

# Differences Between Encoding and Retrieval Failure in Mild Cognitive Impairment: Results from Quantitative Electroencephalography and Magnetic Resonance Volumetry

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## Research

**Keywords:** Mild cognitive impairment, encoding, retrieval, EEG, MRI, qEEG, voxel-based morphometry

**Posted Date:** July 7th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-40373/v1>

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**Version of Record:** A version of this preprint was published on January 4th, 2021. See the published version at <https://doi.org/10.1186/s13195-020-00739-7>.

# Abstract

**Background:** Memory impairments in mild cognitive impairment can be classified into encoding (EF) and retrieval (RF) failure. We explored differences between the two using quantitative electroencephalography (qEEG) and magnetic resonance imaging volumetry.

**Methods:** We compared qEEG power spectra and connectivity between 87 participants with EF and 78 with RF, and gray matter (GM) volume differences between participants with mild cognitive impairment and 71 controls. Demographic and cognitive assessment results between groups were compared with Student's *t*-tests, and obtained qEEG features were analyzed according to statistically significant differences between the groups using iSyncBrain™. GM volume changes underlying EF and RF in amnestic mild cognitive impairment were compared on processed magnetic resonance images of cognitively normal subjects using Student's *t*-tests, with age and total intracranial volume classified as nuisance covariates. We used a voxel-based morphometry analysis to demonstrate significant atrophic GM areas in the two types of patients with amnestic mild cognitive impairment. Results were considered statistically significant at  $p < 0.05$  and were corrected for family-wise errors to avoid multiple-comparison problems.

**Results:** qEEG showed higher frontal theta and lower beta2 band power and higher theta and lower beta connectivity in patients with EF. GM volume reductions due to EF in the left thalamus and bilateral hippocampi and reductions due to RF in the left thalamus, right superior frontal lobe, right superior temporal lobe, and right middle cingulum were observed.

**Conclusions:** Patients with mild cognitive impairment differ functionally and structurally according to their specific memory impairments. EF findings are more consistent with the prodromal Alzheimer's disease stage than RF findings. Since this study is a cross-sectional study, prospective follow-up studies are needed to investigate whether different types of memory impairments can predict the underlying pathology of amnestic MCI. Additionally, insufficient sample size may lead to ambiguous statistical findings in direct comparisons, a larger patient cohort could more robustly identify differences in GM volume reductions between the EF and the RF group.

## 1. Background

Mild cognitive impairment (MCI) is considered an intermediate stage in the trajectory from normal cognition to dementia [1]. MCI is subdivided into non-amnestic and amnestic types and single and multiple domains [2]. Many studies have suggested that the subtypes have different etiologies and future outcomes [2]. Traditionally, non-amnestic MCI is hypothesized to progress to non-Alzheimer's disease (AD) dementia such as frontotemporal lobar degeneration, dementia with Lewy bodies, Parkinson disease with dementia, vascular dementia, or primary progressive aphasia [3]. In contrast, amnestic MCI is hypothesized to be the prodromal stage of dementia due to AD [3]. Approximately 80% of patients with amnestic MCI progress to AD dementia within 6 years [4].

According to memory impairment patterns, amnestic MCI can be divided into two subtypes that show either encoding or retrieval failure [5]. Encoding failure (EF) is a problem of both storing and recalling of information, while retrieval failure (RF) is a problem of recalling only, with intact storing processes in long-term memory [5]. It has been suggested that EF originates from hippocampal dysfunctions such as those observed in AD, and that RF is rather caused by frontal or subcortical dysfunctions [6, 7].

Regarding clinical implications, however, the subtyping of amnestic MCI into EF and RF has drawn little attention so far. Although several studies have investigated clinical characteristics or prognostic values of EF and RF in amnestic MCI [8–10], there is no comprehensive approach to understanding the disease entity. In this study, we thus aimed to explore functional and structural differences between EF and RF using quantitative electroencephalography (qEEG) and magnetic resonance imaging (MRI) volumetry.

## 2. Subjects And Methods

### 2.1 Subjects

This retrospective study used the qEEG and three-dimensional T1-weighted MRI (3D T1 MRI) data of patients who visited the Chung-Ang University Hospital Department of Neurology from January 2012 to May 2019 and were diagnosed with single-domain amnestic MCI. This study was approved by the institutional review board of our center (IRB number 1802-004-16143). Written informed consent was obtained from all participants.

Participants were aged 55 years or older, underwent 3D T1 MRI and qEEG within 2 weeks, and met the single-domain amnestic MCI criteria. The criteria were as follows: (1) presence of memory complaints; (2) intact performance of activities of daily living; (3) objective verbal memory impairments on the Seoul Neuropsychological Screening Battery (at least 1.0 SD below age- and education-adjusted norms); (4) Clinical Dementia Rating of 0.5 (1); and (5) not demented according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria. Subjects were divided into an EF MCI and an RF MCI group. EF was defined as both delayed recall and recognition scores on a verbal learning test below 1.0 SD; RF was defined as only a delayed recall score below 1.0 SD. Resting-state EEG data were obtained from all 165 patients with amnestic MCI comprising 87 with EF and 78 with RF. 3D T1 MRI data were available for brain volume analysis for 147 of all subjects with amnestic MCI (for 78 with EF and 69 with RF) because of problems in the preprocessing of images (Fig. 1).

The 3D T1 MRI imaging data of 71 age-matched normal control (NC) subjects were selected from the repository. The inclusion criteria for NCs were as follows: (1) from a community-based population; (2) no abnormalities based on a health screening questionnaire [11]; (3) absence of memory complaints; (4) a Korean Dementia Screening Questionnaire score  $\leq 6$  [12]; (5) a Mini-Mental State Examination (MMSE) score  $> 26$ ; (6) intact activities of daily living (K-IADL  $\leq 0.42$ ); (7) no history of thyroid dysfunction, vitamin B12 deficiency, or folate deficiency; and (8) at least 6 years of education.

No participant presented any structural abnormalities on MRI, such as territorial infarctions, intracranial hemorrhage, brain tumors, or hydrocephalus; lacunar infarcts or mild to moderate subcortical or periventricular white matter hyperintensities did not lead to exclusion.

## 2.2 qEEG analysis

Resting-state EEG was conducted using the standard 10–20 system (21 electrodes) and a digital electroencephalograph (Comet AS40 amplifier EEG GRASS; Telefactor, USA) (Jaspers, 1958), and all electrodes were referred to linked ear references. Electrode skin impedance was always below 5 kΩ. The EEG signal was analog-filtered with a band pass of 0.5–70 Hz and digitized and stored on magnetic disks for further analysis. EEG sampling was conducted with eyes open for 30 seconds and with eyes closed for 30 seconds, 10 times, at a rate of 200 Hz. The measured eyes-open and eyes-closed data were converted according to the linked ear reference and stored in text format without filtering. While resting-state EEG data were recorded, patients were lying down in a resting position in a sound-attenuated room. EEG noise preprocessing and group analyses were conducted using iSyncBrain™ (iMediSync, Inc., Korea) (<https://isyncbrain.com/>), a cloud-based, artificial intelligence EEG analysis platform. The eyes-closed EEG segments were uploaded to iSyncBrain™. Prior to data analysis, artifacts in the raw data were removed by visual inspection and an advanced mixture independent component analysis (amICA) [13]. All preprocessing steps, denoising using an amICA, and qEEG feature extraction were performed on iSyncBrain™. qEEG features were obtained at the sensor and at the source level. At the sensor level, relative power at eight frequency bands (delta [1–4 Hz], theta [4–8 Hz], alpha1 [8–10 Hz], alpha2 [10–12 Hz], beta1 [12–15 Hz], beta2 [15–20 Hz], beta3 [20–30 Hz], and gamma [30–45 Hz]) was calculated using a power spectrum analysis. In addition, power ratios (TBR2: theta/beta2) according to frequency bands were calculated. In the source level analysis, the current distribution across the brain was assessed using the standardized low resolution brain electromagnetic tomography technique [14], to compare relative power values in 68 regions of interests (ROIs) [15] and connectivity (the imaginary part of coherency) [16] between ROIs. EEG coherence has been studied as a measure of brain connectivity [17], and the imaginary part of coherency (iCoh) has been introduced to avoid volume conduction artifacts [16].

## 2.3 MRI Volumetry

To determine gray matter (GM) volume changes underlying EF and RF in amnestic MCI, we conducted voxel-based morphometry (VBM) on MRI scans acquired on 3-T scanners manufactured by Philips (Achieva, Amsterdam, the Netherlands). The data were analyzed using the Computational Anatomy Toolbox (CAT12) running on Statistical Parametric Mapping software (SPM12). CAT12 is a VBM toolbox designed by The Structural Brain Mapping Group at the University of Jena (Jena, Germany). First, the DICOM files were converted into nifti format, using MRICRON software (<http://people.cas.sc.edu/rorden/mricron/index.html>). VBM preprocessing was performed using the default settings of the CAT12 toolbox and the “East Asian Brains” ICBM template. Imaging files were normalized using an affine model, followed by non-linear registration, corrected for bias field inhomogeneities, and then segmented into GM, white matter (WM), and cerebrospinal fluid (CSF)

components. The segmented scans were normalized into standard Montreal Neurological Institute space using the Diffeomorphic Anatomic Registration Through Exponentiated Lie (DARTEL) algebra algorithm. The modulation process on the normalized, segmented images consisted of a non-linear deformation, which corrects individual differences in brain size. We reviewed morphological abnormalities and applied smoothing processes to all segmented, modulated, and normalized GM images using an 8-mm full-width-half-maximum Gaussian filter.

## 2.4 Statistical analysis

To compare demographic and cognitive assessment results between groups, Student's *t*-tests for continuous variables were performed. We used IBM SPSS version 25 (IBM, Armonk, NY, USA) for all analyses. Statistical significance was set at  $p < 0.05$ . The obtained qEEG features were analyzed according to statistically significant differences between the EF and RF groups using iSyncBrain™ ( $p < 0.05$ ), and results at the sensor and the source level are presented separately. To demonstrate GM volume changes underlying EF and RF in amnestic MCI, we conducted a comparison with processed MR images of cognitively normal subjects using Student's *t*-tests. Age and total intracranial volume (TIV), that is, the sum of the GM, WM, and CSF volumes, were classified as nuisance covariates in the GM volume comparisons between the groups. We used a VBM analysis to demonstrate significant atrophic GM areas in the two types of patients with amnestic MCI. To detect GM volume differences between patients with EF and those with RF, Student's *t*-tests were also conducted on the processed images. Age and TIV were again classified as nuisance covariates in the GM volume comparisons between groups. Absolute threshold masking was used at a threshold of 0.1. Results were considered statistically significant at  $p < 0.05$  and were corrected for family-wise errors to avoid multiple-comparison problems.

## 3. Results

### 3.1 Study subjects

The mean age of all subjects with amnestic MCI was 73.5 years, and their mean MMSE score was 22.4. There was no significant difference between the EF and RF groups in baseline demographics or clinical status ( $p > 0.05$ , Table 1). The mean age of all patients with EF was  $70.4 \pm 10.5$  years, that of the patients with RF was  $74.0 \pm 7.6$  years, and that of the NCs ( $n = 71$ ) was  $70.4 \pm 3.9$  years.

Table 1  
Characteristics of subjects with encoding (EF) and retrieval failure (RF)  
due to mild cognitive impairment

	EF (n = 87)	RF (n = 78)
Age (years ± std)	73.8 ± 8.3	73.4 ± 6.2
Male/Female	39/48	20/58
Education (years ± std)	9.4 ± 5.7	8.0 ± 4.9
MMSE	21.3 ± 6.3	23.4 ± 5.7
CDR	0.49 ± 0.15	0.47 ± 0.11
CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination.		

## 3.2 qEEG sensor level analysis

In the sensor level analysis, the EF group showed significantly higher frontal theta power than the RF group (Fig. 2 (A)). A higher average of theta power values across all channels was also observed in the EF group, as well as lower beta2 power in the frontal, central, temporal, and parietal regions (Fig. 2 (B)). There were no significant power differences in the delta, alpha1, alpha2, beta1, beta3, and gamma bands between the groups. In the power ratio analysis, TBR2 was significantly higher in the EF than in the RF group in the frontal region (Fig. 3).

## 3.3 qEEG source level analysis

Figure 4 shows the statistically significant difference between the EF and RF groups for the source power of 68 ROIs and the connectivity between the ROIs in the theta and beta2 bands. The theta band power in seven ROIs (bilateral superior frontal, left rostral middle frontal, left caudal middle frontal, left medial orbitofrontal, and bilateral caudal anterior cingulate regions) was significantly higher in the EF group. The EF group also showed a higher connectivity in the theta band than the RF group. In contrast, beta2 band power was significantly lower in 46 ROIs in the EF group, and these ROIs also showed lower connectivity. At the source level, significant differences in TBR2 between the groups were observed in the frontal and cingulate regions ( $p < 0.05$ ).

## 3.4 GM volume changes in amnestic MCI

In the VBM analysis, statistically significant atrophic areas in patients with amnestic MCI were overlaid onto an average structural image of the NC group. In amnestic MCI, significant GM atrophy was observed in the left thalamus and precuneus, the bilateral, dorsolateral, and medial temporal areas, the bilateral frontal, and several other areas (Fig. 5 (A) and Table 2). The GM volume reductions underlying EF were located in the left thalamus and the bilateral hippocampi, while those underlying RF were located in the left thalamus, right superior frontal lobe, right superior temporal lobe, and right middle cingulum (Fig. 5

(B) and Table 2). However, the brain volume differences between the RF and EF group were not significant (uncorrected  $p > 0.005$ ).

Table 2

Gray matter volume reductions in amnestic mild cognitive impairment, compared to age-matched normal controls

	x, y, z coordinate			label	Cluster level		Peak level		
					P(FWE- corr)	equivk	P(FWE- corr)	T	equivZ
Amnestic MCI	21	-21	12	Thalamus Lt	< 0.001	2324	< 0.001	7.84	7.34
	-12	-41	6	Precuneus Lt			< 0.001	5.75	5.54
	-30	-21	-23	Parahippocampus Lt			0.001	5.62	5.42
	53	0	-11	Temporal Sup Rt	< 0.001	1573	< 0.001	5.70	5.49
	60	-21	-14	Temporal Mid Rt			0.001	5.48	5.30
	51	-9	-23	Temporal Mid Rt			0.002	5.37	5.19
	12	20	32	Cingulum Mid Rt	< 0.001	567	< 0.001	5.68	5.47
	12	30	33	Cingulum Mid Rt			0.003	5.23	5.07
	14	33	24	Cingulum Mid Rt			0.006	5.09	4.94
	-29	21	42	Frontal Mid Lt		371	< 0.001	5.66	5.46
	-29	33	33	Frontal Sup Lt			0.001	5.45	5.26
	-36	21	33	Frontal Mid Lt			0.009	4.99	4.85
	36	33	24	Frontal Mid Rt		241	0.001	5.63	5.4
	29	27	38	Frontal Mid Rt			0.003	5.23	5.06
	-45	9	-24	Temporal Pole Sup Lt		433	0.001	5.53	5.34
	-27	-3	48	Precentral Lt		166	0.001	5.47	5.28
	12	51	32	Frontal Sup Medial Rt		328	0.001	5.41	5.23
	18	41	35	Frontal Sup Rt			0.002	5.38	5.20
	23	51	23	Frontal Sup Rt			0.003	5.24	5.07
	33	-23	-20	Parahippocampus Rt		621	0.002	5.32	5.15
	30	-5	-30	Parahippocampus Rt			0.004	5.19	5.03

FWE, p < 0.05. Local maximum more than 8.0 mm apart. MCI, mild cognitive impairment; FWE, family-wise error; Rt, right; Lt, left; Sup, superior; Mid, middle.

	27	-32	-3	Hippocampus Rt		225	0.004	5.15	5.00
Encoding failure	-20	-20	14	Thalamus Lt	< 0.001	2926	< 0.001	6.7	6.25
	-12	-38	6	Hippocampus Lt			< 0.001	6.59	6.15
	-26	-23	-9	Hippocampus Lt			< 0.001	6.34	5.95
	26	-33	-3	Hippocampus Rt	< 0.001	879	< 0.001	6.32	5.93
	29	-26	-8	Hippocampus Rt			< 0.001	6.12	5.76
	32	-23	-17	Hippocampus Rt			< 0.001	5.79	5.49
	30	-5	-30	Parahippocampus Rt	0.002	160	< 0.001	6.02	5.68
Retrieval failure	-21	-23	9	Thalamus Lt	0.001	201	0	6.61	6.14
	17	11	59	Frontal Sup Rt	0.002	174	0	5.86	5.53
	51	0	-11	Temporal Sup Rt	< 0.001	390	0.002	5.53	5.24
	44	-17	-9	Temporal Sup Rt			0.003	5.41	5.14
	44	-3	-18	Temporal Sup Rt			0.018	4.92	4.71
	11	26	36	Cingulum Mid Rt	0.004	111	0.005	5.25	5

FWE, p < 0.05. Local maximum more than 8.0 mm apart. MCI, mild cognitive impairment; FWE, family-wise error; Rt, right; Lt, left; Sup, superior; Mid, middle.

\*\*\*\*\* add Table 2 here \*\*\*\*\*

## 4. Discussion

In this study, we explored functional and structural differences between patients with EF and RF using qEEG and GM volume. The qEEG analysis showed an increase in the theta power spectrum and a decrease in beta2 power in the EF group compared to the RF group. Additionally, the VBM analysis demonstrated decreased volumes in the left thalamus and the bilateral hippocampus in the EF but in the right frontal and temporal lobe in the RF group, when compared to the NCs. There was no statistically significant difference in GM volume reductions between the EF and the RF group.

The qEEG pattern observed in the EF group in our study was similar to the pattern observed for AD in numerous previous qEEG studies, which showed increased power in low frequency bands (delta and theta) and decreased power in high frequency bands (alpha and beta) [18–24]. A recent study suggested an increase in relative theta power as a first change in patients with AD [18]. During the disease progression of AD, an early increase in theta and decrease in beta is followed by a decrease in alpha and an increase in delta power [25, 26]. Patients with MCI have also shown increases in theta power and decreases in alpha power when compared with normal elderly subjects [21, 27, 28]. Additionally,

increased theta power and decreased parietal beta power may predict disease progression to AD in patients with MCI [29, 30]. Another study in non-demented and amyloid-positive subjects showed that higher delta and theta power were associated with clinical progression over time [31]. The patients with amnestic MCI with EF in the present study showed increased theta and decreased beta power when compared with the RF group in our power spectrum and ROI source power analyses. Regarding differences between brain regions at the electrode and source level, we observed an increase in the low frequency band in the EF group in the frontal area, and a decrease in the beta band in the tempo-parietal as well as the frontal area. This is consistent with reported EEG patterns as a predictive factor of clinical progression to AD [28, 31] and may be associated with an anterior shift in band frequency source [28]. Accordingly, disease progression to AD may be more easily predictable in patients with amnestic MCI with EF than in those with RF.

Additionally, the EEG connectivity pattern in patients with amnestic MCI with EF in our study seems similar to the AD pattern observed in previous studies. EEG coherence analyses in patients with AD showed a decrease in connectivity in all frequency bands, especially prominent in the alpha frequency band [21, 23, 24, 32, 33]. Furthermore, it has been shown that EEG coherence contributes to the discrimination of AD from normal aging [33] and progression to AD in patients with MCI [34]. Recently, Musaeus et al. reported significant differences in coherence and iCoh in the theta and delta bands between groups with progressive and stable MCI, while higher theta coherence was associated with cognitive decline [35]. In our present study, significant differences in iCoh between EF and RF were found in the theta and beta2 band. Patients with amnestic MCI with EF showed higher theta band connectivity in the frontal-frontal and frontal-temporal connections, but lower beta band connectivity in the temporal-cingulate connection, compared to those with RF. The higher theta coherence in patients with amnestic MCI with EF seems somewhat paradoxical under the hypothesis that EF rather than RF proceeds to AD. However, higher theta band coherence in MCI progressing to AD was also reported in a previous study [35], and one might speculate that this increased connectivity reflects a compensation effect in the early stage of AD. Additionally, our findings of increased theta connectivity in the anterior regions and decreased beta connectivity in the posterior regions in patients with amnestic MCI with EF may be related to the anterior shift of oscillation source in the progression to AD [28, 36, 37].

In our volumetric analysis, significant GM atrophy in the left thalamus and the bilateral hippocampi was observed in patients with amnestic MCI with EF, when compared to the NC group, whereas those with RF showed GM atrophy in the left thalamus, right superior frontal lobe, right superior temporal lobe, and right middle cingulum. These results may be explained by the fact that different brain regions are related to different memory functions. In earlier studies in animals and humans, the medial lobe structure, including the hippocampus, plays an important role in encoding new information and storing it in the neocortex [38, 39], while the dorsolateral prefrontal lobe is involved in retrieval through the frontal-subcortical neuronal circuit [40, 41]. Therefore, if amnestic MCI is divided into EF and RF, it can be assumed that the atrophy of the medial temporal lobe is more prominent in the group with EF, which is in accordance with our results. Additionally, these atrophic patterns including the volume of the hippocampus may be a good biomarker of AD, according to previous studies [42–45]. Although our VBM analysis demonstrated no significant

differences in atrophic cortical regions between the EF and RF groups, when compared to the NCs, the pattern patients with EF showed was more similar to the brain atrophy observed in AD than that observed in patients with RF.

## 5. Limitations

The current study was subject to several limitations. Since this study is a cross-sectional study, it cannot be confirmed that patients with amnesiac MCI patient with EF actually progress to AD. It is just assumed that amnestic MCI patient with EF is more likely to progress to AD than those with RF, as the patterns of qEEG, EEG connectivity, and cortical atrophy in the EF group were more similar to the patterns observed for AD in numerous previous studies. Therefore, longitudinal follow-up studies may be needed to investigate whether patients with amnestic MCI with EF can progress to AD. Additionally, insufficient sample size may lead to ambiguous statistical findings in direct comparisons. Although no significant differences in GM volume reductions between the EF and the RF group were observed, there were different atrophic patterns between the two when compared to the NCs. A larger patient cohort could more robustly identify differences between ER and RF.

## 6. Conclusions

Our findings indicate that patients with amnestic MCI with EF and those with RF differ functionally, and that both show different brain atrophy sites in comparison to NCs. By integrating power spectral, EEG coherence, and MRI volumetry analyses, we found that patients with EF due to amnestic MCI show a pattern that is more consistent with the prodromal stage of AD than the pattern observed in patients with RF. Prospective follow-up studies are needed to investigate whether different types of memory impairments can predict the underlying pathology of amnestic MCI.

## Declarations

## Competing interests

The authors declare that they have no competing interests.

## Funding

This work was supported by an Institute for Information & Communications Technology Promotion (IITP) grant funded by the Korean Government (MSIP) (No. 2017-0-01098: Development of technology for the prediction and diagnosis of cognitive impairment and dementia based on quantitative electroencephalography (QEEG) analyzed with machine learning).

# Authors' contributions

YCY & SWK designed and conceptualized the study. And YCY & SWK collected, analyzed and interpreted the data, and drafted and revised the manuscript. SHH, JP and DWK analyzed and interpreted the data, drafted and revised the manuscript. SY participated in conceptualization of the study, analysis and interpretation of the data. HTJ analyzed and interpreted the data, revised the manuscript. SYK interpreted the data, revised the manuscript. All authors read and approved the final manuscript.

# Acknowledgments

The authors wish to thank the staff at the department of Neurology at Chung-Ang University Hospital and Jaeyoung Youn at the Department of Korean Medicine at Sangji University, who contributed to the collection and preprocessing of the data presented here.

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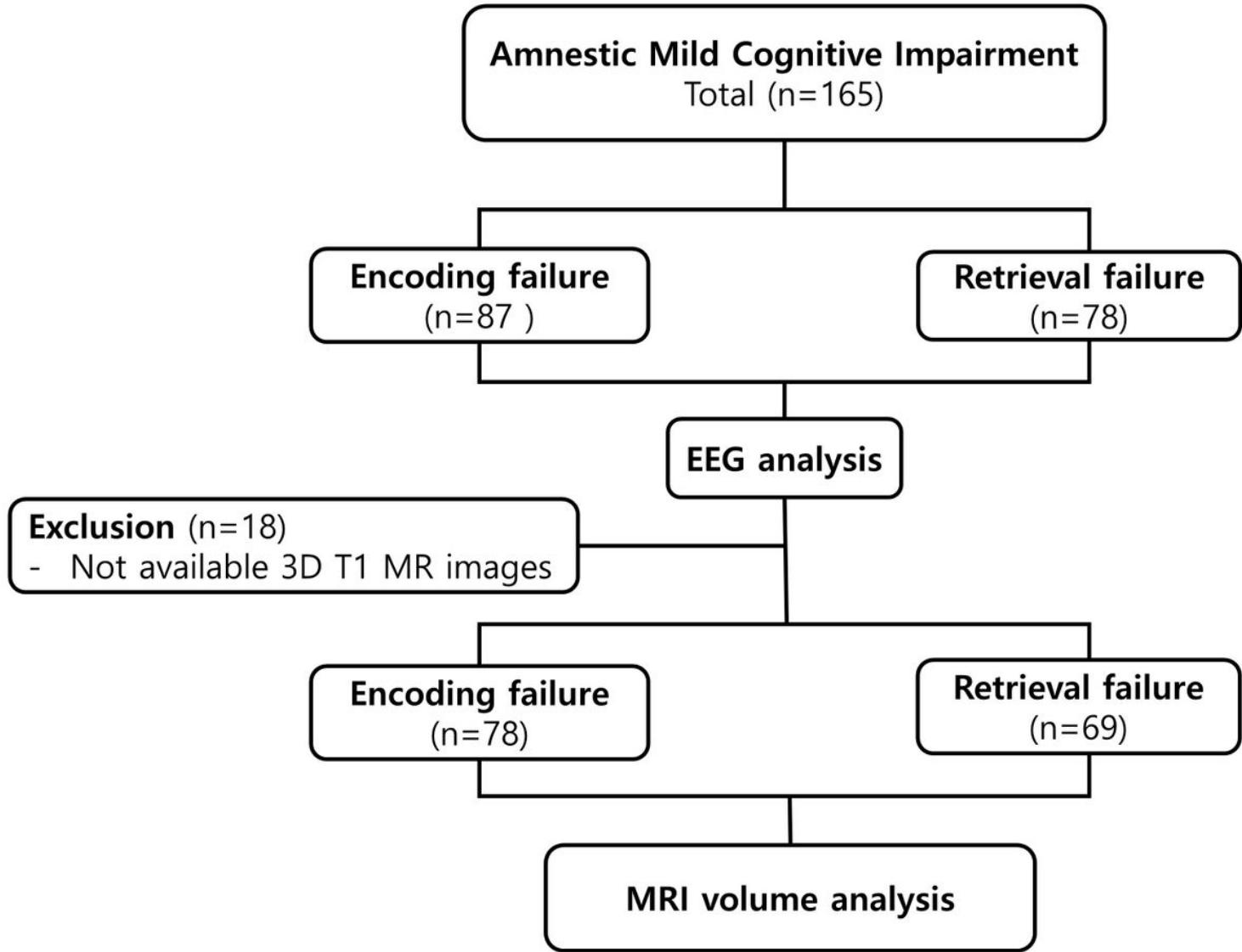
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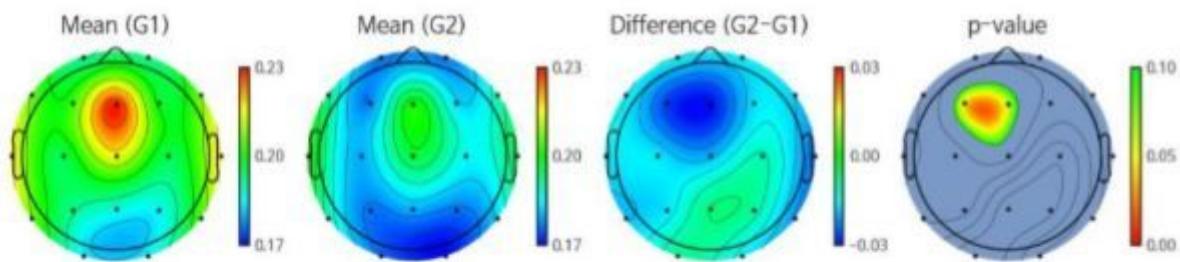
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## Figures

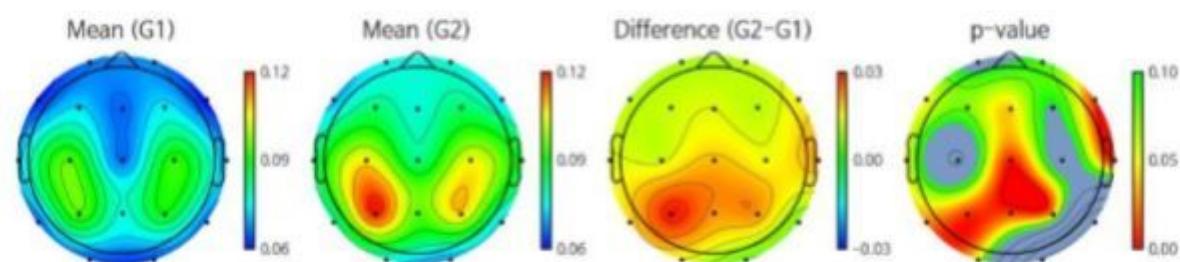


**Figure 1**

Enrollment of subjects with amnestic mild cognitive impairment



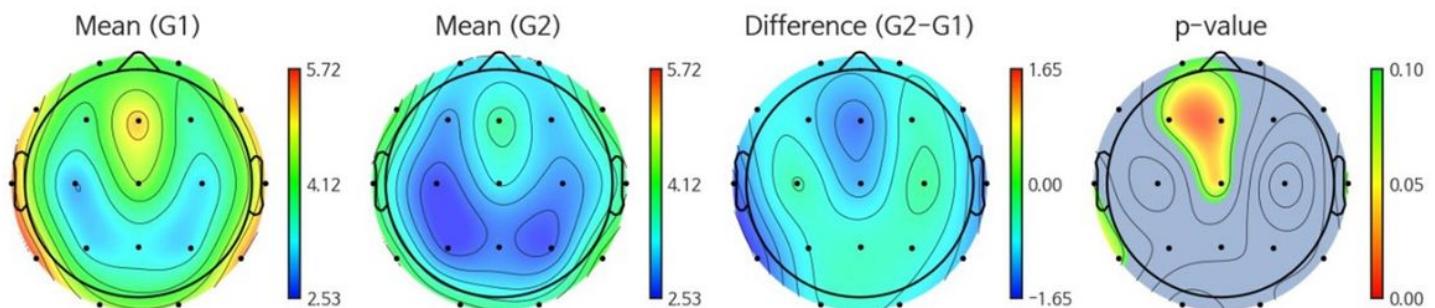
(A) Theta band power



(B) Beta2 band power

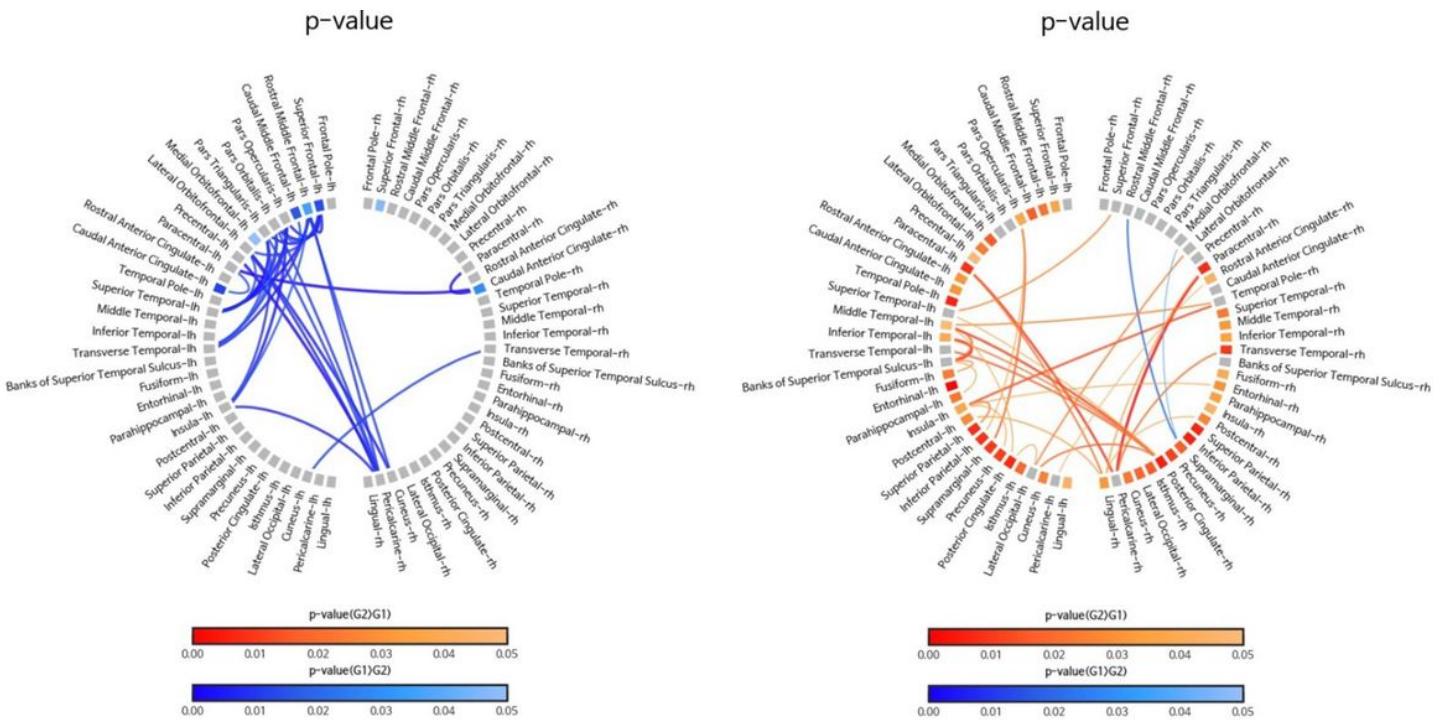
**Figure 2**

Band power for the encoding failure (G1) and retrieval failure (G2) group



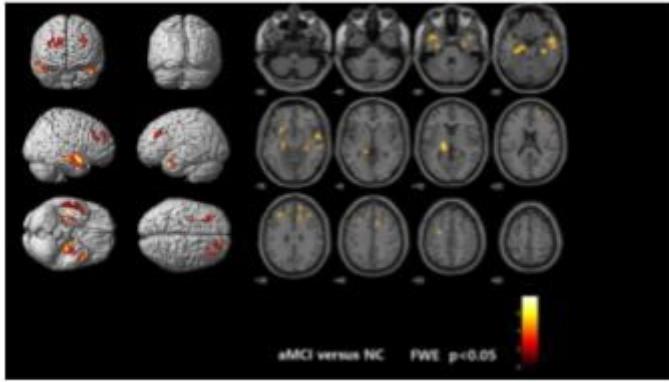
**Figure 3**

Power ratio (TBR2) for the encoding failure (G1) and retrieval failure (G2) groups

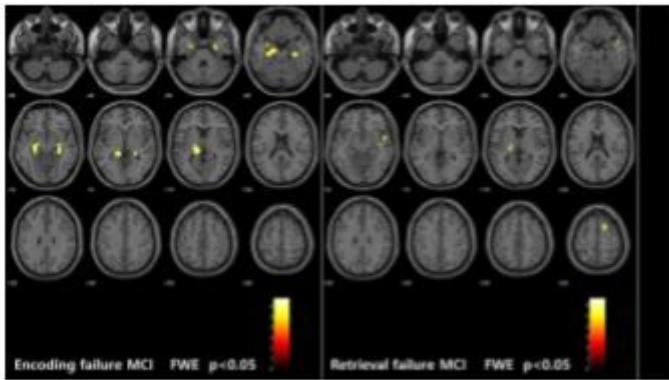


**Figure 4**

Source ROI power and connectivity between the encoding failure (G1) and retrieval failure (G2) groups  
 The left panel shows the theta band, the right panel the beta2 band. The blue color indicates greater significance in the G1 than in the G2 group. Red indicates the opposite.



(A)



(B)

**Figure 5**

Statistical parametric maps of gray matter volume reductions in aMCI(A) and the two subtypes(B) FWE, family-wise error; NC, normal control group; aMCI, amnestic mild cognitive impairment.