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Impaired visuospatial attention revealed by theta- and beta-band cortical activities in idiopathic REM sleep behavior disorder patients

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HIGHLIGHTS

- Attention dysfunction in idiopathic REM sleep behavior disorder (iRBD) patients was studied by event-related EEG analysis.
- Normal cortical activity reflecting 'inhibition of return' (IOR) was absent in iRBD patients.
- The absence of IOR in iRBD may imply dysfunctions in visuoperceptual processing and motor control.

ABSTRACT

Objectives: Idiopathic REM sleep behavior disorder (iRBD) patients are susceptible to cognitive deficits, especially attention dysfunction. The objective of this study is to elucidate the neural mechanism of the dysfunction in attention known as 'inhibition of return' (IOR) in iRBD patients based on an analysis of oscillatory cortical activity during a selective attention task.
Methods: Event-related potentials (ERPs) were recorded from iRBD patients and normal control subjects while performing a Posner task. The differences in N1 ERP and theta- and beta-bands event-related spectral perturbations (ERSPs) between valid and invalid stimuli were compared between groups.
Results: The N1 amplitude was significantly higher for the invalid stimuli in controls, while the valid-invalid difference was not significant in iRBD patients. The valid-invalid differences in ERSPs were prominent in controls at ~100–400 ms for the theta-band and ~200–400 ms for the beta-band, and the valid-invalid differences in ERSPs were not significant in the iRBD patients.
Conclusion: The results demonstrated that valid-invalid differences in neural activity were absent in iRBD patients, and these neural findings were in accord with the behavioral results.
Significance: Our findings imply impairment in sensory-perceptual processing mediated by attentional control and response inhibition in early-stage iRBD before clinical neurodegeneration.

1. Introduction

Rapid eye movement sleep behavior disorder (RBD) is a parasomnia characterized by abnormal loss of muscle atonia during rapid eye movement (REM) sleep and dream enactment behavior. Adults over 60 years of age are affected by RBD with a prevalence of ~1% (Kang et al., 2013; Ismail et al., 2017). Individuals with RBD symptoms are known to have a high risk of developing severe

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neurodegenerative diseases, especially Parkinson's disease (PD) and dementia with Lewy bodies (DLB) within 5–10 years (Iranzo et al., 2014; Postuma et al., 2015). For example, 44–47% of PD patients suffer from symptoms of RBD, and the ratio is even higher for DLB patients (Boeve et al., 2001) and almost 100% for multiple system atrophy (Vetrugno et al., 2004). This strong association may be explained by their common origin of synucleinopathy, and idiopathic RBD (iRBD) is known to precede synucleinopathy onset by several years (Boeve and Mahowald, 2013; Iranzo et al., 2013).

Neuropsychological tests by (Ferini-Strambi et al., 2004) have first revealed that visuospatial constructional dysfunction and altered visuospatial learning may be present in iRBD. Subsequently, it has also been found that approximately 50% of RBD patients suffer from impairments in cognitive functions, particularly visual perception, visuospatial function, attention, and executive control (Massicotte-Marquez et al., 2008; Terzaghi et al., 2008; Gagnon et al., 2009,2012; Marques et al., 2010; Fantini et al., 2011). The neuropsychological tests cannot provide a detailed characterization of the pathophysiological mechanisms underlying specific cognitive domains. Even though cognitive dysfunction/abnormalities may be present before clinical symptoms become apparent, the neuropathophysiological origins of cognitive impairment in RBD and their relationship with brain degeneration have not been elucidated.

The purpose of this paper is to elucidate the neural mechanisms of attention dysfunction associated with RBD, based on the analysis of oscillatory cortical activity during performance of a selective attention task involving visual perceptual processing and motor responses. There are only a few studies in the literature that have observed and analyzed neurophysiological signals or functional neuroimages of iRBD patients during cognitive tasks (Raggi et al., 2007; Byun et al., 2017). Such a study may lead to revealing the relationship between the pathophysiology and abnormal cognitive function associated with iRBD.

Although an event-related potential (ERP) study of iRBD patients during an oddball task was reported in a previous study, significant abnormalities were not found in major ERP components such as P3, which provide information on attentional and executive function, and only problems in initial perceptual processing was suggested (Raggi et al., 2007). Our team has recently shown that P3 ERP amplitude significantly decreased in iRBD patients compared to normal controls during a Posner cueing task, along with decreased visuospatial attention (Byun et al., 2017). This result implied inefficient allocation of attentional resources or reduced attentional focus in iRBD patients, even though they had normal cognitive function in neuropsychological tests. A closer investigation of the behavioral results suggested a problem of 'inhibition of return' (IOR) in the iRBD patients. The IOR refers to a well-known orientation mechanism in attention that enhances the speed and accuracy of detecting an attended object briefly, i.e., 100–300 ms after stimulus, but then impairs speed and accuracy for approximately 300–1600 ms (Samuel and Kat, 2003). The influence of attention on sensory-perceptual processing and/or motor response inhibition have been regarded as underlying origins of the IOR (McDonald et al., 1999), and both may serve as the underlying basis of abnormal IOR in iRBD. The characterization of spatial, temporal, and spectral features of cortical activity in the current study would provide valuable information for the pathophysiological influences of iRBD on cognitive function.

We hypothesized that the neural synchrony in the theta-band, which may reflect attentional control, would show substantial differences in iRBD patients compared to normal controls. This prediction is based on the recognized abnormality in the attentional behavior of iRBD patients.

2. Methods

2.1. Subjects and clinical procedures

Drug-naïve, video polysomnography (PSG)-confirmed iRBD patients who visited Seoul National University Hospital sleep clinic were considered for enrollment in the study. Patients with neurodegenerative disease, neurological disorder, or severe medical illness were excluded. Age- and sex-matched healthy volunteers served as controls. Potential subjects were screened for any sleep-related symptoms and neurological or psychological diseases by a structured questionnaire. The subjects underwent a clinical interview and physical examination by a neurologist (KY Jung). Eventually, data from 16 drug-naïve iRBD and 19 healthy control subjects were analyzed. Ten of the healthy controls underwent PSG (Supplementary Table 1).

We performed all-night PSG (Embla RemLogic; Embla Systems LLC, Broomfield, CO, USA) according to the American Academy of Sleep Medicine (AASM) manual (Berry et al., 2015). The recording system comprised six-channel electroencephalogram (EEG) (C3–A2, C4–A1, F3–A2, F4–A1, O3–A2, and O2–A1), two-channel electrooculography (EOG) channels, two-channel electromyography (EMG) at submentalis and tibialis anterior, and electrocardiography. Total sleep time (TST), sleep stages including N1, N2, N3, and REM sleep, sleep latency, and arousal index values were scored in 30-s epochs. REM sleep without atonia was also scored according to the AASM criteria for sustained muscle activity and excessive transient muscle activity in REM sleep. The time-synchronized video and audio recordings during the overnight PSG were also used to identify REM sleep behavioral events.

Brain MR scans were performed in all except one of the patients with iRBD. Nine of the patients showed a normal MR scan, and six patients showed a mild degree of white matter hyperintensity. No significant cortical atrophy was observed in these 15 patients. None of the normal control subjects underwent neuroimaging studies. We evaluated all participants thoroughly for possible signs of neurodegeneration, such as cognitive decline or signs of parkinsonism, by performing a full cognitive function test and neurologic examination.

Sleep quality and excessive daytime sleepiness were evaluated with the Pittsburgh Sleep Quality Index (PSQI) (Sohn et al., 2012) and Epworth sleepiness scale (ESS) (Cho et al., 2011). RBD symptom severity was assessed by the Korean version of the RBD screening questionnaire-Hong Kong (RBDQ-KR), as its validity and reliability was previously shown (You et al., 2017). Olfactory function was examined by the Korean version of Sniffin' stick (KVSS) test (Cho et al,. 2009). The Scales for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-AUT) questionnaire to assess the symptoms of autonomic dysfunction (Visser et al., 2004). The iRBD patients had higher SCOPA-AUT scores and lower KVSS scores than the controls (Table 1). The iRBD patients showed lower scores related to language, abstraction, memory recall and verbal fluency than the controls, but other cognitive function scores were similar between the iRBD patients and controls (Table 2).

This study was approved by the institutional review board (IRB) of the Seoul National University Hospital (IRB Number 1406-100-589). Written informed consent was obtained from participants. All participants received financial compensation for the completion of each assessment and for transportation costs.

2.2. Experimental procedures

Prior to the main experiment, two sets of tests for cognitive function were performed: Montreal cognitive assessment (MoCA)

Table 1
Demographics, questionnaires.

	Control (n = 19)	iRBD (n = 16)	*p*-value	Cohen's d
Age (years)	63.47 ± 7.37	64.94 ± 6.92	0.552	0.20
Sex[†]	M: 14, F: 5	M: 13, F: 3	0.700	
Education (years)	13.11 ± 3.30	12.81 ± 4.02	0.814	−0.08
RBDQ-KR	5.00 ± 3.89	48.63 ± 18.42	<0.001	3.28
SCOPA-AUT total	5.53 ± 4.35	11.00 ± 4.73	0.001	1.20
KVSS	6.26 ± 0.87	4.81 ± 1.17	<0.001	−1.41
PSQI total	3.32 ± 1.57	4.75 ± 2.29	0.036	0.73
ESS	3.00 ± 1.73	4.63 ± 2.85	0.046	0.69

Data: mean ± standard deviation. *p*-value: independent t-test.
Abbreviations: RBDQ-KR: Korean version of the RBD screening questionnaire-Hong Kong; SCOPA-AUT: Scales for outcomes in Parkinson's disease – Autonomic; KVSS: Korean version of the Sniffin' stick; PSQI: Pittsburgh sleep quality index total; ESS: Epworth sleepiness scale.
[†] Fisher's exact test.

Table 2
Neuropsychological assessment.

	Control (n = 19)	iRBD (n = 15)	*p*-value	Cohen's d
MoCA total	27.37 ± 1.80	25.20 ± 3.03	0.014	−0.87
Visuospatial/executive	4.53 ± 0.70	4.73 ± 0.46	0.306	0.35
Naming	2.95 ± 0.23	2.93 ± 0.26	0.868	−0.06
Attention	5.68 ± 0.48	5.47 ± 0.92	0.414	−0.30
Language	2.89 ± 0.32	2.33 ± 0.62	0.004	−1.15
Abstraction	2	1.67 ± 0.49	0.019	−0.97
Memory recall	3.37 ± 1.07	1.60 ± 1.68	0.002	−1.26
Orientation	6	6		
CERAD-K				
Verbal fluency	19.16 ± 3.59	15.27 ± 3.56	0.002	−1.09
Boston naming test	13.74 ± 0.99	12.87 ± 1.81	0.109	−0.60
MMSE-K	28.89 ± 1.29	27.93 ± 2.46	0.151	−0.49
Word list memory	23.95 ± 2.74	21.00 ± 3.84	0.014	−0.88
Constructional praxis	10.84 ± 2.57	10.73 ± 0.59	0.874	−0.06
Word list recall	8.32 ± 1.29	6.87 ± 2.53	0.038	−0.72
Word list recognition	9.94 ± 0.69	9.07 ± 1.91	0.152	−0.54
Constructional recall	9.26 ± 2.21	8.67 ± 2.38	0.455	−0.26
TMT-A	49.89 ± 19.46	50.67 ± 15.33	0.901	0.04
TMT-B	114.58 ± 73.45	104.47 ± 82.95	0.709	−0.13

Data: mean ± standard deviation. *p*-value: independent t-test.
Abbreviations: MoCA: Montreal cognitive assessment; CERAD-K: Korean version of the Consortium to establish a registry for Alzheimer's disease; MMSE: mini-mental status examination; TMT: trail making test.

for global cognitive function (Nasreddine et al., 2005) and the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) for individual cognitive domains (Lee et al., 2002).

The subjects performed a Posner cueing task (Posner, 1980), while EEGs were recorded as illustrated in Fig. 1. First, a cue stimulus was presented as a white box on either the left- or right-hand side of the central fixation point for 100 ms. Then, a target stimulus was presented for 100 ms on either the same or the opposite side as the cue location for the valid and invalid trials, respectively. The subjects were asked to respond as quickly as possible to the target by pressing the left (red target) or right (yellow target) buttons. The ratio of valid and invalid targets was set to 1:1. The interval between the cue and target stimuli (stimulus onset asynchrony, SOA) was 200 ms or 1000 ms, as shown in Fig. 1. The experimental paradigm was presented on a 17-inch LCD monitor using commercial software (PRESENTATION; Neurobehavioral systems, Berkeley, CA). The distance between the screen and the subjects was 75 cm.

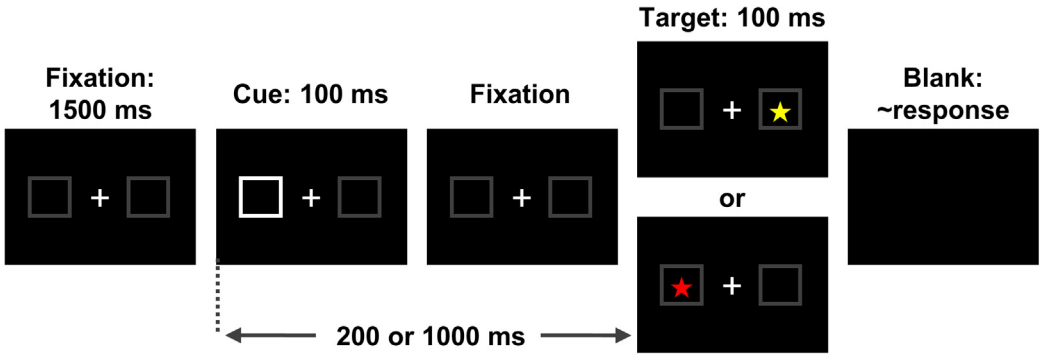

Fig. 1. Experimental paradigm.

2.3. EEG recording and preprocessing

EEGs were recorded from 60 electrodes on an EEG cap (WaveGuard EEG cap, Advanced NeuroTechnology, Enschede, Netherlands) in accordance with the international 10-10 system. The reference and ground electrodes were placed on an ear and the AFz site, respectively. Impedances were kept below 10 kOhm. Two EOG channels were placed on the left and right outer canthi to detect and remove eye-movement-related artifacts. The signals were recorded at a sampling rate of 400 samples/s along with 0.1–70 Hz bandpass filter and 60 Hz notch filter.

After rereferencing according to an average reference (Dien, 1998), the EEG signals within epochs from −1600 ms to 1500 ms according to the target stimulus onsets were segmented. Of the two SOA conditions, only the trials with the long SOA (1000 ms) were analyzed here since the IOR appears only with the long SOA. The single-trial waveforms severely contaminated with non-stereotyped artifacts such as drift or high-frequency fluctuation were eliminated by visual inspection (Jung et al., 2000). The waveforms with amplitudes exceeding ±100 μV were also excluded from the analysis. The mean numbers of epochs used for analysis in each validity condition were 120.4 ± 8.2 for iRBD patients and 120.6 ± 6.6 for control subjects. Independent component analysis was applied to correct for stereotyped ocular and muscular artifacts as in (Jung et al. 2000) using EEGLAB toolbox (version 10.0b). Baseline correction of the single-trial ERP waveforms was performed based on the waveform within the −100 to 0 ms interval around the cue stimulus presentation, and then, averaged ERP waveforms were obtained for all subjects.

2.4. Analysis of ERPs and event-related spectral perturbation (ERSP)

Several ERP components were identified according to polarity, latency, and topography of the grand-averaged ERP waveforms and then further analyzed as reported in (Picton et al., 2000). The ERP amplitudes were measured relative to the prestimulus baseline. We also referred to the cluster-based massive univariate analysis (MUA) (Maris and Oostenveld, 2007; Groppe et al., 2011) to define the space and time in which the differences between stimuli categories were clearly revealed. The mean amplitudes from the determined electrodes and epoch were statistically analyzed using repeated measures analysis of variance (ANOVA).

The temporal profile of spectral characteristics was examined by an ERSP analysis using a continuous wavelet transform based on a complex Morlet wavelet (Tallon-Baudry et al., 1996) and then subjected to further analysis. The time-frequency distribution of ERSP patterns was represented as the ratio of the relative change compared to the power in the baseline interval from −300 to 0 ms prior to cue onset to reduce intersubject variability and to normalize power changes across different frequencies.

The ensemble average of the time-frequency distribution was investigated to explore the overall characteristics of the event-related changes in oscillatory neural activity. Regardless of the validity condition, the increase in theta-band power (theta event-related synchronization, (ERS)) and decrease in beta-band power (beta event-related desynchronization (ERD)) were distinct at ∼100–300 ms and 300–500 ms (shown later in time-frequency distribution). The differences in theta- and beta-band powers between valid and invalid conditions, i.e., the IOR effects in ERSP, were most evident in these temporal windows as well. The time-series of theta- and beta-band powers (4–8 Hz and 13–30 Hz, respectively) and their topographies were inspected, along with the cluster-based MUA on time and space, to find the temporal and spatial points showing a significant IOR effect. The locations and temporal windows showing significant IOR effects were used to set the time-location window of interest for further statistical comparisons of ERSP using ANOVA, as in the case of the ERP.

3. Results

3.1. Characterization of ERP components

Fig. 2A and B show the waveforms and topographies of the grand-averaged ERPs. We found a substantial difference between invalid and valid stimuli for a distinct peak in the ERP waveforms, which is denoted as N1 in Fig. 2A. Overall, the temporal and spatial characteristics of N1 (Fig. 2B) were similar between iRBD patients and normal controls; however, the difference between invalid and valid stimuli was observable only in the normal controls, as shown in Fig. 2C.

Temporal epochs and electrodes showing significant differences in N1 amplitudes between valid and invalid stimuli were determined to be 200–250 ms in the parieto-occipital region for N1. The bottom row of Fig. 2B shows that the valid-invalid difference was greatly reduced in iRBD patients compared to the normal controls, and therefore, a significant valid-invalid difference was not found for any electrodes in the iRBD patients. The epochs and electrodes showing significant valid-invalid differences are indicated by shading in the left panels of Fig. 2A and by red dots in Fig. 2C.

Statistical analysis of the ERP amplitudes averaged within the aforementioned spatiotemporal range was performed by repeated measures ANOVA. For N1, a significant interaction between group and validity was found (F (1, 33) = 5.295, p = 0.028, averaged from 200 to 250 ms at P7, P5, P3, P4, P6, P8, PO7, PO3, PO4, and PO8 electrodes). Post hoc analyses showed that the N1 amplitude was significantly higher for the invalid stimuli than valid stimuli (t (18) = −2.356, p = 0.03, Cohen's d = −0.54) in normal controls, while the valid-invalid difference in N1 amplitude was not significant in iRBD patients (t (15) = 0.913, p = 0.376, Cohen's d = 0.23).

In addition, it was found that the difference in N1 amplitude between valid and invalid stimuli was significantly correlated with the CERAD J6 scores (word list recall, r = 0.532, p = 0.041) in iRBD patients, and scores on this measure were significantly different between normal controls and iRBD patients (Table 2).

3.2. ERSPs in theta- and beta-bands

Fig. 3 shows the time-frequency distribution of neural activity in response to the target stimuli. Regardless of the validity of the stimuli, sustained ERS in the theta-band (4–8 Hz) and ERD in beta-band (13–30 Hz) were observed in both groups. The differences in the spectrogram (the rightmost panel in Fig. 3) revealed that the valid-invalid differences were prominent in normal controls at ∼100–400 ms for theta ERS and ∼200–400 ms for beta ERD. It is remarkable that the valid-invalid differences in both theta ERS and beta ERD were much smaller in iRBD patients than in normal controls, meaning that the differences between valid and invalid stimuli, i.e., IOR effects, become absent in iRBD as described below.

The temporal and spatial characteristics of the theta ERS and beta ERD are shown in Figs. 4 and 5 in detail. The theta ERS peaked at ∼200 ms, and its difference between valid and invalid stimuli was focused in the frontal and parieto-occipital regions and was significantly higher in the normal controls than in the iRBD patients (Fig. 4). The beta ERD became prominent in the centro-parietal region after ∼200 ms and peaked at ∼400 ms. Similar to ERP and theta ERS, the valid-invalid difference in beta ERD was significant only in the normal controls (Fig. 5). The cluster-based MUA confirmed that statistically significant valid-invalid differences in theta ERS and beta ERD were present only in the normal controls.

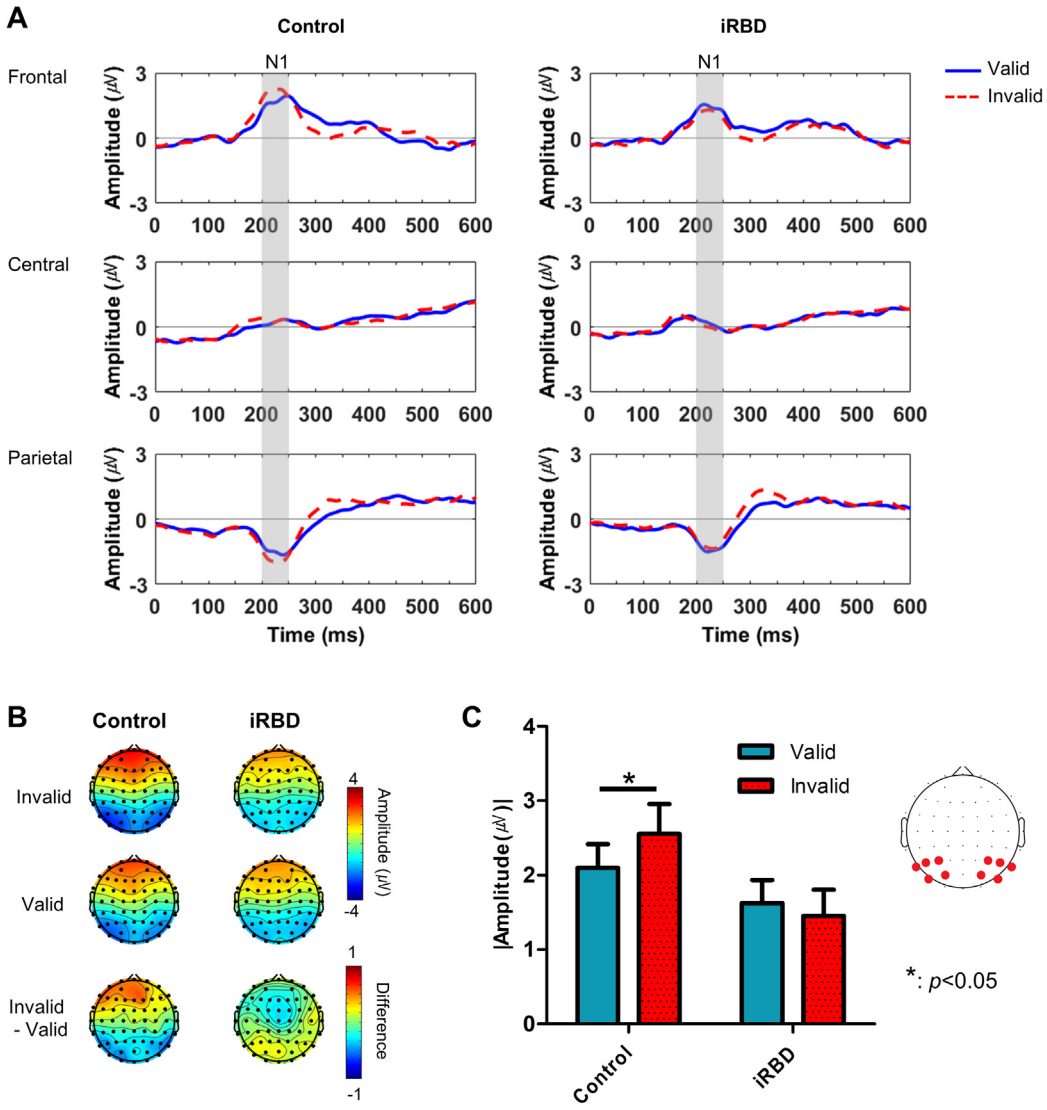

Fig. 2. Grand-averaged ERP waveforms and topography. (A) ERP waveforms in frontal (F3, F1, Fz, F2, and F4), central (C3, C1, Cz, C2, and C4), and parietal (P3, P1, Pz, P2, and P4) regions. The shadings indicate temporal epochs of the N1 component. (B) Topographical distribution of N1 amplitudes during 200–250 ms. (C) Comparison of N1 amplitudes between valid and invalid stimuli averaged within the 200–250 ms period over the parieto-occipital electrodes (indicated by red dots). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

The epoch and electrodes showing significantly different theta ERS between valid and invalid stimuli were found only in the normal controls in the 100–300 ms period in the parieto-occipital region (Fig. 4B). Likewise, the beta ERD was significantly different between valid and invalid stimuli in the 300–500 ms period in the centro-parietal region only in the normal controls (Fig. 5B).

There was a significant interaction between group and validity in the theta ERS power averaged within the determined spatiotemporal region (F (1, 33) = 6.701, p = 0.014, from 100-300 ms in the parieto-occipital electrodes P7, P5, P6, P8, PO7, PO3, PO4, and PO8). As in the case of the ERP amplitudes, the differences in theta ERS power between valid and invalid stimuli were significant only in the normal controls (valid < invalid, t (18) = −4.537, p < 0.001, Cohen's d = −1.04) and not in the iRBD patients (valid = invalid, t (15) = −0.870, p = 0.398, Cohen's d = −0.22). Similar results were obtained for the beta ERD power averaged within the determined spatiotemporal region. The group × validity interaction was found to be significant (F (1, 33) = 9.028, p = 0.005, from 300-500 ms in the centro-parietal electrodes C3, C1, C2, C4, CP3, CP1, CP2, and CP4). The beta ERD was significantly different between validity conditions only in the normal controls (control: valid < invalid, t (18) = −4.512, p < 0.001, Cohen's d = −1.04; iRBD: valid = invalid, t (15) = −0.631, p = 0.537, Cohen's d = −0.16).

The valid-invalid difference of the theta ERS was significantly correlated with the CERAD J4 (word list memory, r = 0.632, p < 0.05) and J6 (word list recall, r = 0.718, p < 0.01) scores in iRBD patients. The CERAD J4 and J6 scores were also significantly lower in the iRBD patients than in the normal controls (Table 2).

4. Discussion

'Inhibition of return' (IOR) refers to an effect wherein behavioral responses are slower to a target presented at a location that was recently stimulated or inspected compared to a target presented at a new location (Dukewich and Klein, 2015). During a visuospatial selective attention task, the IOR was absent in the behavior of iRBD patients as had been previously reported (Byun et al., 2017), whereas it was evidently present in normal controls. Here, we also showed that the differentiated neural activity associated with the

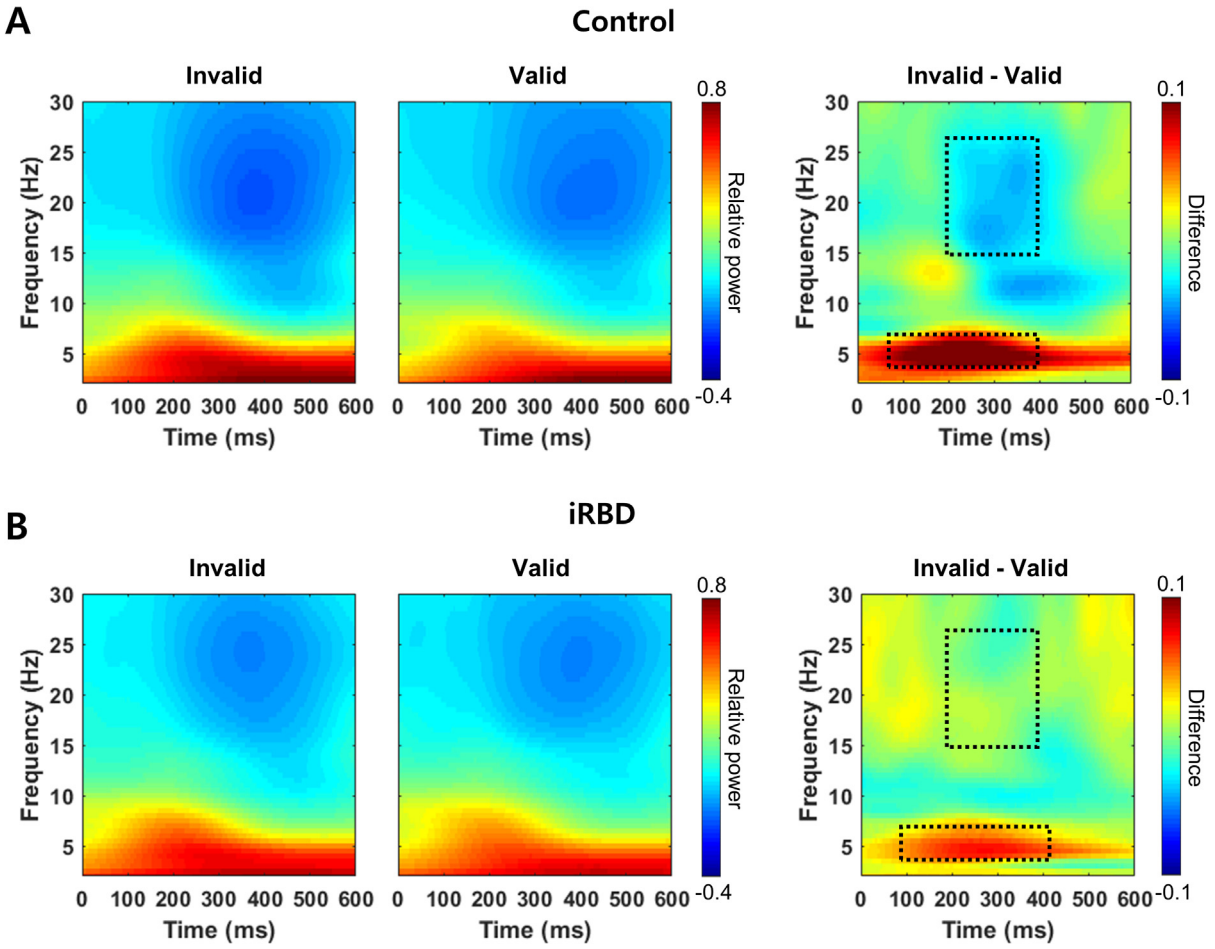

Fig. 3. Time-frequency distribution of the induced ERSP averaged over all electrodes ((A): normal controls, (B) iRBD patients). The rightmost columns show the differences in spectral powers between valid and invalid stimuli.

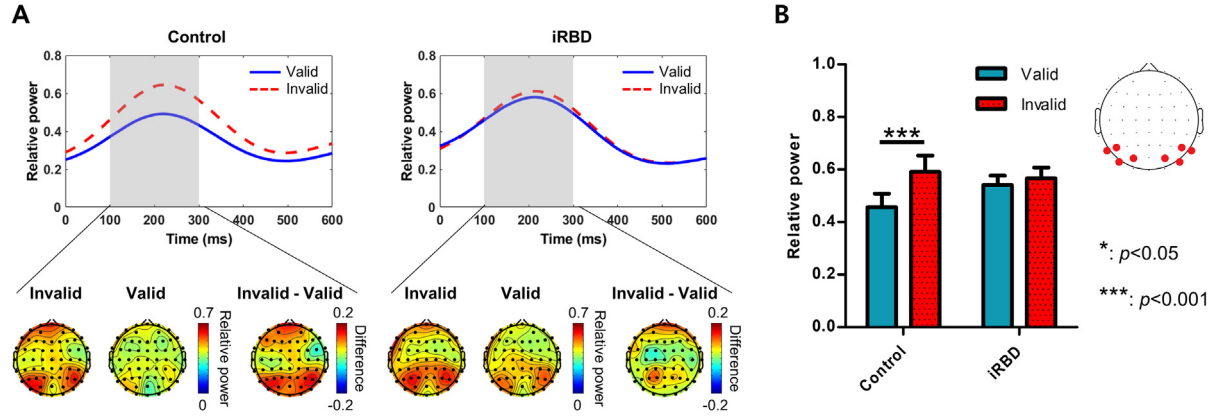

Fig. 4. Theta ERS in the control and iRBD groups. (A) Temporal and spatial profiles of theta ERS. (B) Comparison of theta ERS power between valid and invalid stimuli averaged within the 100–300 ms period over the parieto-occipital electrodes (indicated by red dots). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

IOR, i.e., ERP and ERSP differences between valid and invalid stimuli, were observed only in the normal controls.

Time-frequency analyses showed that prominent theta ERS and beta ERD were observed regardless of stimulus validity in both groups (Fig. 3). Theta ERS was observable throughout the task with a peak at ~200 ms (Fig. 4A), which seems to reflect the attentional control required for efficient processing of visual stimuli. After that, the beta ERD became prominent and peaked at ~400 ms, which may underlie motor inhibition. Valid-invalid differences were found in theta ERS and beta ERD at ~200 ms and ~400 ms, respectively, only in the normal controls. Similar to the theta ERS and beta ERD findings, the valid-invalid difference in N1 ERP was observed in the normal controls, whereas it was not found in the iRBD patients.

Cortical information processing for the Posner task consists of multiple stages, including sensory-perceptual processing, decision making, response generation, and execution. The IOR is known to originate from the suppression of stimulus processing from a

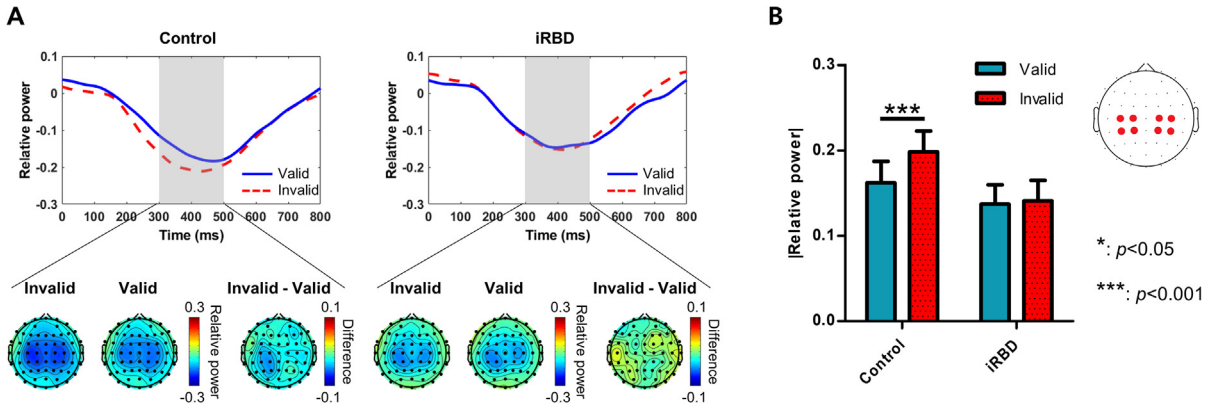

Fig. 5. Beta ERD in the control and iRBD groups. (A) Temporal and spatial profiles of beta ERD. (B) Comparison of beta ERD power between valid and invalid stimuli averaged within the 300–500 ms period over the centro-parietal electrodes (indicated by red dots). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

previous focus of attention and to encourage orienting toward novelty (Tian et al., 2014). A previous ERP study on the IOR attributed the decrease in early ERP (P1/N1) to suppression of perceptual processing (Prime and Ward, 2006). In addition, response inhibition was suggested as a source of the IOR behavioral effect based on motor-related beta ERD (Pastötter et al., 2008).

The results in the current study imply that abnormal cortical activity underlies the visuospatial attentional dysfunction in iRBD, which has been repeatedly observed in previous studies using neuropsychological tests (Byun et al., 2017). On the basis of temporal, frequency, and location information, which showed prominent differences between the valid and invalid stimuli only in normal controls, it is feasible to infer the detailed mechanisms of the dysfunction in cortical information processing associated with iRBD patients, specifically that involved in visuoperceptual processing, attentional control, and motor inhibition. We infer that two steps in cognitive information processing required for the task are impaired in iRBD patients: 1) early visuoperceptual processing under attentional control, which is reflected in N1 and theta ERS, and 2) inhibition of the motor response, which is reflected in beta ERD.

Cognitive dysfunction associated with iRBD is well known, especially on attention, but its neuropathological origins are not. Structural and functional abnormalities in iRBD patients have been observed in recent studies (Vendette et al., 2011; Rahayel et al., 2015). Rahayel et al. found reduced cortical thickness in the frontal cortex, lingual gyrus, and fusiform gyrus and reduced gray matter volume in the superior frontal sulcus (Rahayel et al., 2015). Vendette et al. found a reduction in blood flow in the superior/middle frontal area and, more importantly, that this reduction was correlated with cognitive scores (Vendette et al., 2011). On the whole, the results of these previous studies were commensurate with the impaired attentional control and associated abnormal theta rhythm observed here.

Attentional dysfunction has also been reported in other neurodegenerative/neurological diseases that are thought to originate from synucleinopathy (Calderon et al., 2001; Poliakoff et al., 2003; Hall et al., 2016; Bin Yoo et al., 2018). The most renowned example is the disrupted attentional inhibitory system in PD (Poliakoff et al., 2003). It is suspected that basal ganglia dysfunction results in the loss of descending inputs from frontal or parietal areas, and thus, the integration of sensory and contextual information is lost. A similar neuropathological mechanism may be involved in the attentional dysfunction in the iRBD patients observed here, however additional studies are needed.

The areas in the neural substrate of the IOR identified by Müller and Kleinschmidt (2007) significantly overlapped with the frontoparietal attentional system as well (Corbetta, 1998). The theta ERS enhancement that we observed with invalid stimuli during the early period (~200 ms) in normal controls was also in line with the activation of the frontoparietal attention network. Due to the limitations of temporal resolution in fMRI and spatial resolution in EEG, it is not easy to further reveal the spatiotemporal activation profile and the underlying neuropathological mechanism of the absence of the IOR in iRBD patients. However, we predict that the fast transient attentional system is responsible for IOR dysfunction in iRBD patients rather than sustained attention, based on the claim of Müller and Kleinschmidt (2007), which suggested that saccadic eye movement was crucial for stimulus-driven transient attentional shifts, instantaneous enhancement of visual activity in response to salient stimuli, and in turn, initial facilitation and subsequent inhibition of stimuli processing.

The abnormal function of the motor network may underlie the absence of beta ERD enhancement for invalid stimuli in iRBD patients. The beta ERD has been interpreted to signify cortical activation and found to be important for motor function (Pfurtscheller and Lopes da Silva, 1999; Jurkiewicz et al., 2006). In line with this, we found cortical current sources of beta ERD in the premotor area and superior parietal region (not shown here). It is plausible that the active inhibition of the motor response was reflected in the beta ERD, which is critical for successful IOR (Pastötter et al., 2008). An fMRI study of the neural substrates for the IOR revealed that the oculomotor control system, including the frontal eye field, supplementary motor area, and posterior parietal cortex, were responsible for the IOR and showed stronger cortical activity for the invalid stimuli (Müller and Kleinschmidt, 2007). This is interpreted as the necessity of stronger activation of the motor network for successful response inhibition and is thus equivalent to the stronger beta ERD for invalid stimuli, which was present in the normal controls but absent in the iRBD patients.

After RBD was first recognized by (Schenck et al., 1986), many longitudinal observational studies have shown that more than 80% of RBD patients will eventually develop PD, DLB, or multiple system atrophy (Iranzo et al., 2014; Postuma et al., 2019). This means that RBD is a prodromal phase of neurodegenerative disease, particularly synucleinopathies. There is now an argument against using the term ‘idiopathic’ because the idiopathic form of RBD no longer seems appropriate as RBD is now appreciated as a manifestation of early-stage α-synucleinopathy. The alternative term ‘cryptogenic’ or ‘isolated’ RBD has been suggested to replace idiopathic RBD in cases with no signs of neurodegeneration. Despite this controversy, as the term ‘idiopathic’ RBD is still used in most of the literature, we also use idiopathic RBD in this paper.

Several limitations should be considered regarding this study. This was a single center study, and not all controls underwent PSG. Not all normal controls underwent PSG or neuroimaging studies; therefore, subclinical signs of neurodegeneration, such as the presence of mild cortical atrophy, cannot be excluded. However, we stringently evaluated the controls for cognitive deficits or neurodegeneration by clinical interviews and physical examinations.

Our results provide useful information on the time and frequency of neural activity underlying abnormal cognitive function in iRBD, along with rough spatial information. However, because our results were obtained from the EEG signals recorded at scalp electrodes, it does not provide information on the exact location of the cortical activity underlying the pathophysiological abnormalities. Further studies using source localization analysis, such as low-resolution electromagnetic tomography (LORETA), may contribute to further revealing the spatial origin of the pathophysiology of iRBD.

In a recent review article, potential biomarkers representing degenerative central nervous system dysfunction in iRBD have been suggested, including marked EEG slowing, decreased striatal 123I-FP-CIT binding, substantia nigra hyperechogenicity, and impaired olfactory function and color vision (Ferini-Strambi, 2011). We would like to emphasize the major contribution of our study is that the abnormal changes in the ERSPs provide promising potential markers of neurodegeneration in iRBD, which are directly extracted from neural signals during cognitive task performance. However, this finding should be further confirmed in a longitudinal study.

The purpose of this study was not to contribute to differential diagnostic procedures. However, it is certain that the characteristics of the ERSP in time, frequency, and space that are differential between the patients and normal controls may be utilized to develop a computer-aided diagnostic system using statistical or machine-learning-based pattern recognition.

5. Conclusion

The differences in ERPs and ERSPs between valid and invalid stimuli were prominent in normal controls, while they were absent in iRBD patients. These results are in accordance with the absence of the IOR in behavior, implying an impairment in sensory-perceptual processing mediated by attentional control and motor response inhibition, in early-stage iRBD patients prior to clinical neurodegeneration.

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Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.07.030.

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