Analysis of Neuropsychiatric Symptoms in Patients with Alzheimer's Disease Using Quantitative EEG and sLORETA

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Keywords

Neuropsychiatric symptoms · Alzheimer's disease · Electroencephalography

Abstract

Objective: The electrocortical activities associated with the neuropsychiatric symptoms (NPSs) of Alzheimer's disease (AD) were investigated using frequency-domain electroencephalography (EEG) spectral source analysis, and the potential electrocortical indices identified. **Materials and Methods:** Scalp EEG data were obtained from 51 patients with AD to investigate the presence of four NPS subdomains, hyperactivity, psychosis, affective symptoms, and apathy. EEG power spectra and the standardized low-resolution brain electromagnetic tomography (sLORETA)-localized EEG cortical sources were compared between the groups with and without the four NPS subdomains in eight frequency bands: 1–4, 4–8, 8–10, 10–12, 12–18, 18–20, 20–30, and 30–45 Hz. **Results:** The power spectral analysis of EEG data showed that AD patients with psychosis had lower values at

the α_2 -band in most areas. In patients with apathy, the θ -to- β power ratio showed a greater activity over the frontal and central regions. The cortical source analysis using sLORETA revealed that patients with psychosis showed decreased values in the α_2 -band and patients with apathy showed higher δ -values, especially in the right frontal and temporal regions. **Conclusion:** The results of the present study showed that both classical EEG spectral and EEG source analysis could differentiate patients with and without NPSs, especially psychosis and apathy subdomains. Spectral and sLORETA analyses provided information helpful for a better characterization in patients with NPSs.

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that usually starts slowly and gradually worsens over time. Episodic memory loss is one of the earliest manifestations and is accompanied by word-find-

ing difficulty, visuospatial dysfunction, and executive function impairment [1, 2]. In addition to the cognitive symptoms, various neuropsychiatric symptoms (NPSs) emerge during the disease course, including delusions, depression, agitation, sleep disturbances, and eating problems, which can cause significant burden and stress to caregivers [3–6]. However, few therapies exist for the treatment of NPSs in dementia to date [7].

For many years, electroencephalography (EEG) has been used in the field of dementia as a noninvasive, less expensive, and easily available diagnostic and research method [8]. In previous studies, patients with AD exhibited slow EEG waves, reduced complexity of EEG signals, and loss in EEG synchrony [9]. Although visual inspection of EEG remains useful in clinical practice, one of the most common methods in the research field is quantitative EEG (qEEG) analysis [8, 10, 11]. In numerous studies, AD and mild cognitive impairment were associated with an increased power in low frequencies (e.g., δ - and θ -bands), and a decreased power in higher frequencies (α - and β -bands) [11]. In addition, increased global slow-to-fast power ratios were strongly correlated with AD progression [12–14].

Currently, few studies have reported on the association of EEG with the NPSs in patients with AD [15]. In a study on EEG complexity, identifying the neuropsychiatric correlates provided insight into how brain-specific regional activity is associated with these symptoms; disinhibition was associated with frontal EEG complexities, depression and anxiety were correlated with temporal and parietal complexity, and apathy, aberrant behavior, and sleep changes were correlated with parieto-occipital EEG changes [15]. NPSs can always be present during the disease course; however, specific symptoms are more common at different stages. Almost all symptoms worsen with disease severity; however, certain symptoms such as delusions, agitation, and apathy tend to become much more prevalent [16]. Evaluation of the frequency and region-specific qEEG changes associated with NPSs based on qEEG and brain structural change would be informative.

In the present study, the qEEG of patients with AD was evaluated to investigate the presence of NPSs such as hyperactivity, psychosis, affective symptoms, and apathy to determine whether qEEG frequencies and spectral powers differ by scalp region in patients with AD. Based on the hypothesis that NPSs can provide insight into possible relationships between clinical features and their underlying causal and/or risk factors, different therapeutic strategies targeting subsyndromes may be more effective.

Materials and Methods

Participants

The study group included 51 patients with AD (34 females, 17 males) who were recruited from the Dementia Clinic at the Catholic University of Korea, Bucheon St. Mary's Hospital, from January 2018 to December 2018. The diagnosis for AD was based on the criteria of the National Institute of Neurological and Communicative Disorders and the Stroke/Alzheimer's Disease and Related Disorders Association [17]. All patients received neurological examinations, laboratory tests, EEG monitoring, and neuroimaging evaluation during the diagnostic process. Retrospective analysis of the patients' clinical and EEG data was approved by the Institutional Review Board of the Catholic University of Korea, Bucheon St. Mary's Hospital. Subjects provided informed consent. Patients who had other conditions that might cause cognitive impairment, such as vascular dementia, Parkinson's disease, hypothyroidism, vitamin B₁₂ deficiency, syphilis, and history of major psychiatric illness (e.g., major depression, bipolar disorder, or schizophrenia) were excluded.

The severity of dementia was assessed using the Clinical Dementia Rating (CDR) scale [18], and general cognition was evaluated using the Mini-Mental State Examination (MMSE) [19]. NPSs were evaluated using the Neuropsychiatric Inventory (NPI) [3], and a score >3 was considered to indicate the presence of clinically relevant symptoms [20–24]. The 12 NPI items were classified into four subsyndromes, corresponding to hyperactivity (agitation, disinhibition, irritability, aberrant motor behavior), psychosis (delusions, hallucinations, night-time behavior disturbances), affective behaviors (depression, anxiety), and apathy (apathy, appetite and eating abnormalities) [25].

Patients who underwent qEEG and did not show an EEG abnormality were included in the present study. An EEG abnormality was defined as asymmetry of background activity, continuous θ -range slow waves, generalized or focal δ -range slow waves, or epileptiform discharges. Patients taking cholinesterase inhibitors, benzodiazepines, or antidepressants that could influence EEG rhythms were excluded [26]. There was no one taking antiepileptic drugs in the study participants.

EEG Recording

All participants received a routine EEG (COMET plus EEG, Grass Technologies Inc., West Warwick, RI, USA) in a specialized examination room as a part of the initial assessment before starting any specific AD therapy (e.g., acetylcholinesterase inhibitors). Procedures were performed on weekdays between 9 a.m. and 5 p.m.

EEG was recorded under waking-rest conditions (eyes closed) from 19 scalp electrodes positioned based on the International 10–20 System (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, and O2) with linked ear reference, 256 Hz sampling rate, high-pass filter of 1 Hz, low-pass filter of 70 Hz, notch filter of 60 Hz, and impedance below 5 k Ω . Activation maneuvers, including opening of eyes, hyperventilation, or photic stimulation were performed under instruction from technicians. Vigilance was monitored by the EEG technician who alerted patients when signs of drowsiness appeared in the tracings; 9–12 artifact-free 4-s epochs were finally obtained per patient. One independent investigator blinded to the diagnosis of participants visually confirmed the EEG segments were acceptable for further analyses.

Fig. 1. Absolute (a) and relative (b) electroencephalogram power spectra for each of the 19 channels in groups without (G1) and with (G2) psychosis. Blue letters indicate decreased power in G2.

EEG Analysis

For preprocessing steps, the EEG data were high-pass filtered offline above 1 Hz, low-pass filtered below 45 Hz, and recomputed to the common average reference. Transient artifacts were rejected with a visual inspection, and stationary artifact components originating from eye movement, muscle tensions, or heartbeat were removed using adaptive mixture independent component analysis [27].

Following the removal of artifacts from the EEG signals, sensor level analysis using spectopo function based on EEGLAB [20] was performed in the following eight spectral bands: δ (1–4 Hz), θ (4–8 Hz), α_1 (8–10 Hz), α_2 (10–12 Hz), β_1 (12–15 Hz), β_2 (15–20 Hz), β_3 (20–30 Hz), and γ (30–45 Hz). In the power spectral density 2-dimensional map, topomaps of absolute and relative power in 1-Hz bins (1–45 Hz) as well as each frequency band are presented. Absolute power is the sum of the component powers for each frequency band. Relative power is the absolute power in a specific frequency band divided by the total power. This feature provides absolute and relative power based on five brain regions (frontal, temporal, central, parietal, and occipital). The power spectra for each of the 19 channels are shown in the power spectral density spectrum, which presents the amplitude of power in units of microvolts squared per hertz or decibels per hertz to obtain the frequency characteristics of the α -band or β -band, respectively. Furthermore, the following band power ratios were calculated: θ -to- α (TAR), δ -to- α (DAR), and θ -to- β (TBR). Source reconstructions were performed using standardized low-resolution brain electromagnetic tomography (sLORETA) plugin [21] using a Colin 27 Head model [22] with 68 regions of interest segmentations based on the Desikan and Killiany atlas [23]. All preprocessing steps, denoising using adaptive mixture independent component analysis, sensor level feature extractions, and source level feature extractions were performed on iSyncBrain® [24].

Statistical Analysis

For the four NPSs (hyperactivity, psychosis, affective behaviors, and apathy), clinical characteristics and qEEG analyses were compared between patients with and without NPSs using the Mann-Whitney U test. Statistical significance was accepted for a p value < 0.05 and performed automatically using the iSyncBrain® [24] program.

Results

Clinical Characteristics

A total of 51 patients (17 males, 34 females) with AD were analyzed in the present study. The clinical characteristics were as follows: mean age 77.73 ± 7.28 years; duration of education 4.44 ± 3.90 years; MMSE score 16.36 ± 6.43 ; CDR score 1.16 ± 0.66 , range 0.5–3.0; CDR sum of boxes score 6.01 ± 3.83 , range 0–16.

Differences in age, sex, duration of education, MMSE score, CDR score, and CDR sum of boxes score were not observed between groups with and without the four NPSs (hyperactivity, psychosis, affective symptoms, and apathy), except for the distributions of sex between groups with and without affective symptoms (9 males:28 females vs. 8 males:6 females, $p = 0.028$). Although duration of education of patients was low, below 6 years, there was no difference between groups with and without the NPSs.

Fig. 2. Scalp topographies of absolute (a) and relative (b) electroencephalogram power differences between groups with (G2) and without (G1) psychosis in the α_2 -frequency band.

Power Spectral Analysis

Figure 1 shows the absolute and relative EEG power spectra for each of the 19 channels in groups without (G1) and with (G2) psychosis. Blue letters indicate decreased power in G2. Differences between groups with and without hyperactivity, affective symptoms, and apathy were not observed. The EEG power spectrum had lower values at the α_2 (10.0–12.0 Hz) frequency band in the channels of Fp1, Fp2, Fz, T3, Cz, T5, and Pz in AD patients with psychosis compared with patients without psychosis. This result was further confirmed by the scalp topographies of EEG power differences between groups with and without psychosis in the α_2 -frequency band (Fig. 2). Patients with psychosis showed decreased power of the α_2 -band in frontal (1.580 ± 1.395 vs. $2.590 \pm 1.897 \mu\text{V}^2$, $p = 0.016$), central (1.915 ± 1.917 vs. $2.838 \pm 2.354 \mu\text{V}^2$, $p = 0.044$), and temporal (2.219 ± 1.787 vs. $3.480 \pm 1.962 \mu\text{V}^2$, $p = 0.009$) areas. Over most scalp locations, the average power in α_2 (10–12 Hz) largely decreased in patients with psychosis.

Figure 3 shows power ratios (TBR, TAR, and DAR) between groups with and without apathy. Patients with apathy had increased TBR values in frontal (3.634 ± 2.568

vs. 3.197 ± 4.266 AU, $p = 0.032$) and central (2.772 ± 2.061 vs. 2.799 ± 3.567 AU, $p = 0.030$) areas. Scalp topographies of TBR showed prominent differences between patients with and without apathy over the frontal and central regions. Patients with apathy had a greater slow-to-fast-wave power ratio. A further comparison between groups with and without apathy based on the Mann-Whitney U test did not show significance when TAR or DAR was used as the power ratio parameter.

Results of absolute power spectrum are usually similar to relative power measure. However, in the present study, the results with significance in both the absolute and relative power spectra were presented to attenuate the inter-individual variability of the absolute spectral power value [28].

Cortical Source Analysis

Neuronal sources with significant power changes in 1–4, 4–8, 8–10, 10–12, 12–18, 18–30, and 30–45 Hz between patients with and without psychosis and apathy were localized in widespread brain regions based on sLORETA (Table 1). Specifically, the significantly decreased source activities included α_2 -wave oscillatory activity in the right transverse

Fig. 3. θ -to- β (TBR), θ -to- α (TAR), and δ -to- α (DAR) power ratios between groups with (G2) and without (G1) apathy.

temporal area in patients with psychosis. The significantly increased source activities included δ -wave oscillatory activity in the right superior, middle, and inferior temporal areas and the left parahippocampal regions in patients with apathy. The default mode network showed increased δ -changes in the right temporal (superior and middle) and bilateral entorhinal and parahippocampal areas in patients with apathy. These significant source activities were combined into 68 regions of interest based on anatomic location and frequency band.

Discussion

The present study was the first in which a power spectral analysis of the four NPSs, hyperactivity, psychosis, affective symptoms, and apathy, was performed in AD patients. In addition, NPSs at the cortical level were characterized based on frequency-domain EEG source localization using sLORETA.

The power spectral analysis of EEG data showed that AD patients with psychosis had lower values at the α_2 -

Table 1. Neuronal sources with significant power changes in δ - and α_2 -frequency bands between patients with and without psychosis and apathy, localized based on standardized low-resolution brain electromagnetic tomography in 68 brain regions of interest

Brain structure	δ		α_2	
	L	R	L	R
Frontal pole				
Superior frontal				
Rostral middle frontal				
Caudal middle frontal				
Pars opercularis				
Pars orbitalis		△		
Pars triangularis		△		
Medial orbitofrontal				
Lateral orbitofrontal		△		
Precentral				
Paracentral				
Rostral anterior cingulate				
Caudal anterior cingulate				
Temporal pole		△		
Superior temporal		▲		
Middle temporal		▲		
Inferior temporal		▲		
Transverse temporal		△		●
Banks of superior temporal sulcus				
Fusiform		△		○
Entorhinal	△	△		
Parahippocampal	▲	△		
Insula		△		
Postcentral				
Superior parietal				
Inferior parietal				
Supramarginal				
Precuneus				
Posterior cingulate				
Isthmus				
Lateral occipital			○	
Cuneus				
Pericalcarine			○	○
Lingual			○	

The number of voxels with significant power changes is listed separately for the left (L) and right hemispheres (R) for each frequency band. Blue colors indicate decreased power and red colors indicate increased power in groups with neuropsychiatric symptoms. Circles indicate psychosis, triangles indicate apathy. Empty symbols indicate borderline significance.

band in most areas. Decreased α indicates failure to relax and self-warming for external stimulation [29]. Patients with apathy showed abnormal findings in the power ratio where scalp topographies of TBR showed a greater slow-to-fast-wave power ratio over the frontal and central regions. TBR is the ratio of θ (4–8 Hz) to β (13–21 Hz) pow-

er during resting conditions and tends to reflect attention-related functions [30, 31]. Increased TBR is associated with increased reward responsiveness, risk taking, and impulsiveness and tends to reflect attentional control functioning and behavioral inhibition processes. Researchers also demonstrated an increased slow-to-fast band power ratio in advanced AD over all brain regions except the frontal area, which may be caused by contamination of the EEG signal by eye movement [14].

The cortical source analysis of EEG showed the NPSs induced significant changes in source power across different frequency bands in many brain regions. Patients with psychosis showed decreased values in the α_2 -band and patients with apathy showed higher values in δ , especially in the right frontal and temporal regions. In the present study, sLORETA results were similar to the classical spectral analysis, which is consistent with previous reports regarding the LORETA approach in AD [32–34]. The sLORETA results of patients with apathy showed increased δ -power, primarily in the right side and central areas. Both spectral and sLORETA values for α -rhythm were relatively preserved over the frontal areas in patients with psychosis compared with patients without psychosis. This finding may indicate the so-called “anteriorization” of α -rhythm in AD; in healthy controls, α -wave generators are localized in the posterior brain regions while decreased posterior α -activity produces a shift of α -wave generator to more anterior regions in patients with AD, as previously reported [35–37].

New neuroimaging techniques have been used in recent neurobiological studies to elucidate behaviorally relevant circuits and networks associated with these subsyndromes [38]. Several frontosubcortical circuits, corticocortical networks, and neurotransmitter systems have been proposed as regions and mechanisms underlying NPS-AD. Common to most of these subsyndromes is the broad overlap of regions associated with the salience network (anterior cingulate and insula), mood regulation (amygdala), and motivated behavior (frontal cortex). Physiologically, EEG cortical activity depends on a complex balance among different neurotransmitter systems, primarily cholinergic pathways [39]. α -Rhythms are mainly modulated by thalamocortical interactions facilitating or inhibiting the transmission of sensorimotor and cognitive information among subcortical and cortical pathways [40–42]. Therefore, the magnitude reduction of fast cortical rhythms in mild AD is hypothetically associated with impairment of the cholinergic pathway resulting in an abnormal increase in cortical excitation or disinhibition during the resting state. Developing rational thera-

peutic approaches for NPS-AD will require a better understanding of the underlying etiology, which can be aided with qEEG analysis. Furthermore, qEEG can be useful to predict the effects of treatment for NPSs. The results of the present study are meaningful for the implementation of EEG for the timely and proper treatment based on pathophysiological aspects of the NPSs of dementia although certain limitations remain.

The present study had several limitations. First, pathological or biomarker confirmation was not obtained; however, all the diagnoses were clinically performed with supportive MRI findings. Use of biomarkers such as amyloid positron emission tomography or cerebrospinal fluid can help detect other causes of dementia than AD. Second, the number of participants was relatively small. In addition, EEG activity can be influenced by various factors such as age and the severity of dementia [43, 44]. Further studies with a larger study cohort, analysis of individual NPI items, and adjusted analysis of covariates including age and MMSE can strengthen our results.

In summary, the results of the present study showed that both classical EEG spectral analysis and EEG source analysis can classify patients with and without NPSs including hyperactivity, psychosis, affective symptoms, and apathy. Spectral and sLORETA analyses provided helpful information for a better characterization of qEEG in patients with NPSs. A more accurate analysis could be obtained in further studies if a greater sample size and a combination of spectral and sLORETA analyses with imaging techniques are used.

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Statement of Ethics

This retrospective study was performed in accordance with the World Medical Association Declaration of Helsinki and approved by the Institutional Review Board of the Catholic University of Korea, Bucheon St. Mary's Hospital (HC18OESI0114). We confirm that we have read the position of *Neurodegenerative Diseases* on issues involved in ethical publication and affirm that this work is consistent with the guidelines.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

Yong S. Shim: concept and design, organization and execution of the study, analysis and interpretation of data, and drafting of the manuscript, review and critique of the manuscript. Hae-Eun Shin: acquisition of data and drafting of the manuscript, review and critique of the manuscript. All authors (Yong S. Shim and Hae-Eun Shin): final approval of the version to be published.

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