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Electroencephalography for Early Detection of Alzheimer's Disease in Subjective Cognitive Decline

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Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Background and Purpose: Early detection of subjective cognitive decline (SCD) due to Alzheimer's disease (AD) is important for clinical research and effective prevention and management. This study examined if quantitative electroencephalography (qEEG) could be used for early detection of AD in SCD.
Methods: Participants with SCD from 6 dementia clinics in Korea were enrolled. ^{18}F-florbetaben brain amyloid positron emission tomography (PET) was conducted for all the participants. qEEG was performed to measure power spectrum and source cortical activity.
Results: The present study included 95 participants aged over 65 years, including 26 amyloid PET (+) and 69 amyloid PET (−). In participants with amyloid PET (+), relative power at delta band was higher in frontal (p=0.025), parietal (p=0.005), and occipital (p=0.022) areas even after adjusting for age, sex, and education. Source activities of alpha 1 band were significantly decreased in the bilateral fusiform and inferior temporal areas, whereas those of delta band were increased in the bilateral cuneus, pericalcarine, lingual, lateral occipital, precuneus, posterior cingulate, and isthmus areas. There were increased connections between bilateral precuneus areas but decreased connections between left rostral middle frontal area and bilateral frontal poles at delta band in participants with amyloid PET (+) showed. At alpha 1 band, there were decreased connections between bilateral entorhinal areas after adjusting for covariates.
Conclusions: SCD participants with amyloid PET (+) showed increased delta and decreased alpha 1 activity. qEEG is a potential means for predicting amyloid pathology in SCD. Further longitudinal studies are needed to confirm these findings.

Keywords: Cognitive Dysfunction; Alzheimer Disease; Amyloid; Positron-Emission Tomography; EEG

Author Contributions

Conceptualization: Yang DW; Formal analysis: Yang DW; Funding acquisition: Yang DW; Investigation: Yang DW, Ho S, Hong YJ, Jeong JH, Park KH, Kim S, Wang MJ, Choi SH; Methodology: Yang DW; Software: Kang SW; Supervision: Yang DW; Writing - original draft: Shim Y, Ho S; Writing - review & editing: Shim Y.

INTRODUCTION

Subjective cognitive decline (SCD) refers to an individual's self-reported decline of various cognitive functions without objective neuropsychological deficits.[1] Numerous studies have reported that some older adults with SCD have biomarker abnormalities consistent with Alzheimer's disease (AD).[2,3] Thus, SCD can also be considered a risk factor for dementia.[1] It has been reported that SCD occurs approximately 15 years before mild cognitive impairment (MCI) and dementia.[4] Therefore, SCD, the first help-seeking stage and the last stage before clinical disease, can be considered the best time for prevention and early treatment.

Predicting dementia in preclinical and prodromal stages of AD based on the AD continuum is important.[5] SCD can progress to dementia through MCI.[1,6] Similar to MCI due to AD and AD dementia, SCD often exhibits AD biomarkers such as abnormal levels of amyloid and tau proteins in cerebrospinal fluid (CSF),[7] amyloid uptake on positron emission tomography (PET),[2] and medial temporal atrophy on magnetic resonance imaging (MRI) which indicate a high likelihood of further cognitive decline and dementia.[1,6] Therefore, finding reliable biomarkers for AD in SCD is currently a primary research interest.

Synaptic loss in AD develops earlier before neuronal death and results in cognitive decline,[8,9] electroencephalography (EEG) has been used to directly reflect synaptic functions in real time[10,11] and offers several advantages such as noninvasiveness and low cost.[11] It has been postulated that both synaptic and neuronal losses can reduce connections in brain function and influence EEG signals.[10] In addition to brain connectivity and network analyses,[12,13] various studies such as cortical excitability and microstate complexity have also been performed using EEG for early diagnosis of AD.[14,15] Quantitative EEG (qEEG) has shown that patients with MCI or AD show decreased activity at fast-frequency bands but increased activity at slow-frequency bands.[16,17]

However, a few clinical studies have investigated biological correlates of qEEG findings in patients with AD, according to the clinical stages. To date, just one has reported the relationship between qEEG parameters and CSF biomarkers of neurodegeneration with a modest sample size.[18] An early screening biomarker is necessary to identify older adults with SCD at the preclinical stage who are at a higher risk of progressive cognitive decline. Although remarkable advances in biomarkers for early diagnosis have been conducted with structural MRI, amyloid PET, and CSF analysis, electrophysiological measurements are economically and noninvasively more promising with the highest time resolution to reflect brain dynamics in cognition.

In the present study, we investigated whether qEEG findings in SCD participants could be different according to amyloid PET positivity.

METHODS

Participants

This was a multicenter, prospective observational study aimed at identifying predictors for the Clinical progression to MCI or dementia from SCD (CoSCo). The CoSCo study enrolled 120 SCD participants aged 60 years or older from 6 different memory clinics. Assessments included clinical and neuropsychological examination, blood sampling, MRI, ^{18}F-florbetaben PET, and EEG at baseline. Exclusion criteria were: (1) patients diagnosed with dementia

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or MCI; (2) patients who had brain lesions or blood test abnormalities that might affect cognitive function; (3) patients who had uncontrolled depression, schizophrenia, alcoholism, or drug dependence; and (4) participants who were taking antiepileptic drugs or showing an EEG abnormality such as asymmetry, continuous slow wave, or epileptiform discharge. Medications such as anxiolytics and antidepressants that could exert an influence on EEG results were stopped before EEG examination.[19]

All the participants underwent some parts of the Seoul Neuropsychological Screening Battery-2nd version (SNSB-II) test to evaluate their cognitive function.[20] The SNSB consists of the Digit Span T, the Korean-Boston Naming Test, the Rey-Osterrieth Complex Figure Test, the Seoul Verbal Learning Test (SVLT)-Elderly's version, the Digit Symbol Coding, the phonemic Controlled Oral Word Association Test, the Korean-Trail Making Test-Elderly's version, and the Korean-Color Word Stroop Test. All the tests were analyzed based on z-scores. The z-scores are standardized using the age and the educational years that are presented in the SNSB-II based on a large, nationwide Korean sample (1,100 people), thereby making it possible to make comparisons with the population averages. Although SCD subjects have been defined as those with –1.5 standard deviation (SD) or higher on the neuropsychological test,[1] we selected the high-risk group which seems to progress to MCI or dementia rapidly among these subjects. Therefore, only participants with SVLT delayed recall score between –1.5 SD and 0 were included in this study. All the participants had graduated from elementary school or higher. The Institutional Review Board (IRB) of the Catholic University of Korea, Seoul St. Mary's Hospital approved this study (KC18ONDI0394). All the local IRBs and ethical committees approved the study protocol. Written informed consent was obtained from all the participants.

PET and MRI images

^{18}F-florbetaben PET scans were acquired by the standardized protocol.[21] An average of 296 MBq ^{18}F-florbetaben was injected intravenously, and 90 minutes later the scan was initiated. A low-dose computed tomography scan was performed for attenuation correction, and immediately followed by PET in a 3-dimensional mode for 20 minutes. To minimize motion artifacts, the participant's head was fixed using a head holder. All PET images were reviewed by nuclear medicine physicians blinded to results of neuropsychological testing who had successfully completed the electronic training program provided by the manufacturer. Results were dichotomized into amyloid positivity or negativity using a visual rating scale of florbetaben PET scans, the brain amyloid plaque load score (1=negative finding, 2=moderate depositions, 3=pronounced depositions).[22] Brain amyloid plaque load scores of 2 or 3 indicated a positive finding for amyloidosis.

All the participants underwent 3.0-Tesla brain MRI. On the brain MRI, white matter hyperintensities (WMHs) including periventricular WMHs and deep WMHs (DWMHs) were measured as proposed by the Clinical Research Center for Dementia of South Korea.[23] In addition to the numbers of lacune and cerebral microbleed, medial temporal atrophy rating was evaluated as described previously.[24]

EEG recording and analysis

On weekdays between 9 am and 5 pm, under waking-rest, eyes closed conditions, EEGs were recorded from 19 scalp electrodes according to the International 10–20 System with linked ear reference. The state of vigilance was controlled by visual inspection of EEG recording traces. The drowsiness of each participant was avoided by verbal alerts. All the artifact-free

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EEG data were remade reference offline to a common average montage. After preprocessing, transient artifact epochs such as head, eye, and body movement, heartbeat, swallowing, teeth biting, and electrode wire swaying were rejected by the expert's component selections from the advanced mixture independent component analysis.[25] Electrode impedance was kept below 10 kOhm. All data were digitalized in a continuous recording mode (approximately 3 minutes of EEG; sampling rate: 200 or 250 Hz, to avoid aliasing).

The power spectral density was computed using a Fast Fourier Transform analysis at 0.25 Hz of frequency resolution with an iSyncBrain® auto-analysis system[26-28] according to the frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha 1 (8–10 Hz), alpha 2 (10–12 Hz), beta 1 (12–15 Hz), beta 2 (15–20 Hz), beta 3 (20–30 Hz), and gamma (30–45 Hz). Absolute power was the sum of the component powers for each frequency band. Total power was the total sum of frequency band power from delta to gamma band, 1–45 Hz. Relative power was the absolute power in a specific frequency band divided by the total power. In addition, theta-to-alpha (TAR), delta-to-alpha (DAR), and theta-to-beta (TBR) were calculated. On the iSyncBrain®, standardized low-resolution brain electromagnetic tomography (sLORETA) and default mode network (DMN) analysis were performed.[27,29-31]

Statistical analysis

According to the presence of amyloid uptake in ^{18}F-florbetaben PET, the participants were divided into 2 groups: amyloid PET (+) and amyloid PET (−). Clinical and MRI findings were compared between the 2 groups using an independent *t*-test, χ^2-test, Mann-Whitney *U* test, or Fisher's exact test, as appropriate. All the qEEG analyses such as power spectral density, sLORETA, and DMN were performed automatically using the iSyncBrain® program. All other statistical analyses, including adjustment for confounding factors such as age, sex, and education, were performed using the Statistical Package for the Social Sciences version 28.0 software program (IBM Corp., Armonk, NY, USA). Statistical significance was set at p-value < 0.05.

RESULTS

Clinical characteristics

To reduce the confounding effects of aging, only participants older than 65 years were included in the present study. There were a total of 95 participants (42 males, 53 females) with a mean age of 72.89±4.95 years, a mean duration of education of 11.05±4.16 years, and a mean mini-mental state examination score of 27.23±1.98. **Table 1** shows the clinical characteristics of 26 participants with amyloid PET (+) and 69 with amyloid PET (−). Participants with amyloid PET (+) had a higher frequency of apolipoprotein E4 genotype, lower z-score of the delayed recall score of the SVLT, and less lacunae and DWMHs on MRI. Severe DWMHs were not observed in any of the participants with amyloid PET (+).

Power spectral analysis

Relative power of delta band in participants with amyloid PET (+) was higher in the frontal (22.05%±8.55% vs. 17.66%±7.78%, p=0.025), parietal (18.47%±8.50% vs. 14.25%±6.93%, p=0.005), and occipital (16.89%±8.36% vs. 11.60%±8.40%, p=0.022) areas (**Fig. 1**), even after adjusting for age, sex, and education. Relative power in alpha 1 band in participants with amyloid PET (+) was lower in frontal (19.54%±12.39% vs. 27.63%±17.40%), central (18.00%±10.83% vs. 25.18%±15.27%), and occipital (25.97%±16.37% vs. 36.86%±21.58%) regions (**Fig. 1**), although the significance disappeared after adjusting for confounding factors.

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Table 1. Clinical characteristics of participants with subjective cognitive decline (with or without amyloid uptake)

Characteristics	Amyloid negative (n=69)	Amyloid positive (n=26)	*p*-value
Age (yr)	72.55±4.69	73.81±5.59	0.272
Sex, male:female	26:43	16:10	0.063
Education (yr)	10.57±4.10	12.35±4.12	0.063
APOE4	7 (10.1)	12 (46.2)	< 0.001
FHx	21 (30.4)	9 (34.6)	0.805
MMSE	27.39±1.84	26.81±2.28	0.201
Neuropsychological assessment (z-score)			
DST-F	0.67±1.11	0.49±1.22	0.485
K-BNT	0.49±1.07	0.22±1.06	0.265
RCFT	0.24±0.64	0.31±0.60	0.631
SVLT	−0.61±0.45	−0.82±0.49	0.049
RCFT-DR	0.05±0.74	−0.14±0.89	0.301
DSC	0.49±0.97	0.13±1.08	0.116
COWAT	0.14±0.90	0.32±1.32	0.437
K-TMT-EB	0.33±0.62	0.20±0.66	0.388
K-CWST-CR	0.15±0.77	−0.06±0.94	0.274
MRI			
Lacune, number	0.17±0.45	0.04±0.20	0.045
CMB, number	0.07±0.26	0.12±0.33	0.507
DWMH (range)	1.46±0.68 (1–3)	1.12±0.33 (1–2)	0.001
PVH (range)	1.61±0.77 (1–3)	1.46±0.76 (1–3)	0.407
MTA-L (range)	1.38±0.99 (0–4)	1.31±0.88 (0–3)	0.755
MTA-R (range)	1.23±0.91 (0–4)	1.23±0.76 (0–3)	0.996

Values were presented as means ± standard deviations or raw numbers of participants. Analyses were performed using the independent *t*-test, χ^2 test, Mann-Whitney *U* test, or Fisher's exact test.
APOE4: apolipoprotein E4, FHx: family history of dementia, MMSE: mini-mental state examination, DST-F: Digit Span Test-Forward, K-BNT: Korean version of Boston Naming Test, RCFT: Rey Complex Figure Test, SVLT: Seoul Verbal Learning Test, RCFT-DR: Rey Complex Figure Test-delayed recall, DSC: Digit Symbol Coding, COWAT: Controlled Oral Word Association Test, K-TMT-EB: Korean version of Trail Making Test-Elderly Part B, K-CWST-CR: Korean version of Color Word Stroop Test-Color Reading, MRI: magnetic resonance imaging, CMB: cerebral microbleed, DWMH: deep white matter hyperintensity, PVH: periventricular white matter hyperintensity, MTA-L: medial temporal atrophy-left, MTA-R: medial temporal atrophy-right.

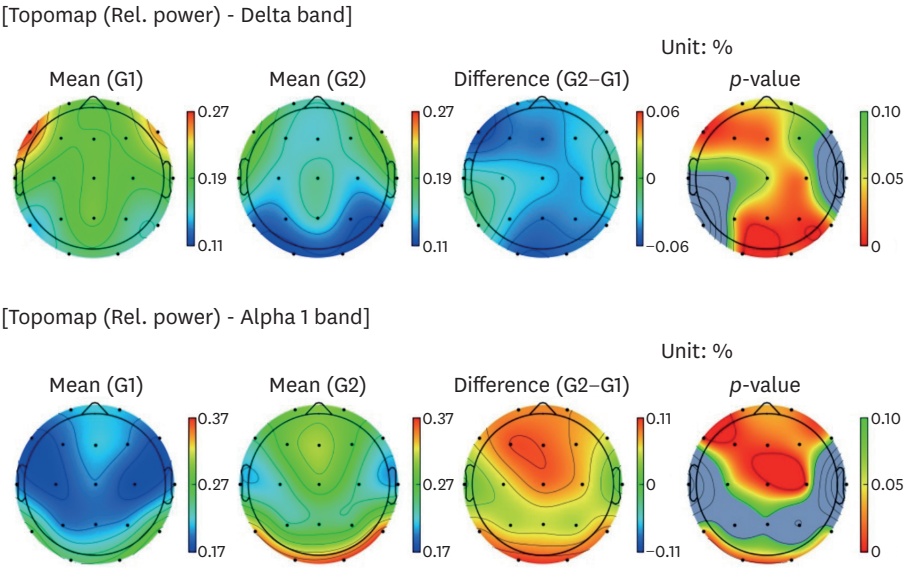

Fig. 1. Scalp topographies of relative electroencephalogram power differences between subjective cognitive decline participants with and without amyloid uptake. In participants with amyloid PET (+), delta power was higher in the frontal, parietal, and occipital areas but alpha 1 power was lower in frontal, central, and occipital regions. Even after adjusting for age, sex, and education, relative power of delta band was higher in the frontal (22.05%±8.55% vs. 17.66%±7.78%, p=0.025), parietal (18.47%±8.50% vs. 14.25%±6.93%, p=0.005), and occipital (16.89%±8.36% vs. 11.60%±8.40%, p=0.022) areas.
PET: positron emission tomography, G1: amyloid positron emission tomography (+), G2: amyloid positron emission tomography (−).

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[Delta/alpha ratio (DAR)]

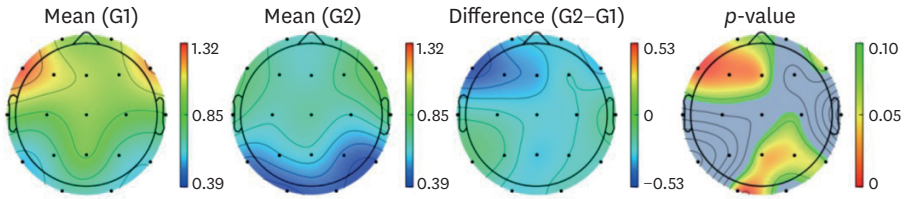

Fig. 2. Power ratios between subjective cognitive decline participants with and without amyloid uptake. Participants with amyloid PET (+) had increased DAR values in the frontal area. Participants with amyloid PET (+) had a greater slow-to-fast-wave power ratio.
PET: positron emission tomography, G1: amyloid positron emission tomography (+), G2: amyloid positron emission tomography (−), DAR: delta-to-alpha.

Differences in 3 power ratios, TBR, TAR, and DAR, were also compared between the 2 groups. After adjusting for age, sex, and education, participants with amyloid PET (+) had increased DAR values in the frontal area (1.095±0.831 a.u. vs. 0.731±0.682 a.u., p=0.044) (**Fig. 2**). Participants with amyloid PET (+) had a higher slow-to-fast-wave power ratio than those with amyloid PET (−). However, there was no other difference, when TBR or TAR was analyzed as the power ratio parameter.

Cortical source analysis

Neuronal sources with significant differences in delta and alpha 1 relative powers according to amyloid positivity were localized in widespread brain regions based on sLORETA analysis (**Fig. 3A**). Even after adjusting for age, sex, and education, alpha 1 oscillatory activity in the bilateral fusiform (p=0.048 in the left side and 0.035 in the right side) and inferior temporal areas (p=0.043 in the left side and 0.014 in the right side) were significantly decreased in participants with amyloid PET (+). Delta oscillatory activity of the bilateral cuneus (both, p=0.001), pericalcarine (p=0.011 in the left side and 0.003 in the right side), lingual (p=0.022 in the left side and 0.005 in the right side), lateral occipital (p=0.017 in the left side and 0.004 in the right side), precuneus (both, p=0.002), posterior cingulate (p=0.002 in the left side and 0.004 in the right side), and isthmus (p=0.003 in the left side and 0.004 in the right side) areas were significantly increased in participants with amyloid PET (+). **Fig. 3B and C** shows differences in DMN between groups with and without amyloid uptake. Participants with amyloid PET (+) showed increased connections between bilateral precuneus (p=0.042) and decreased connections between the left rostral middle frontal area and bilateral frontal poles (p=0.018 on the left side and 0.028 on the right side) in the delta frequency band after adjusting for age, sex, and education. There were more differences in connections in the alpha 1 frequency band between groups with and without amyloid uptake. Among them, connections between bilateral entorhinal areas decreased significantly (p=0.023) even after controlling for age, sex, and education. These significant source activities were combined into 68 regions of interest based on anatomic location and frequency band.

DISCUSSION

In the present study, decreased alpha 1 (in frontal, central, and occipital areas) but increased delta (in frontal, parietal, and occipital areas) powers were observed in SCD participants with amyloid PET (+) who had a higher slow-to-fast-wave power ratio such as DAR, especially in frontal areas. Cortical source analyses showed decreased alpha 1 in the bilateral fusiform

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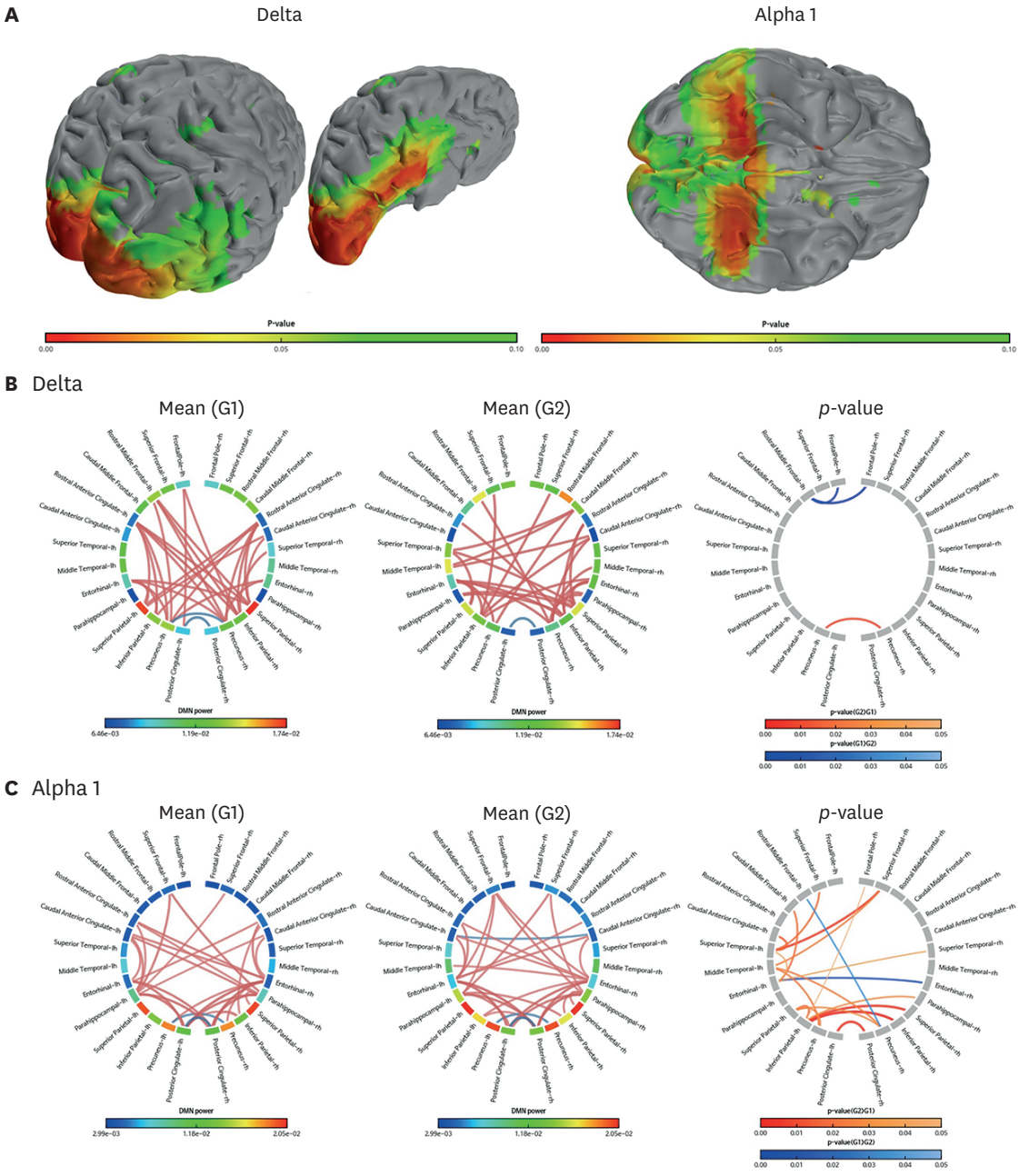

Fig. 3. Findings of neural sources with significant relative power change in delta and alpha 1 frequency bands between SCD participants with and without amyloid uptake. (A) Using the standardized low-resolution brain electromagnetic tomography, participants with amyloid PET (+) showed significantly decreased source activities of alpha 1 oscillatory activities in the bilateral parahippocampal, fusiform, inferior temporal, precuneus, posterior cingulate, lateral occipital, cuneus, and pericalcarine areas. In addition, in the bilateral cuneus, pericalcarine, lingual, lateral occipital, precuneus, posterior cingulate, and isthmus areas, delta oscillatory activity was significantly increased (B, C). In the default mode network, SCD participants with amyloid PET (+) showed more connections between bilateral precuneus but less connections between bilateral frontal poles and left rostral middle frontal area in the delta frequency band, even after adjusting for age, sex, and education. For the alpha 1 frequency band in participants with amyloid PET (+), more connections were observed between right parahippocampal and superior parietal areas and left inferior parietal area. Specifically, connections between bilateral entorhinal areas were decreased after adjusting for confounding factors.
SCD: subjective cognitive decline, PET: positron emission tomography, G1: amyloid positron emission tomography (+), G2: amyloid positron emission tomography (–).

and inferior temporal areas but increased delta in the bilateral cuneus, pericalcarine, lingual, lateral occipital, precuneus, posterior cingulate, and isthmus areas. Alpha 1 bands showed increased connections globally. Delta bands showed increased connections in the

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posterior areas but decreased connections in the anterior areas. These findings suggest that qEEG measurements are associated with and possibly sensitive to amyloid PET results, even in participants with SCD. Thus, qEEG measurements are promising early noninvasive biomarkers for AD.

The finding of reduced alpha 1 power in SCD participants with amyloid PET (+) was similar to previous EEG studies on MCI and AD dementia.[32,33] As older adults with normal cognition progress through MCI to very mild AD, the generalized relative power of alpha frequency was reduced on the earliest EEG. Babiloni et al.[34] showed the results of mapping distributed sources of cortical rhythms in mild AD, using the sLORETA. They reported alpha power reduction as a hallmark of mild AD and that EEG change was specific in the central, parietal, temporal, and limbic regions and pronounced in the parietal, temporal, and cortical regions. In contrast, activity changes at a slower frequency, and their relationships with cognition were less consistent.[35,36] Delta activity was not different between cognitively normal adults and early mild AD patients. However, patients with moderate-to-severe AD accounted for a significantly greater percentage of total EEG power than both cognitively normal adults and mild AD patients. Furthermore, delta activity was an excellent predictor of dementia severity.[37] In qEEG studies, a reduction of mean frequency was observed with increases of delta and theta powers and parallel decreases of alpha and beta powers in patients with AD than in cognitively normal older adults.[26,38]

The major source of alpha activity is the thalamo-cortical reciprocal relay neurons, particularly the parietooccipital areas, and the intercortical projecting neurons.[39] Reduced alpha activities may reflect early neuropathological changes in MCI and very mild AD. Alpha amplitude is negatively correlated with progressive atrophy of the hippocampus and cortical gray matter in patients with MCI and AD.[40,41] Conversely, increased slow wave activity has been associated with reduced cerebral blood flow[42,43] and diminished cholinergic neuronal activities.[44] Another possible mechanism explaining the increased slow EEG activities in AD can be based on Aβ and cholinergic deficits. Aβ disrupts muscarinic signaling[45] and reduces acetylcholine synthesis and release.[46] Concurrently, decreased cortical cholinergic activities are related to increased slow EEG activities.[47] Thus, the negative effect of Aβ on the brain cholinergic transmission could increase the activities of low-frequency waves.

The present study had several limitations. First, this was a cross-sectional, observational study. Therefore, longitudinal studies are needed to confirm that changes in qEEG parameters have prognostic potential. Previous studies showed that an early increase in the theta activity, accompanied by decreased beta and subsequently decreased alpha waves and a late increase in delta power resulted in general EEG slowing.[18] However, the decrease gets less pronounced once neurodegeneration and neuronal loss reach a critical level. Widespread increases in theta power and mean frequency as the hallmark of early AD were followed by the changes of alpha and delta powers in advanced dementia.[48,49] Second, this study only compared 2 SCD groups with and without amyloid uptake without comparing SCD with cognitively normal controls. Extending this study to include cognitively normal controls and alternative neuroimaging modalities of synaptic dysfunction, and brain functional connectivity could provide more valuable information.

SCD was thought to be caused by anxiety and depression in the past, but it tends to be seen as a part of AD spectrum because SCD subjects show a higher tendency to develop AD based on previous longitudinal studies.[50] According to the 2011 National Institute on Aging and

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Alzheimer's Association, preclinical AD stage 3 is defined as when there are biomarkers of amyloid accumulation and early neurodegeneration with evidence of subtle cognitive decline.[5] Preclinical AD stage 3 is the last stage before MCI, represented as SCD, and the risk of progression to MCI or AD for 5 years is 34.2% and 10.7%, respectively.[51] Therefore, SCD can be considered the best time for the prevention and treatment of MCI and AD. Notably, recently, disease modifying drugs have been developed to slow the onset and progression of AD dementia, but most of drugs have failed. The most plausible explanation for failure is improper timing and therefore late AD treatment initiation where treatment may have started after brain tissue injury in AD.[52] Therefore, AD related clinical studies should begin in the preclinical stage in the future.[53] Identifying risk factors which strongly predict amyloid positivity in SCD would facilitate the process of clinical trial recruitment and help in studying AD pathogenesis.

In conclusion, results from the qEEG power and source analysis were different according to the amyloid PET findings in participants with SCD. The qEEG is a potential noninvasive method for early detection of amyloid pathology in older adults with SCD. Further longitudinal studies are needed to confirm the predictive value of qEEG findings in SCD for clinical progression to MCI and AD.

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