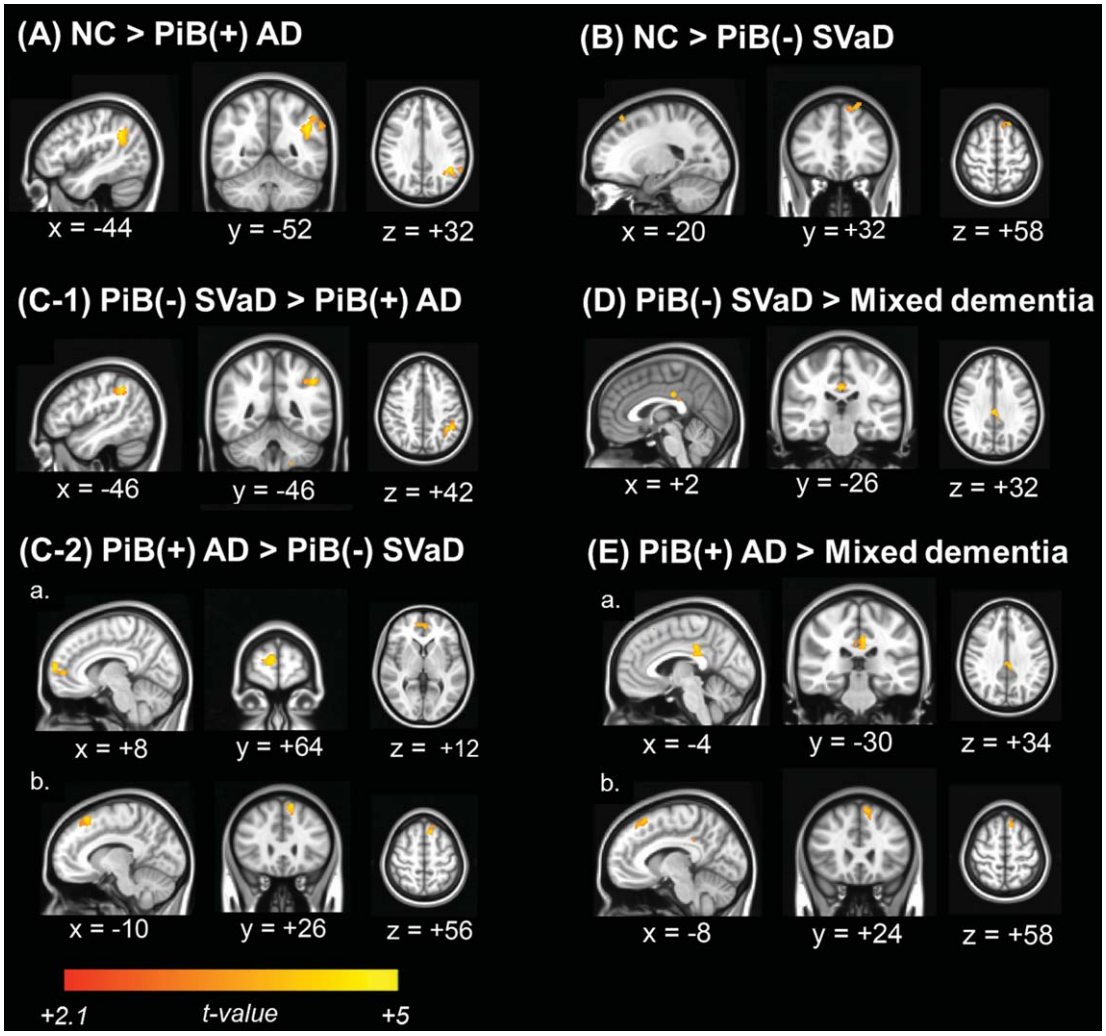

Fig. 1. Brain regions with significant differences in resting-state functional connectivity within the default mode network among the groups. Colored areas indicate significantly lower connectivity in the latter group in each comparison. >120 voxel size after *post hoc* tests with age, gender, and education adjusted.

Table 3
Brain regions with significant differences in resting-state functional connectivity within the central executive network among the groups

Brain regions	R/L	MNI coordinates (mm)			Maximum	Number of Voxels
		x	*y*	*z*	*t*	
NC > PiB(–) SVaD						
Insula	L	–32	16	6	4.57	219
PiB(+) AD > PiB(–) SvaD						
Insula	L	–40	10	–4	3.7	216
PiB(–) SVaD > Mixed dementia						
Inferior frontal gyrus	L	–48	32	6	4.24	121
PiB(+) AD > Mixed dementia						
Inferior frontal gyrus	L	–50	34	6	4.13	130

NC, normal control; AD, Alzheimer's disease; SVaD, subcortical vascular dementia; R, right; L, left; MNI, Montreal Neurological Institute.

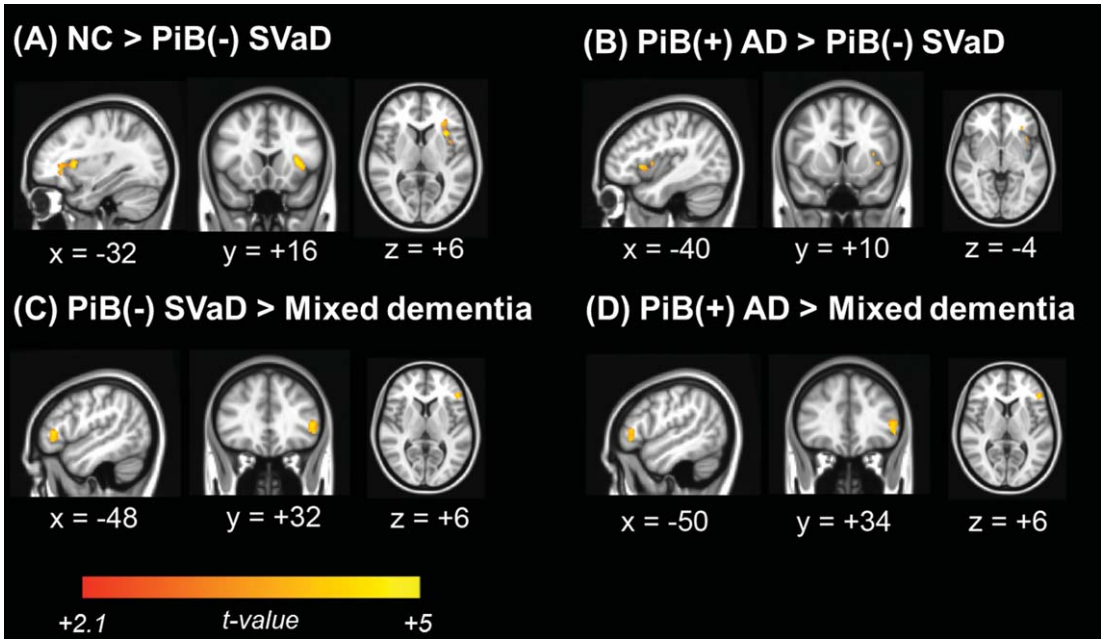

Fig. 2. Brain regions with significant differences in resting-state functional connectivity within the central executive network among the groups. Colored areas indicate significantly lower connectivity in the latter group in each comparison. >120 voxel size after *post hoc* tests with age, gender, and education adjusted.

no differences in functional connectivity within the CEN between the NCs and the PiB(+) AD or the mixed dementia patients. However, when we used W-score, the PiB(+) AD patients displayed higher W-score in several areas and the mixed dementia patients displayed higher W-score in widespread areas, representing lower functional connectivity within the CEN compared to the NCs (Supplementary Figure 3). Further analyses without depressed patients (GDS <18) showed similar results (Supplementary Figure 4).

In the direct comparison between the PiB(+) AD and PiB(–) SVaD patients, the PiB(–) SVaD patients displayed lower functional connectivity within the CEN in the left insular area while there was no region where the PiB(+) AD patients displayed lower functional connectivity (Table 3, Fig. 2B). Compared to the PiB(–) SVaD patients, the mixed dementia patients displayed lower functional connectivity within the CEN in the left inferior frontal gyrus while there was no region where the PiB(–) SVaD patients displayed lower functional connectivity compared to the mixed dementia patients (Table 3, Fig. 2C). Compared to the PiB(+) AD patients, the mixed dementia patients displayed lower functional connectivity within the CEN in the left inferior frontal gyrus while there was no region where the PiB(+) AD patients displayed lower functional connectivity (Table 3, Fig. 2D).

There was no correlation between resting-state CEN connectivity and neuropsychological test results (Supplementary Table 1).

DISCUSSION

In this study, we reported novel findings concerning altered resting-state DMN and CEN connectivities in the PiB(+) AD, PiB(–) SVaD and mixed dementia patients, who were analyzed using rs-fMRI and amyloid imaging. The major findings of this study were as follows: 1) When the resting-state DMN of PiB(+) AD and PiB(–) SVaD patients were compared, the PiB(+) AD patients displayed lower functional connectivity especially in the inferior parietal lobule while the PiB(–) SVaD patients displayed lower functional connectivity especially in the medial frontal and superior frontal gyri. Compared to the PiB(–) SVaD or PiB(+) AD patients, the mixed dementia patients displayed lower functional connectivity within the DMN especially in the posterior cingulate gyrus. 2) When the resting-state CEN connectivity of PiB(+) AD and

PiB(–) SVaD patients were compared, the PiB(–) SVaD patients displayed lower functional connectivity especially in the anterior insular region. Compared to the PiB(–) SVaD or PiB(+) AD patients, the mixed dementia patients displayed lower functional connectivity within the CEN especially in the inferior frontal gyrus. Taken together, our findings suggested that the DMN is disrupted in both PiB(+) AD and PiB(–) SVaD patients with disease specific vulnerability while the CEN disruption is more unique to PiB(–) SVaD. Furthermore, patients with combined AD and SVD burdens exhibited more disrupted DMN and CEN than patients with only AD or only SVD burdens.

Our first major finding was that within DMN, the PiB(+) AD patients had lower functional connectivity in the inferior parietal lobule while the PiB(–) SVaD patients displayed lower functional connectivity in the medial frontal and superior frontal regions. To our knowledge, this is the first study suggesting that both the PiB(+) AD and PiB(–) SVaD patients had disease specific vulnerability in the DMN disruption. The DMN is known to comprise several distinct interacting subsystems [8]. In particular, the DMN includes the medial prefrontal regions, which are responsible for self-referential judgments and self-relevant mental simulations [38]. On the contrary, the inferior parietal lobule is responsible for monitoring the external environment [8]. Further studies are needed to examine whether PiB(+) AD and PiB(–) SVaD patients demonstrate the distinct deficits in these specific tasks.

We also found that the PiB(–) SVaD patients had lower functional connectivity in the anterior insular region compared to PiB(+) AD patients, suggesting that CEN disruption is more unique to PiB(–) SVaD. Accumulating evidence suggests that the anterior insular region plays a critical role in attention and executive function [39]. We have previously reported that executive dysfunction is a core feature of PiB(–) SVaD that distinguishes it from PiB(+) AD [16]. Thus, the lower functional connectivity within the CEN in the anterior insular region might be one of the pathophysiologic mechanisms that would explain executive dysfunction in PiB(–) SVaD patients.

There are several possible mechanisms that explain why PiB(–) SVaD patients had a unique pattern of altered resting-state DMN and CEN connectivity. It is possible that SVD might have disconnected white matter tracts in the frontal region, which leads to functional connectivity problem especially in the anterior part of DMN or CEN. Alternatively, it is possible that the lower connectivity within the networks shown in PiB(–) SVaD are more reflective of alterations in vascular physiology rather than underlying differences in neural activation [12]. Indeed, previous studies suggested that patients with microangiopathy have reduced intrinsic microvascular oscillation [40].

Our second major finding was that patients with combined AD and SVD burdens exhibited more disrupted DMN and CEN than patients with only AD or only SVD burdens. This is in line with our previous study which showed that mixed dementia causes more memory dysfunction than PiB(–) SVaD [4]. The lower functional connectivity within the DMN and CEN in the frontal region of the mixed dementia patients compared to the PiB(+) AD patients might be explained by the extra SVD effects on the frontal region in the mixed dementia patients.

The reason that the mixed dementia patients revealed more disrupted DMN in the posterior cingulate region compared to the PiB(+) AD and more disrupted CEN in the inferior frontal gyrus compared to the PiB(+) AD or PiB(–) SVaD remains unclear. However, considering that these regions are characteristically apt to be affected in AD or SVaD patients, this finding might be related to the synergistic effects of AD and SVD pathologies on resting-state network of DMN and CEN in these regions. These findings are consistent with previous studies showing that amyloid and SVD burdens synergistically affect visuospatial and cortical thinning in the posterior region [18, 19]. Further investigation is needed to determine whether amyloid and SVD synergistically disrupt the DMN or CEN connectivity in these regions.

There are some limitations in this study. First, PiB-PET scans was not performed in the NCs. Previous studies showed that approximately 10 to 40% of cognitively normal elderly people are PiB-positive [41]. Thus, the degree of decreased functional connectivity in the patients' groups compared to NCs may have been underestimated. Second, the lack of significant difference between mixed dementia and controls raises concerns about the internal validity of the results. However, it might be related to the small number of mixed dementia patients. When W-scores were calculated in each patient using NCs as reference and entering age, gender, and education as covariates, mixed dementia patients exhibited lower functional connectivities within DMN and CEN compared to NCs. Third, the demographics showed some differences across the four groups. However, we believe this reflects the characteristics of participants, and we controlled for these factors in the analyses. Finally, PiB-PET may not be sufficiently sensitive to detect soluble amyloid oligomers or very low levels of compact plaques.

In summary, our findings suggest that PiB(+) AD and PiB(–) SVaD have distinct patterns of altered connectivity in the resting-state DMN and CEN. Furthermore, the DMN and CEN in patients with combined AD and SVD burdens (mixed dementia) are more disrupted than in patients with only AD (PiB(+) AD) or only SVD burdens (PiB(–) SVaD). Our findings highlight that there may be distinct pathobiological mechanisms of intrinsic network connectivity in AD and SVaD patients.

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SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-150637.

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