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Differential changes in visual and auditory event-related oscillations in dementia with Lewy bodies

Yevgenia Rosenblum [a,b,d], Inbal Maidan [a,d,e], Firas Fahoum [c,d], Nir Giladi [a,b,c,d,e], Noa Bregman [b,d,e], Tamara Shiner [b,d,e,1], Anat Mirelman [a,d,e,*,1]

[a] Laboratory of Early Markers of Neurodegeneration, Center for the Study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Medical Center, Tel Aviv, Israel
[b] Cognitive Neurology Unit, Neurological Institute, Tel Aviv Medical Center, Tel Aviv, Israel
[c] Epilepsy Unit, Neurological Institute, Tel Aviv Medical Center, Tel Aviv, Israel
[d] Department of Neurology and Neurosurgery, Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[e] Sagol School of Neuroscience, Tel Aviv University, Tel Aviv, Israel

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HIGHLIGHTS

- The study directly compares auditory and visual event-related oscillations in dementia with Lewy bodies.
- Early sensory and later cognitive processing activity in theta band is impaired in the visual, but not in the auditory task.
- Visual event-related oscillations are characterized by a decrease in theta and lack of inhibition in alpha bands.

ABSTRACT

Objective: Aside from the cognitive impairment, patients with dementia with Lewy bodies (DLB) have a high frequency of visual hallucinations and a number of other vision-related symptoms, whereas auditory hallucinations are less frequent. To better understand the differential dysfunction of the visual network in DLB, we compared auditory and visual event-related potentials and oscillations in patients with DLB.
Methods: Event-related potentials elicited by visual and auditory oddball tasks were recorded in 23 patients with DLB and 22 healthy controls and analyzed in time and time-frequency domain.
Results: DLB patients had decreased theta band activity related to both early sensory and later cognitive processing in the visual, but not in the auditory task. Patients had lower delta and higher alpha and beta bands power related to later cognitive processing in both auditory and visual tasks.
Conclusions: In DLB visual event-related oscillations are characterized by a decrease in theta and lack of inhibition in alpha bands.
Significance: Decreased theta and a lack of inhibition in alpha band power might be an oscillatory underpinning of some classical DLB symptoms such as fluctuations in attention and high-level visual disturbances and a potential marker of dysfunction of the visual system in DLB.

1. Introduction

Dementia with Lewy bodies (DLB) is a common neurodegenerative dementia with a prevalence of 0.4% in people over 65 year old (Jones and O'Brien, 2014). The core clinical features of DLB are parkinsonism, fluctuating cognition and recurrent visual hallucinations (McKeith et al., 2017), which are present in 62% (range 49–73%) of DLB patients (Eversfield and Orton, 2018). In contrast,

Abbreviations: AD, Alzheimer's disease; DLB, dementia with Lewy bodies; ERP, event-related potentials; ERO, event-related oscillations; ITPC, inter-trial phase clustering; MCI, mild cognitive impairment; MDS-UPDRS, Movement disorders Society Unified Parkinson's Disease Rating Scale motor part III; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; PDD, PD with dementia.

* Corresponding author at: Laboratory for Early Markers of Neurodegeneration, Center for the Study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Medical Center, Tel-Aviv University, 6 Weizmann Street, Tel Aviv 64239, Israel.
E-mail address: anatmi@tlvmc.gov.il (A. Mirelman).
[1] Equal contribution.

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the estimated prevalence of auditory hallucinations is about 31% (range 18–42%) (Suárez-González et al., 2014; Eversfield and Orton, 2018). Besides visual hallucinations, DLB patients often have a number of other vision-related behavioral symptoms including delusional misidentification, sideway passage, presence sensation (McKeith et al., 2017), visual agnosia, impaired visuoperception and spatial memory (Ota et al., 2015).

In DLB, abnormalities throughout the visual network have been related to altered blood flow and reduced metabolism in the primary visual cortex, dorsal and ventral visual pathways (Perneczky et al., 2008; Kantarci et al., 2010; Nagahama et al., 2009). Pathologically, visual misidentification and hallucinations have been associated with white matter spongiform changes with coexisting gliosis in the occipital lobe (Higuchi et al., 2000), and greater Lewy bodies pathology in the secondary visual pathway (Yamamoto et al., 2006).

A useful tool to link high-order visual impairments with dynamically changing brain activity is EEG measured during a cognitive task. For example, a controlled oddball task elicits brain response called event-related potentials (ERP). ERP waveform consists of several components: 1) early exogenous C1, P1, N1, P2, which are obligatorily triggered by a sensory stimulus; 2) motor components and 3) late endogenous cognitive N2 and P3 components, which are task-dependent (Luck, 2014). P3 (also called P300) component is a positive deflection in voltage at 300–500 ms after stimulus presentation. P3 is mainly associated with short-term memory and attention (Polich, 2007; Luck, 2014), and is modulated by dopamine and acetylcholine (Nieuwenhuis et al., 2005; Polich, 2007; Brown et al., 2015; Caldenhove et al., 2017), two of the neurotransmitters that play a key role in the pathogenesis of DLB.

ERP have been extensively investigated in the literature in the spatio-temporal domain with a main focus on amplitudes and latencies of ERP components. In DLB, however, the studies reporting EEG during cognitive tasks are scarce, and EEG has been mainly investigated at rest, showing generalized slowing as well as focal abnormalities (i.e., temporal slow wave transients and frontal intermittent rhythmic delta activity) compared to other dementias (see Chatzikonstantinou et al., 2020 for an updated review).

Only two studies explored ERP elicited by the oddball task in DLB: Bonanni et al. (2010) reported increased latency and lower amplitude of auditory P3 component in DLB compared to patients with Alzheimer's disease (AD), whereas Kurita et al. (2010) reported comparable auditory P3 latencies among patients with AD, DLB and Parkinson's disease dementia (PDD). Only one study compared visual to auditory P3 latency ratio in DLB, reporting that it is larger in DLB patients compared to controls (Kurita et al., 2010). In addition, longer visual latencies of both P2 and P3 components were reported in DLB and PDD as compared to controls, suggesting that the impairment occurs at the early stage of visual information processing (Kurita et al., 2010).

The analysis of ERP in the time-domain reveals, however, only certain aspects of the information available in EEG recordings, focusing mainly on the timing of the phase-locked (i.e., locked to a stimulus or response) signal (Cohen, 2014). In contrast, time-frequency analysis reveals both the timing and frequency composition of the signal and enables the exploration of neural oscillations, i.e., rhythmic fluctuations in excitability of populations of neurons (Buzsáki and Draguhn, 2004). Importantly, time-frequency response (i.e., event-related oscillations (ERO)) contains both complementary and independent information about the signal, which is not necessarily revealed with ERP analysis in time domain (Cohen and Donner, 2013; Munneke et al., 2015). Principal component analysis (PCA) enables further identification of the internal structure of the signal and reveals its unique features (Bernat et al., 2007; Cohen, 2014). For example, time-frequency transform and PCA approaches revealed that in healthy subjects the response elicited by the oddball task, consisted of early anterior theta and later posterior delta ERO, as well as alpha-band suppression (Bernat et al., 2007; Caravaglios et al., 2010; Jang et al., 2019).

Despite growing research on neural oscillations, ERO have not been explored in DLB. Furthermore, visual and auditory ERO have not been directly compared. Given the differential dysfunction of the visual network in DLB, we aimed to 1) compare visual and auditory ERP and ERO in DLB patients; 2) compare the frequency configuration of ERO in patients with DLB *vs* controls; 3) evaluate correlations between ERO and behavioral characteristics of DLB patients. We hypothesized that patients with DLB will show different frequency structures of ERO as compared to controls. Moreover, we hypothesized that in DLB patients visual ERO will be more affected than the auditory ones, and will correlate with cognitive and motor characteristics of the patients.

2. Methods

2.1. Participants

Twenty three patients with DLB and 22 healthy controls participated in this exploratory pilot study. DLB patients were recruited from the Cognitive Neurology Unit at the Tel Aviv Medical Center. Patients were included if they met the consensus criteria for possible or probable DLB (McKeith et al., 2017) and had stable medical condition. Patients were tested on their regular medications in order to assess performance in their usual clinical state. Controls were included if they were older than 60 years of age and were not diagnosed with a neurological or psychiatric disorder. The study was approved by local ethical committee according to the Principles of the Declaration of Helsinki. Only participants who were able to give a valid consent were recruited to the study and all participants gave their informed written consent prior to participation.

2.2. Neurological assessment

Participants underwent a complete neurological evaluation including assessment of medical history, present symptoms and current medications. Sufficient visual and auditory function was evaluated by an experienced neurologist (T.S.) to ensure ability to perform the oddball tasks. Motor symptoms were evaluated using the motor part of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz et al., 2008), while global cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). After the clinical assessment, subjects were introduced to the oddball tasks.

2.3. Oddball tasks

The auditory and visual oddball tasks were preformed while recorded using a wireless EEG system (Enobio20 Neuroelectrics, Spain) with 19 electrodes configured based on the international 10–20 system, with a sampling rate of 500 Hz. Two additional electrodes were placed on the right earlobe and served as a reference during recording.

After fitting the system and ensuring stable EEG recording, the participants were seated comfortably in front of a computer screen to perform the tasks. The auditory oddball task consisted of odd stimuli presented as a high pitch tone (1200 Hz instead of 600 Hz). The visual oddball task consisted of odd stimuli presented as different color squares (black-and-white instead of white) (Fig. 1 A-B). The stimuli were presented on or by the computer in a pseudo-randomized order to avoid learning effect, with a stimulus

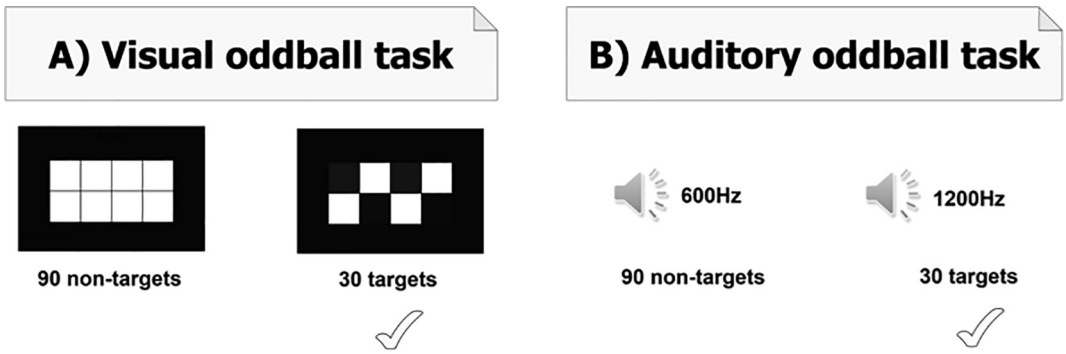

Fig. 1. The design of the oddball tasks. Target and non-target stimuli used in the visual (A) and auditory (B) oddball tasks.

interval 2.8–3.2 s. Each block consisted of 30 standard and 10 odd pictures or tones. Each task consisted of three 2-minutes blocks. The participants were asked to press a button when the odd stimulus appeared. Hit rate, false positive rate, reaction time and reaction time variability were explored as behavioral measures.

2.4. EEG preprocessing

EEG preprocessing was conducted using EEGLAB toolbox (Delorme and Makeig, 2004). Data was filtered using band-pass finite impulse response filter 1–40 Hz, and divided into 3 s epochs: 1 s pre-stimulus and 2 s post-stimulus. Only the trials related to target stimuli detection were further processed and analyzed. The mean voltage of the pre-stimulus baseline activity (−200 to 0 ms) was subtracted from the post-stimulus signal. Epochs with voltage >100 μV from the mean across all epochs were rejected from further analysis to reduce noise. Components related to eye blinks and muscle artifacts were rejected based on visual inspection using independent components analysis algorithm of the EEGLAB. All ERP components were measured from Pz channel as Pz is known to have the largest amplitude of P3 component (Polich, 2007).

2.5. EEG analysis in time domain

EEG analysis was conducted using custom scripts written in Matlab (Mathworks, USA). Firstly, the data was analyzed in time domain. Trial-averaged ERP were calculated for each subject and then averaged over each group for each condition. The amplitude of P3 component was identified as the largest positive potential at 300–650 ms post-stimulus and the latency - as the timing of P3 occurrence. To reduce noise, mean maximal amplitude was calculated as mean voltage within ±50 ms from maximal peak (Luck, 2014). To compare the data in time domain with its time-frequency transform, we calculated coefficients for correlations between the mean maximal amplitude and time-frequency power in each frequency band.

2.6. Time-frequency transform

Time-frequency data transform was computed using complex Morlet wavelet convolution based on the codes accompanying Cohen's textbook (Cohen, 2014). Thirty log-spaced frequencies (2–30 Hz) were estimated from the data using a log-spaced number of cycles. Wavelet length increased from 3 cycles at 2 Hz to 10 cycles at 30 Hz. Frequencies >30 Hz were not studied since these are particularly affected by muscle artifacts, eye movements and microsaccades (Babiloni et al., 2020).

Power (the amount of oscillations' energy which reflects cortical processing capacities) and phase angle (timing of oscillations) were calculated from the result of the complex convolution for each trial. To remove the activity unrelated to the task, power was averaged over all trials, normalized to the baseline and converted to a decibel scale as follows:

$$power_{TF} = 10\log10\left(\frac{activity_{TF}}{baseline}\right),$$

where TF is a time-frequency point, activity is power at each time-frequency point and baseline is the mean power across baseline period defined as −200 to 0 ms prior to stimulus presentation for each frequency band (Cohen, 2014).

Phase was transformed to inter-trial phase clustering (ITPC) index as follows:

$$ITPC_{TF} = \left| n^{-1} \sum_{k=1}^{n} e^{i\varphi TF} \right|,$$

where TF is a time-frequency point, φ–phase angles and n-trials. ITPC (also known as phase locking value/factor or phase resetting/coherence) measures the uniformity of phase angles distribution across trials, and thus reflects frequency-dependent synchronization to stimulus onset (Cohen, 2014). It ranges from 0 (random phases) to 1 (perfect phase clustering). Trial-averaged ITPC was baseline-normalized. Power and ITPC were averaged over all subjects for each condition and each group separately.

The time-frequency windows of interest were defined as follows: 50–300 ms after stimulus presentation to analyze early sensory components, and 300–600 ms to analyze late cognitive components of ERO for delta (2–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–30 Hz) frequency bands.

To measure correlations between power and clinical characteristics of the patients, power was averaged over trials for each subject individually for each frequency-band over a time window 300–600 ms after stimulus presentation, the window of the maximal strength of the memory and attention-associated P3 component (Polich, 2007; Luck, 2014).

Principal component analysis was used to identify differential features of visual *vs* auditory activity in the DLB patients. Eigen decomposition was performed on channel-by-channel covariance matrix constructed from the raw filtered EEG data via the Matlab's function *eig* (Cohen, 2014). The eigenvector accounting for the most variance in the data was convoluted to calculate its time-frequency power for auditory and visual tasks separately as described above.

2.7. Statistical analysis

All data was explored for normality and homogeneity of variance using Q-Q plot and Leven's homogeneity test, respectively.

Demographic, clinical, behavioral and P3 characteristics were analyzed using a two-tailed Student's *t*-test.

EEG power and ITPC were analyzed using non-parametric permutation-based t-test with 1000 randomization (Maris and Oostenveld, 2007). Cluster-based correction for multiple comparisons was incorporated to the permutation test framework (Cohen, 2014). Time-frequency clusters >100 ms-by-2 Hz (representing 50% of expected length of P3 signal (Polich, 2007) and 50% of a conventionally defined EEG frequency band) were defined as statistically significant. Clusters smaller than that, were considered a false positive. Effect sizes were calculated using Cohen's d (Cohen, 1988; Sawilowsky, 2009). Spearman correlation coefficients were used to evaluate the association between EEG power in different frequency bands and reaction times, MoCA and MDS-UPDRS scores in the DLB patients' group. Matlab was used for these analyses.

3. Results

3.1. Demographic, clinical and behavioral characteristics

Demographic and clinical characteristics of the participants are presented in Table 1. DLB patients and controls were of similar age but the groups differed in gender ratio. As expected, patients had significantly lower MoCA and significantly higher MDS-UPDRS scores than controls ($p < 0.0001$). Twenty of 23 (87%) patients had visual hallucinations, none of them had auditory hallucinations.

Behavioural characteristics of the participants during the auditory and visual oddball tasks are presented in Table 2. Overall performance of the patients in the oddball tasks was significantly worse than that of the controls, including lower reaction times and higher inter-trial variability in both tasks and a higher rate of false positives in the visual task.

3.2. Electrophysiological characteristics in time domain

Fig. 2 presents auditory and visual ERP in the time domain, whereas Table 2 reports the values of the amplitudes and latencies of the P3 component. DLB patients had significantly longer latencies than controls in the visual ($p = 0.04$) but not auditory task, whereas the amplitudes were comparable in both tasks in both groups. The amplitudes of P3 correlated with the time-frequency power in delta band in both tasks (both $r = 0.3$, $p = 0.05$).

3.3. Electrophysiological characteristics in time-frequency domain

Fig. 3 and Fig. 4 present event-related power, ITPC and z maps for the auditory and visual oddball tasks in DLB patients and controls, whereas Table 3 summarizes the mean values of time-frequency power, ITPC, corrected p-values and effect sizes of all studied time-frequency windows of interest.

3.3.1. Delta ERO

The patients had a significantly lower delta power than the controls at 200–800 ms after target presentation in both the auditory and visual tasks ($p < 0.02$, Table 3, Fig. 3), with large to very large effect sizes (Cohen's $d > 0.8$).

The patients had a significantly lower ITPC than the controls at 50–400 ms after target presentation in the auditory but not visual task ($p < 0.03$, Table 3, Fig. 4) with a low-medium effect size (Cohen's $d > 0.47$).

Correlation analysis in the DLB group revealed that visual delta power at 300–600 ms significantly negatively correlated with the motor MDS-UPDRS ($r = -0.459$, $p = 0.028$, Fig. 5A) but not reaction times and MoCA scores of the patients.

Table 1
Participants' demographic and clinical characteristics (means ± SD).

Parameter	Dementia with Lewy bodies	Healthy controls
Number of participants	23	22
Age, years (range)	70.8 ± 6.2 (60–81)	71.9 ± 7.3 (60–84)
Gender (Male/Female)	19/4**	8/14
Montreal cognitive assessment	20.0 ± 6.7*	26.9 ± 1.6
MDS-UPDRS, motor part	32.0 ± 15.8*	4.7 ± 2.0
Time since diagnosis, years	4.1 ± 2.4	–
Hallucinations, No. (%)	20 (87%)	–
Treated with AChEI, No. (%)	22 (96%)	–
Treated with Levodopa, No. (%)	21 (91%)	–
Levodopa equivalent daily dose, mg/day	308 ± 245	–

* indicates significant t-test's p-values < 0.005, ** indicates significant chi-squared test's p-values < 0.005. MDS-UPDRS: MDS Unified Parkinson Disease Rating Scale; AChEI: acetylcholine esterase inhibitors.

3.3.2. Beta ERO

Patients showed a significantly higher beta power at 300–700 ms after target presentation in both the auditory and visual tasks as compared to the controls ($p < 0.015$, Table 3, Fig. 3), with large to very large effect sizes (Cohen's $d < -0.84$).

Visual beta power at 300–600 ms significantly positively correlated with the motor MDS-UPDRS ($r = 0.495$, $p = 0.016$, Fig. 5B) but not reaction times and MoCA scores of the patients.

3.3.3. Theta ERO

The patients had a significantly lower early (50–300 ms) and late (300–700 ms) theta power ($p < 0.02$) with large effect sizes (Cohen's $d > 0.91$) during the visual but not auditory task (Table 3, Fig. 3). Likewise, the patients had a significantly lower visual ITPC at 50–250 ms than the controls ($p = 0.045$, Table 3, Fig. 4) with a medium effect size (Cohen's $d = 0.63$).

No significant correlations were observed between theta-band power and reaction times, motor and cognitive characteristics of the patients.

3.3.4. Alpha ERO

The patients had a significantly higher alpha power at 300–700 ms than the controls in both the auditory and visual tasks ($p < 0.02$, Table 3, Fig. 3), with medium to large effect sizes (Cohen's $d > 0.67$).

No significant correlations were observed between alpha-band power and reaction times, motor and cognitive characteristics of the patients.

3.4. Auditory vs visual ERO in DLB

Fig. 6 highlights the distinguishing features of auditory and visual event-related power in the patients with DLB. Eigen decomposition of the auditory EEG data showed that the first principal component accounted for 68 ± 15% of the variance of the data. This component consisted of an increase in early theta and late delta bands activity.

The first principal component in the visual EEG data accounted for 64 ± 16% (similar to auditory) of the variance and consisted of a decrease in delta and theta bands activity. The activity during the visual task was significantly lower than the activity during the same period of the auditory task at three time-frequency clusters: 1) 5–7 Hz at 100–300 ms ($z = 2.28$, $p = 0.011$), 2) 4–8 Hz at 600–800 ms ($z = 2.13$, $p = 0.016$), 3) 2–4 Hz at 300–700 ms after stimuli presentation ($z = 1.93$, $p = 0.027$, Fig. 6).

Table 2
Behavioral and P3 characteristics per group and condition (means ± SD).

	Auditory task			Visual task		
Parameter	DLB	HC	p	DLB	HC	p
Target hits, %	96.1 ± 11	99.4 ± 1	0.155	96.0 ± 12	99.4 ± 3	0.212
False positives, %	2.0 ± 2.7	1.2 ± 2.1	0.294	3.3 ± 3.9	1.1 ± 2.0	0.022*
Response time, ms	582 ± 204	477 ± 91	0.035*	633 ± 141	492 ± 64	0.000*
Response time variability	188 ± 153	96 ± 31	0.009*	174 ± 102	93 ± 27	0.001*
Latency, ms	496 ± 105	482 ± 96	0.652	509 ± 76	470 ± 92	0.040*
Amplitude, μV	6.4 ± 4.1	7.1 ± 3.5	0.513	7.2 ± 5.8	7.5 ± 5.3	0.806

DLB: dementia with Lewy bodies; HC: healthy controls; * indicates significant p-values.

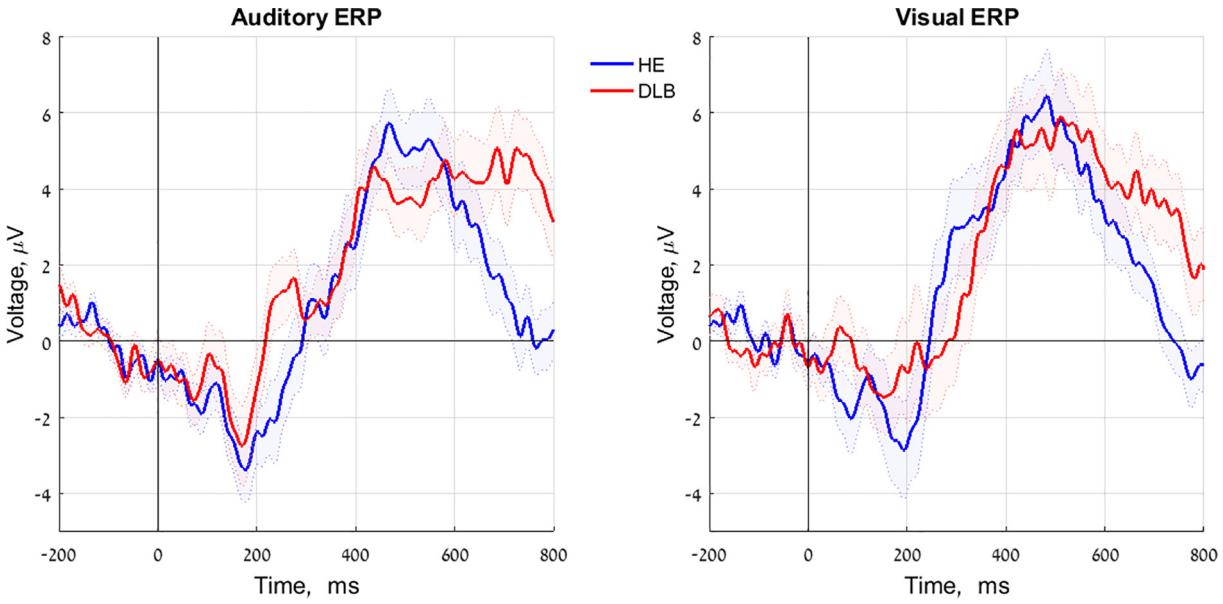

Fig. 2. Grand averaged auditory and visual ERP in time domain. Auditory (left) and visual (right) ERP with standard errors recorded from Pz electrode. DLB: dementia with Lewy bodies; HC: healthy controls.

4. Discussion

To our knowledge, this is the first study to characterize and directly compare auditory and visual ERO in DLB patients. In this pilot exploratory study, we opted to examine the power and phase coherence of ERO as these reflect the number of neurons discharging synchronously at a critical time at specific brain regions. Our findings revealed that: 1) similar to a previous report (Kurita et al., 2010), DLB patients present with a greater latency of the visual P3 than controls; 2) changes in early and later cognitive processing differed based on oscillation frequency; 3) DLB patients had decreased theta band activity related to both early sensory and later cognitive processing in the visual, but not in the auditory task; 4) patients had different activity related to later cognitive processing compared to controls in delta, alpha and beta frequency bands in both auditory and visual tasks; 5) delta and beta visual event-related power correlated with motor impairments of the patients.

Decreased delta band activity was observed in both auditory and visual conditions, consistent with the cognitive impairment of patients, whereas decreased theta band activity was observed only in the visual task. This potentially reflects the impairment in sensory stimulus processing in the visual network in DLB patients and is consistent with the time domain findings on longer latencies of visual but not auditory P3 in DLB compared to controls in this study and in the literature (Kurita et al., 2010). Below we discuss the unique findings for each frequency band across the entire spectrum.

4.1. Delta ERO

An implicit EEG assumption states that the efficiency of information processing is proportional to the magnitude of neural oscillations (Klimesch, 2012). Consistent with this are reports on reduced delta ERO in such neurodegenerative disorders as mild cognitive impairment (MCI), AD, PD and PD-MCI (Başar et al., 2010; Yener et al., 2008, 2019; Kurt et al., 2014; Güntekin et al., 2018). Similarly, we found that in DLB patients, both auditory and visual event-related oscillations in delta-band were decreased compared to that observed in the controls with a large effect size, reflecting the importance of delta in healthy brain.

Previous studies linked delta responses to signal detection, motivation, and decision making (Başar et al., 2001; Knyazev, 2012). Our results showed that the magnitude of both auditory and visual delta ERO correlated with global cognitive and motor function of all participants as a whole group. However, when the analysis was conducted for the DLB group separately, a correlation was found between visual delta ERO and the severity of motor but not cognitive function. A possible explanation could be that the distribution of the MoCA test in DLB was small, reflecting patients' impairment and causing a floor-effect, while the larger distribution spread over the entire group enabled this association. In addition, the MoCA evaluates global cognitive function, and it is possible that specialized neuropsychological tests designed to evaluate domain specific cognitive function (e.g., visuo-spatial, attentional) would reveal more nuanced associations between ERO in different

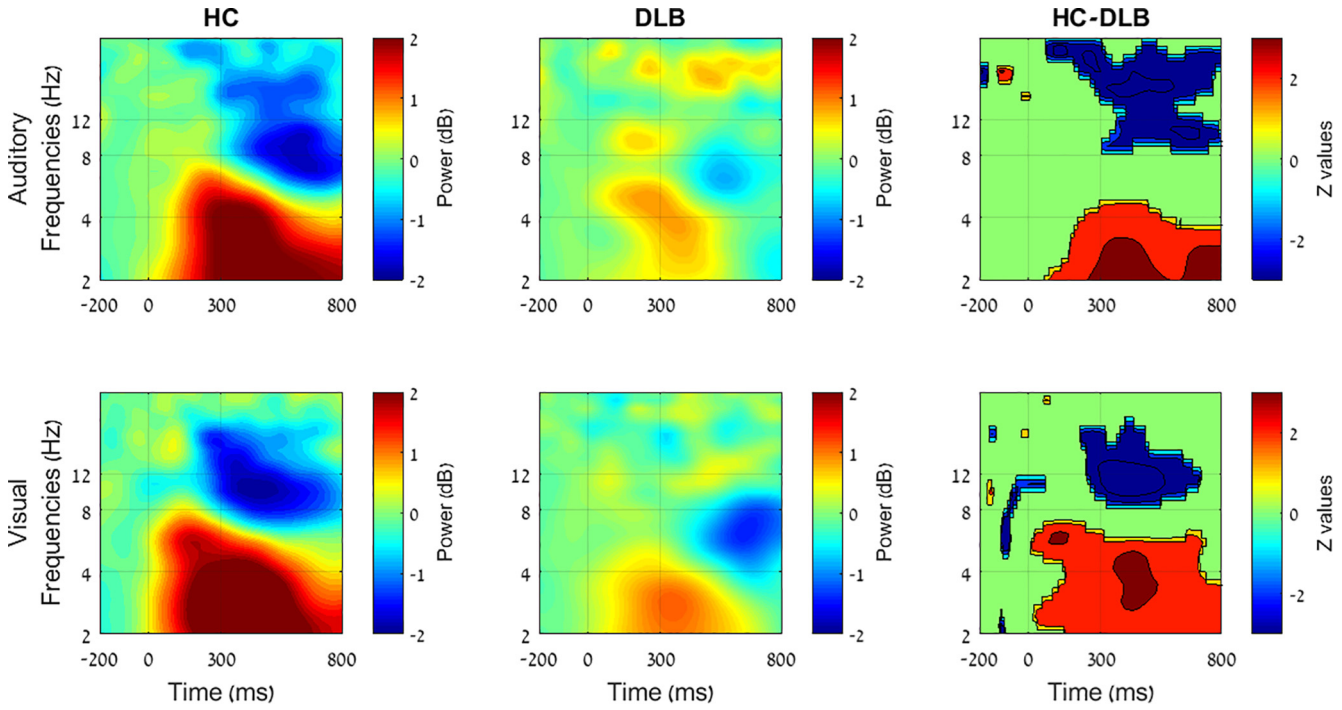

Fig. 3. Time-frequency power maps for auditory and visual oddball tasks. Baseline-normalized to the decibel scale power recorded from Pz electrode was averaged over target trials over HC (left) and DLB (middle) subjects for auditory (top) and visual (bottom) oddball tasks. Right: z-maps obtained by permutation test with incorporated cluster-based correction for multiple comparisons to assess the difference in power between HC and DLB groups. Time-frequency clusters <100 ms-by-2 Hz were considered a false positive. Green areas on z-maps refer to statistically non-significant z-values ($-1.96 < z < 1.96$). Red and blue indicate a power increase or decrease, respectively, in HC relative to the DLB group. DLB patients had decreased theta band activity in the visual, but not auditory task. Patients had lower delta and higher alpha and beta bands power in both auditory and visual tasks. DLB: dementia with Lewy bodies; HC: healthy controls.

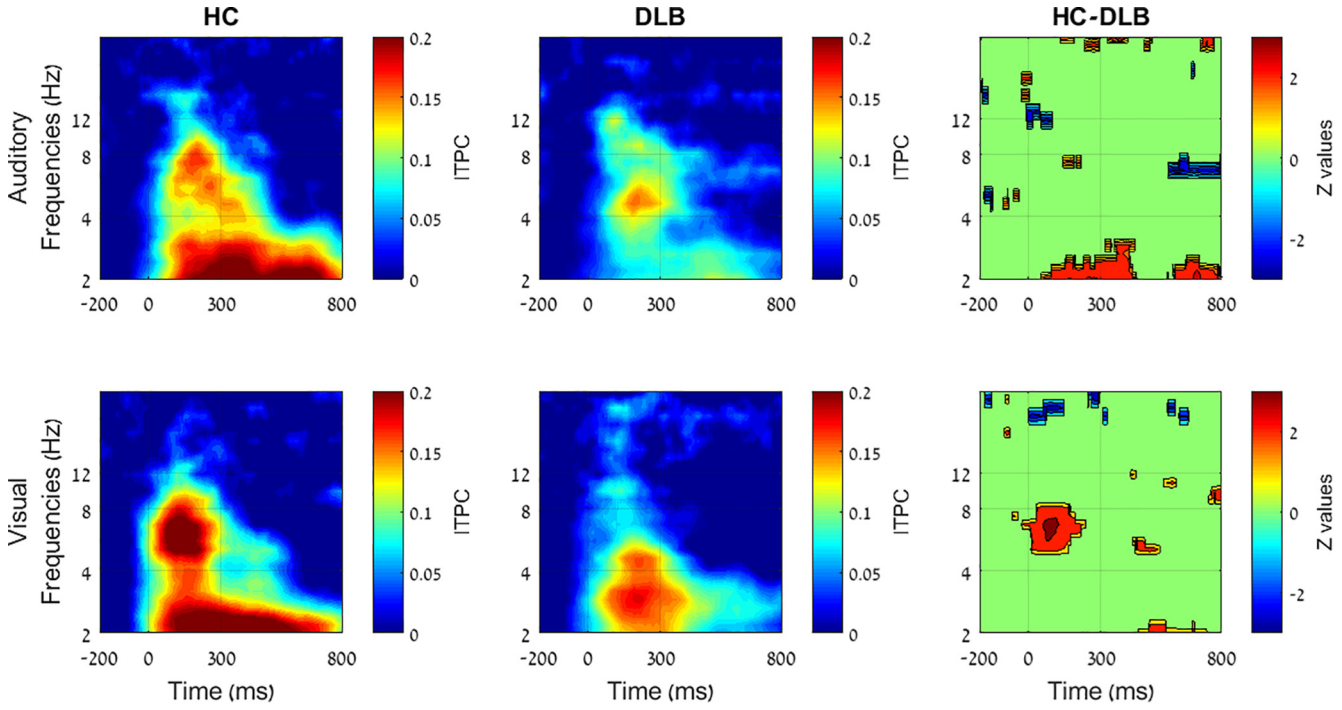

Fig. 4. Time-frequency maps of inter-trial phase clustering for auditory and visual oddball tasks. Baseline-normalized ITPC over target trials over HC (left) and DLB (middle) subjects for auditory (top) and visual (bottom) oddball tasks. Right: z-maps obtained by permutation test with incorporated cluster-based correction for multiple comparisons to assess the difference in ITPC between HC and DLB groups. Time-frequency clusters <100 ms-by-2 Hz were considered a false positive. Green areas on z-maps refer to statistically non-significant z-values ($-1.96 < z < 1.96$). Red indicates an increase of ITPC in HC relative to the DLB group. The patients had a significantly lower ITPC in 2–3 Hz at 50–400 ms after an auditory target presentation, and a significantly lower ITPC in 4–8 Hz at 50–250 ms after visual target presentation than the controls. DLB: dementia with Lewy bodies; HC: healthy controls; ITPC: inter-trial phase clustering.

Table 3
Time-frequency power and phase during auditory and visual oddball tasks (means ± SD, Cohen's d, p-values).

Frequency, Hz	Time, ms	Modality	Power				Inter-trial phase clustering			
			DLB	HC	d	p	DLB	HC	d	p
Delta, 2-4	50-300	auditory	0.4 ± 1.0	1.4 ± 1.4	0.81	0.019*	0.09 ± 0.11	0.14 ± 0.14	0.47	0.021*
		visual	0.4 ± 1.1	2.1 ± 1.7	1.12	0.016*	0.16 ± 0.13	0.16 ± 0.13	0	0.182
	300–600	auditory	0.7 ± 1.4	2.2 ± 1.7	1.11	0.002*	0.08 ± 0.15	0.15 ± 0.13	0.63	0.031*
		visual	0.4 ± 1.3	2.6 ± 1.9	1.35	0.003*	0.11 ± 0.19	0.12 ± 0.13	0.11	0.148
Theta, 4-8	50–300	auditory	0.6 ± 1.2	1.0 ± 1.5	0.27	0.253	0.12 ± 0.10	0.13 ± 0.13	0.14	0.282
		visual	0.1 ± 0.9	1.4 ± 1.6	1.02	0.010*	0.11 ± 0.17	0.17 ± 0.15	0.63	0.045*
	300–600	auditory	−0.1 ± 1.5	0.5 ± 1.8	0.33	0.117	0.06 ± 0.10	0.06 ± 0.10	0.02	0.391
		visual	−0.6 ± 1.0	0.6 ± 1.8	0.91	0.019*	0.00 ± 0.06	0.05 ± 0.09	0.32	0.239
Alpha, 8–12	50–300	auditory	0.4 ± 1.1	0.1 ± 1.2	−0.28	0.285	0.09 ± 0.08	0.10 ± 0.13	0.11	0.471
		visual	0.1 ± 1.1	−0.3 ± 1.7	−0.28	0.162	0.04 ± 0.11	0.11 ± 0.13	0.52	0.125
	300–600	auditory	−0.1 ± 1.2	−1.1 ± 1.8	−0.67	0.019*	0.02 ± 0.06	0.02 ± 0.08	−0.06	0.434
		visual	−0.1 ± 0.9	−1.6 ± 2.2	−0.88	0.003*	−0.02 ± 0.05	0.00 ± 0.10	0.32	0.235
Beta, 12–21	50–300	auditory	0.1 ± 0.6	−0.3 ± 0.5	−0.81	0.374	0.01 ± 0.05	0.02 ± 0.05	0.31	0.362
		visual	0.0 ± 0.7	−0.4 ± 0.8	−0.47	0.254	0.02 ± 0.05	0.02 ± 0.07	−0.04	0.472
	300–600	auditory	0.2 ± 0.9	−0.8 ± 0.6	−1.24	0.004*	0.00 ± 0.05	0.00 ± 0.04	0.1	0.45
		visual	0.0 ± 0.7	−0.6 ± 0.8	−0.84	0.015*	0.00 ± 0.03	0.00 ± 0.03	−0.18	0.422

Table 3 is complementary to Figs. 3 and 4 and shows mean values of time−frequency power (in dB) and inter-trial phase clustering index (range −1–1) at 50–300 ms (early exogenous processing) and 300–600 ms (late endogenous processing) after target odd stimulus presentation for delta, theta, alpha and beta frequency bands. p-values were calculated by permutation test with incorporated cluster-based correction for multiple comparisons. * indicates significant p-values; Cohen's d>|0.2| indicates a small, d>|0.5|- a medium, d>|0.8| - a large, d>|1.2| - a very large effect size; DLB: dementia with Lewy bodies; HC: healthy controls.

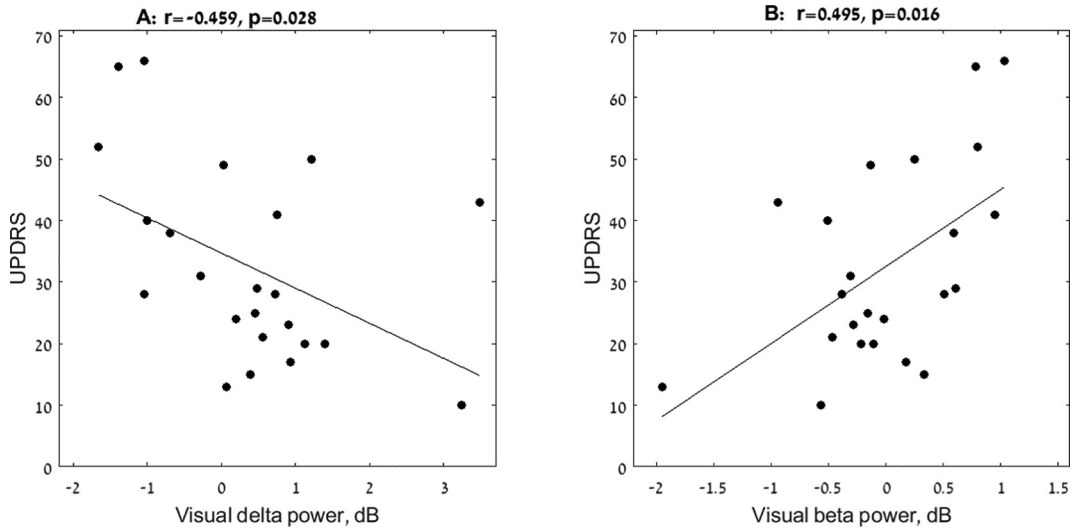

Fig. 5. Correlations between EEG power and motor function of the patients with dementia with Lewy bodies. Spearman correlations were calculated between the scores on the motor part of the MDS-UPDRS and EEG power averaged over the time window 300–600 ms after visual stimuli presentation A) in the delta-band; B) in the beta-band. r: Spearman correlation coefficient; UPDRS: MDS Unified Parkinson's Disease Rating Scale.

frequency bands and cognitive function in specific domains. This is an area needing more research.

4.2. Beta ERO

Beta oscillations generated by motor areas of the cortex have been reported to be inhibited during execution of motor tasks (Neuper and Pfurtscheller, 2001, 2010; Pfurtscheller et al., 2005). Given that our participants pressed a button when a target stimulus appeared, we expected to measure beta inhibition in both tasks in both groups. Beta-band power suppression, however, was only observed in the controls but not in the DLB patients. This is consistent with reports on increased or no beta suppression during motor tasks in other neurodegenerative conditions. Crowell et al. (2012) measured an increased beta power during a movement task in PD using an electrocorticography over the motor cortex, while Hughes et al. (2018) reported no beta suppression during a Go/NoGo task in frontotemporal dementia linking it with increased impulsivity of the patients. Moreover, we found that the visual EROs in beta-band positively correlated with severity of motor impairment of the DLB patients. These findings suggest that a lack of beta inhibition might be an oscillatory correlate of impaired execution of motor-cognitive actions (i.e., dual tasking) and bradyphrenia (cognitive slowing) seen in DLB.

4.3. Theta ERO

Whereas during the auditory task ERO in theta-band was comparable among DLB patients and controls, during the visual task the patients had decreased theta activity related to both early sensory and later cognitive processing. Interestingly, at rest, high theta (also called pre-alpha, 6–7.5 Hz) is the dominant frequency in DLB patients, in contrast with AD and controls, where the dominant frequency is alpha (Franciotti et al., 2020). This abnormal EEG pattern

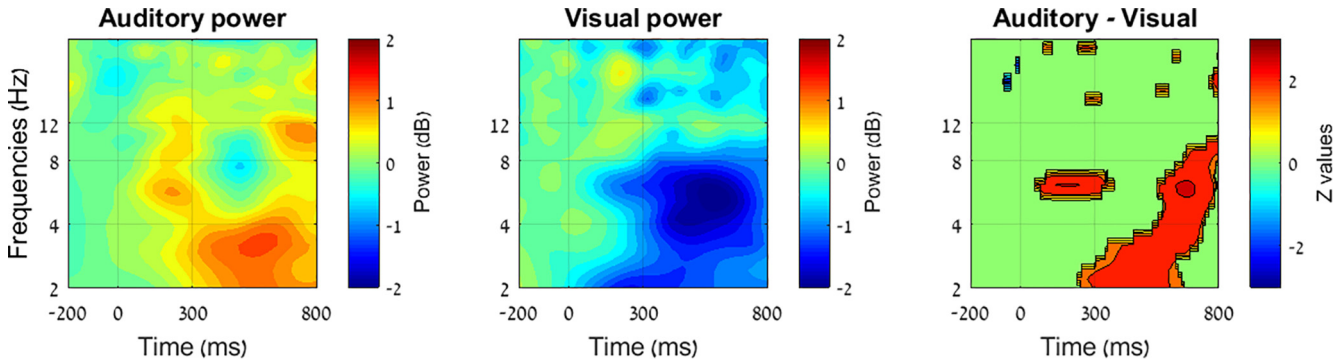

Fig. 6. The differential changes in power during auditory *vs* visual oddball tasks in patients with dementia with Lewy bodies. Principal component analysis was applied to identify differential patterns of visual activity of the patients. The eigenvector which accounted for the most variance in the data was convoluted and its time-frequency power was calculated. Left: Power map of the auditory task shows an increase in early theta and late delta bands. Middle: Power map of the visual task shows a decrease in delta and theta bands. Right: Three clusters (early theta and late theta and delta bands clusters) of statistically significant differences between auditory and visual conditions are indicated as red areas on a z-map. Green areas refer to statistically non-significant z-values ($-1.96 < z < 1.96$).

correlates with cognitive impairment and possibly arises from a thalamocortical dysrhythmia (Franciotti et al., 2020).

Similar to this study, the literature reports that cognitive tasks are characterized by decreased auditory and visual ERO in theta band in AD patients compared to controls (Yener et al., 2007; Caravaglios et al., 2010) and decreased visual theta ERO in PD-MCI patients compared to amnesic MCI patients and controls (Yener et al., 2019). Furthermore, in AD, decreased visual ERO have been linked to cholinergic depletion, since theta band activity seen in AD patients treated with acetylcholine esterase inhibitors was as strong as that seen in controls and higher than in non-treated patients (Yener et al., 2007). In DLB cortical acetylcholine is depleted due to basal forebrain damage, leading to disrupted bottom-up orienting of attention (Gratwicke et al., 2015), fluctuating cognition (O'Dowd et al., 2019) and visual hallucinations (Uchiyama et al., 2012), the core features of DLB. It is therefore possible that the decrease in visual theta ERO in DLB is a reflection of the abnormal cholinergic neural network. Intriguingly, the majority of our patients received cholinergic medication, but this did not seem to compensate for the impaired neural response.

Of specific interest is the finding that decreased theta ERO during the visual task was identified as a principal component which accounted for most of the variance of the visual EEG data in the patients with DLB and was statistically different from the theta activity during the auditory task. Therefore, we suggest that decreased theta oscillations during the visual task might serve as a unique EEG marker of dysfunction of the visual system in DLB.

4.4. Alpha ERO

Alpha-band power suppression is well detailed in the literature as an active process that facilitates information processing while filtering unnecessary neural background noise (Klimesch, 2012). One of the proposed functions of alpha oscillations is a top-down control of the signals from frontal and parietal cortices (Wang et al., 2016). When attention is addressed to external visual events, alpha power in the visual cortex decreases, whereas when attention is directed to internal representations, such as in visual imagery and working memory maintenance, alpha power increases in the visual dorsal stream (Klimesch, 1999; Tuladhar et al., 2007; Rajagovindan and Ding, 2011). Importantly, in DLB and PDD, eyes-open alpha power at rest is increased compared to controls and AD with evidence for an involvement of the cholinergic system in modulating alpha reactivity (Schumacher et al., 2020). This is in accordance with studies, which show that performance is highest if pre-stimulus alpha power is low for visual stimuli, attention and general cognitive performance (Hanslmayr et al., 2007). Furthermore, in DLB, resting state EEG is characterized by abnormal "functional cortical connectivity" in alpha band, resulting in compromised network efficiency (Babiloni et al., 2018).

In our study event-related inhibition of alpha power in both tasks was observed in the controls, but not in the DLB patients. This finding taken together with the above mentioned theory suggests that the lack of inhibition in alpha-band power during the processing of external stimulus may result in the predominance of task-irrelevant processes in the brain. Clinically this might be expressed as inattention, unresponsiveness, and possibly visual hallucinations.

4.5. Functional interaction between oscillations

Even though neural oscillations are often studied as separate entities, this separation is artificial, since in the brain different oscillations act in concert, and thus their functional interaction should be also investigated. A recent theory proposes that oscillations in different frequency bands differently contribute to the fluctuations in the background neuronal noise at the time of neural computations (Griffiths et al., 2019). Briefly, the authors claim that inhibition in alpha/beta ERO does not carry any stimulus-specific information per se, yet it reduces background neuronal noise. This provides favorable conditions for another mechanism (possibly, theta power increases) to forward information processing through increase of signal strength. This theory is in line with the observation that the activation of cholinergic neural networks enhances neural signals in response to external stimuli (Gratwicke et al., 2015), and strengths the link between decreased theta oscillations and cholinergic depletion (Yener et al., 2007).

Our findings suggest that DLB patients fail both to reduce neuronal background noise (insufficient alpha/beta inhibition) and enhance the neuronal signal (insufficient theta/cholinergic activation) when visual processing is performed. It is likely that a decrease in theta and lack of inhibition in alpha oscillations lead to predominance of task-irrelevant neural processes in the DLB patients, which may be expressed clinically as fluctuation in attention/alertness and high-level visual disturbances.

4.6. Relationship between ERP and ERO

In this study time-frequency analysis revealed that ERO in almost all frequency bands showed pronounced differences between DLB and healthy controls, whereas time domain analysis showed significant difference only in the latency of the visual P3.

This finding might stem from the fact that rich spatio-temporal information contained in the neural response to an event is often reduced by averaging across trials to obtain grand-average ERP in time domain leaving only phase-locked activity (i.e., locked to a stimulus), whereas the time-frequency response sums together the neural activity whether or not it is aligned in phase with stimulus onset and contains both phase-locked and non-phase-locked (i.e., endogenous/induced) dynamics (Cohen, 2014; Helfrich and Knight, 2019). Furthermore, it has been proposed, that ERP and ERO could be related to independent neuronal events produced in two distinct cortical populations (Mazaheri and Jensen, 2006). This means that ERP and ERO are neither completely redundant nor independent, and time-frequency analysis measures somewhat unique information, which is not necessarily revealed with ERP averaging in time domain (Cohen and Donner, 2013; Munneke et al., 2015). However, the direct comparison between ERP and ERO was beyond the scope of this study, and future works are needed to further understand the relationship between ERP and ERO.

This exploratory pilot study has several limitations. The study included a small sample of possible or probable DLB cases unconfirmed by pathology. As AD and DLB pathology may overlap and as we did not have an AD group, we cannot directly attest that the findings are solely specific to DLB, but rather they may reflect dementia in general. This should be further explored in future studies. Despite the known modulatory effect of both acetylcholine and dopamine on P3 component, we opted that patients use their regular medications in order to assess function during usual clinical state. The gamma-band activity was not analyzed since it is particularly affected by muscle artifacts and tremor, which are common in DLB. Functional connectivity and interplay between different oscillations were not considered in this study since we used an EEG system with only 19 electrodes. Of note is that this pilot study is exploratory and the findings should be confirmed by investigating additional groups of patients with neurodegenerative diseases to further explore the specificity of the results and their clinical utility. Nevertheless, our findings provide for the first time, a new view of abnormal EEG activity in DLB, which can suggest a mechanistic explanation for impaired processing of visual information and cognitive dysfunction.

5. Conclusions

Visual oddball task in DLB is characterized by a distinguishing EEG signature: a decrease in theta ERO related to both early sensory and later cognitive processing of a stimulus and a lack of inhibition in alpha power related to later cognitive processing of a stimulus. We suggest that this abnormal activity might be an oscillatory underpinning of such core DLB symptoms as fluctuations in attention and high-level visual disturbances.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors Contributions

Study concept and design: AM, TS.
Data acquisition: YR, IM, TS.
Data analysis: YR.
Data interpretation: YR, IM, FF, TS, AM.
Drafting the article: YR, AM.
Critical revision of the manuscript for important intellectual content: YR, IM, FF, NB, NG, TS, AM.
All authors approved the final version.

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