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Short Report

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Event-related oscillations in dementia with Lewy bodies with a mutation in the *GBA* gene

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Abstract

Introduction. In dementia with Lewy bodies (DLB), mutations in the *GBA* gene are associated with a more severe cognitive phenotype. In basic science, event-related oscillations have traditionally been used to explore the neurophysiological underpinnings of various aspects of cognitive performance. Here, we aimed to compare event-related oscillations in DLB patients who are carriers and non-carriers of *GBA* mutations.

Method. EEG was recorded during a visual oddball task in eight clinically diagnosed Ashkenazi Jewish DLB patients with the N370S mutation in the *GBA* gene (*GBA*-DLB) and eleven DLB non-carriers. The time-frequency power and inter-trial phase coherence were calculated from the Morlet wavelet convolution from the Fz electrode.

Results. Task performance and cognitive assessments were comparable between groups. While the within-non-*GBA*-DLB group analysis revealed a significant increase relative to the baseline in the delta-band power ($p=0.01$, Cohen's $d=1.0$), the within-*GBA*-DLB-group analysis did not detect any event-related power change. In contrast, both subgroups showed an increase relative to the baseline in the delta and theta bands inter-trial phase coherence (all $p<0.03$, $d>1.3$). The between-group analysis revealed that event-related power - but not coherence - was lower in *GBA*-DLB compared to non-carriers in the delta band ($p=0.04$, $d=-0.9$).

Conclusions. *GBA*-DLB patients showed decreased delta-band power compared to non-carriers despite the similar cognitive performance, whereas inter-trial phase coherence was comparable in both groups. These findings suggest that in carriers, preserved inter-trial phase coherence possibly compensates for the impaired power by eliciting the appropriate functional configuration needed for stimulus processing and task performance.

Keywords: dementia with Lewy bodies, *GBA* mutations, event-related neural oscillations, visual oddball task.

Introduction

Dementia with Lewy bodies (DLB) is a common neurodegenerative dementia characterized by motor parkinsonism, visual hallucinations and fluctuations in attention and alertness (McKeith et al., 2017). Mutations in the *GBA* gene are frequent among patients with DLB and Parkinson's disease (PD) and are associated with a younger age of onset and a more severe cognitive and motor phenotype (Shiner et al., 2016; 2021).

Neural oscillations as measured by EEG have traditionally been used to explore various aspects of behaviour, including perception, and cognitive and motor performance (Cohen 2014). Correspondingly, abnormal oscillations have been linked to several neurological and psychiatric diseases (Guntekin and Basar, 2016). Indeed, one of the supportive biomarkers of DLB is a prominent spontaneous posterior slow-wave activity with periodic fluctuations in the pre-alpha/theta range recorded during resting-state EEG (McKeith et al., 2017). In addition, event-related potentials in DLB are characterized by increased latency and lower amplitude of the neural response as compared to controls, suggesting impaired information processing (Bonnani et al., 2010). Time-frequency analysis has revealed that DLB patients show decreased event-related synchronization in the delta and theta bands, and impaired desynchronization in the alpha and beta bands, which were related to both early sensory and later cognitive processing of the visual stimulus (Rosenblum et al., 2020). However, whether EEG activity differs between patients with DLB with and without mutations in the *GBA* gene is unclear.

Here, we explored the EEG signal recorded during a visual oddball task in *GBA*-DLB and non-*GBA*-DLB patients. Specifically, we analyzed 1) the time-frequency power of neural oscillations as a reflection of the amount of activity in certain frequency bands during a cognitive task, and 2) the inter-trial phase coherence as a measure of coupling or consistency of the timing of the signals (Cohen, 2014). Based on the literature reporting more severe cognitive dysfunction associated with the presence of *GBA* mutations, we hypothesized that the genotypic differences between the two subgroups would be reflected by more severe alterations of event-related neural oscillations in the *GBA*-DLB group of patients.

Methods

Nineteen clinically diagnosed patients with DLB of Ashkenazi Jewish (AJ) origin who visited the Cognitive Neurology Unit at the Neurological Institute, Tel Aviv Medical Center, between May 2016 and February 2021 participated in this cross-sectional study. DLB patients were included if they met the consensus clinical criteria for possible or probable DLB (McKeith et al., 2017). All patients were screened for the nine most common *GBA* mutations reported among the AJ (N370S, L444P, c.84insG, IVS2+1G->A, V394L, R496H, 370Rec, E326K, and T369M) (see Shiner et al., 2021 for details). Seven patients were carriers of one copy of the N370S mutation in the *GBA* gene, one patient was homozygous for this mutation (a Gaucher patient with DLB). All patients were tested on their regular medications, in their alert and good clinical state. The study was approved by the local ethical committee and performed according to the Principles of the Declaration of Helsinki and all participants gave their informed written consent prior to participation and after we made sure they understood the consent and to the PI judgment were eligible to sign an informed consent.

Patients underwent a complete neurological evaluation. Sufficient visual function was evaluated by a neurologist to ensure the ability to perform the visual oddball task. The presence of visual hallucinations was assessed by direct questioning as described previously (Rosenblum et al., 2021). Motor symptoms were evaluated with the motor part of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), whereas the global cognitive function was assessed using the Montreal cognitive assessment (MoCA).

Following the clinical assessment, subjects were introduced to the visual oddball task (see Rosenblum et al., 2020 for details). EEG was recorded using a wireless 19-channels EEG cap (Enobio20 Neuroelectronics, Spain). After preprocessing, the power and inter-trial phase coherence, as measures of synchronization and the timing of signals, respectively (Cohen, 2014), were calculated from the target trials using complex Morlet wavelet convolution (see Rosenblum et al., 2020 for details). A vast literature confirms that event-related response is stronger at the midline electrodes, with the largest amplitude recorded at Pz. However, in DLB, reversed amplitude distribution gradient was found with the largest amplitudes observed at Fz (Bonnani et al., 2010). Furthermore, due to frontal dysexecutive dysfunction, DLB patients would be expected to express prevalent alterations of the anterior component of the event-related response (Bonnani et al., 2010). Based on these premises, in this study, we analyzed the signal recorded from Fz.

The time-frequency maps of the two study groups were compared using the permutation-based test with 1000 randomization with cluster-based correction for multiple comparisons. Effect sizes were calculated using Cohen's d. Demographic, clinical, and behavioural characteristics of the patients were compared using the non-parametric Mann-Whitney U two-tailed test or Fisher's exact test. All analyses were conducted using custom scripts written in Matlab (Mathworks, USA).

Results

Demographic, clinical and behavioural characteristics

The mean time since diagnosis, levodopa equivalent dose, MoCA and UPDRS scores were similar in both groups (Table 1). The majority of patients in both groups received both levodopa and acetylcholinesterase inhibitors. *GBA*-DLB patients were younger than non-carriers ($p=0.004$). Overall task performance was comparable between groups, including similar reaction time and reaction time variability. *GBA*-DLB patients had a trend towards a lower target hit rate ($p=0.07$).

Table 1: Patients' demographic, clinical and behavioural characteristics (means $\pm$ SD)

Parameter	Non- <i>GBA</i> -DLB	<i>GBA</i> -DLB	p
Number of subjects	11	8	-
Age, years (range)	75.1 $\pm$ 5.2 (66-81)	67.0 $\pm$ 4.5 (60-72)	0.004*
Gender, Male (%)	10 (91%)	7 (88%)	1.000
Montreal cognitive assessment	21.0 $\pm$ 5.0	17.8 $\pm$ 6.2	0.272
Education, years	16.9 $\pm$ 4.4	15.4 $\pm$ 4.2	0.428

MDS-UPDRS, motor part	36.2±16.0	33.4±17.5	0.591
Disease duration, years	3.6±1.8	4.4±3.1	0.717
Treated with acetylcholinesterase inhibitors, No. (%)	10 (91%)	8 (100%)	1.000
Treated with Levodopa, No. (%)	8 (73%)	8 (100%)	0.228
Levodopa equivalent daily dose, mg/day	284±274	188±174	0.492
Target hits, %	100.0±0.0	97.9±3.2	0.072
False positives, %	2.7±3.0	5.5±6.0	0.322
Response time, ms	589±119	611±66	0.462

* - significant p-values, MDS - UPDRS-Movement Disorders Society Unified Parkinson Disease Rating Scale.

Power

The non-GBA-DLB group analysis revealed a significant synchronization (i.e., increase in activity) relative to the baseline in the delta-band (2-4Hz) power at 200-400ms ($z=2.4$, $p=0.007$, Cohen's $d=1.0$) and desynchronization in the alpha-band (7-10Hz) power at 500-800ms ($z=-2.2$, $p=0.01$, $d=-0.9$) after stimulus presentation with large effect sizes. At the same time, the GBA-DLB group analysis did not detect any event-related activity (Fig.1). Between-group analysis revealed that event-related power was decreased in GBA-DLB patients compared to non-carriers in the delta band at 200-300ms after stimulus presentation with a large effect size ($z=-1.7$, $p=0.04$, $d=-0.9$). EEG power in the theta, alpha and beta bands was comparable between groups.

Figure 1: Event-related power and inter-trial phase coherence maps in patients with dementia with Lewy bodies with and without GBA mutations. Baseline-normalized to the decibel scale EEG time-frequency recorded from the Fz electrode during the visual oddball task averaged over target trials. Red and blue indicate a power/phase coherence increase or decrease, respectively, relative to the baseline (-200-0ms). Black lines highlight the area of significant difference ($p < 0.05$) between the event-related activity and baseline within each group separately as assessed by permutation test with incorporated cluster-based correction for multiple comparisons.

Inter-trial phase coherence

The GBA-DLB group analysis revealed significant synchronization in the delta-band inter-trial phase coherence relative to the baseline at 200-400ms ($z=1.8$, $p=0.03$, $d=1.3$) and in the theta band (4-8Hz) at 0-380ms ($z=1.9$, $p=0.03$, $d=1.3$) after stimulus presentation with large effect sizes (Fig.1). Similarly, the non-carrier-group showed synchronization in delta-band phase coherence relative to the baseline at 0-400ms ($z=2.8$, $p=0.00$, $d=1.6$), and in low theta-band (4-6Hz) phase coherence at 180-380ms ($z=3.1$, $p=0.00$, $d=2.9$) after stimulus presentation with very large effect sizes (Fig.1). Event-related phase coherence was comparable between groups in all frequency bands.

Discussion

In this study, we analyzed event-related oscillations elicited by a visual oddball task in DLB patients with and without mutations in the *GBA* gene at the midline frontal electrode. The findings revealed that *GBA*-DLB patients showed decreased delta-band power compared to non-carriers despite the similar cognitive performance, whereas inter-trial phase coherence was similar in both groups.

A delta response is the amplest signal associated with an event-related response (Guntekin and Basar, 2016), which increases during mental tasks that require concentration by increasing functional inhibition of the sensory afferents. In other words, a delta response increases the inhibition of networks that should be inactive to accomplish a task (Harmony, 2013). Correspondingly, a decreased delta response is a general EEG marker of cognitive dysfunction, mainly in decision-making and attentional processes (Guntekin and Basar, 2016). A decreased delta response has been reported in many neurological and psychiatric diseases, including Alzheimer's disease, vascular dementia, PD, bipolar disorder, schizophrenia, alcoholism and DLB compared to healthy age-matched controls (Guntekin and Basar, 2016; Rosenblum et al., 2020).

Several generators of delta oscillations, including thalamo-cortical cells, nucleus accumbens, dopaminergic neurons in the ventral tegmental area, ventral pallidum, and brainstem, have been reported in the human brain (Guntekin and Basar, 2016). It is thus possible that a disrupted event-related response observed in *GBA*-DLB patients may be associated with similar dysfunction of the above-mentioned brain areas, reflecting a more severe network dysfunction. Unfortunately, EEG has low spatial resolution and poor ability to measure neural activity below the upper layers of the cortex, e.g., at the sub-cortical structures.

The properties of EEG, such as a low signal-to-noise ratio, may also explain the lack of findings in the theta, alpha and beta bands activity. These frequencies are weaker and harder to detect, especially, in DLB patients, who show dampened event-related activity as compared to controls (Rosenblum et al., 2020).

Interestingly, in the current study, both groups were comparable in their cognitive and motor function as well as in task performance. Despite these similarities, carriers showed impaired event-related delta-band power, a finding that suggests the presence of possible compensatory mechanisms. One of the explanations is a younger age of the *GBA*-DLB patients, which may account for potentially better preserved compensatory abilities. An alternative explanation relates to the inter-trial phase coherence findings.

Contrary to the event-related power, inter-trial phase coherence in the delta and theta bands was detectable and comparable between the groups. Inter-trial phase coherence is mostly independent of power and can be conceptualized as a "functional configuration used to maximize information processing or facilitate inter-regional coupling" (Cohen, 2014). A specific functional configuration, in turn, might be driven by consistency in the timing of afferent signals from lower areas that reset the ongoing oscillations to the appropriate functional configuration (Cohen, 2014).

In this context, preserved inter-trial phase coherence observed in carriers could explain equal task performance despite impaired event-related power through compensation. Thus, it is probable that *GBA* carriers are still able to elicit an appropriate functional configuration needed for stimulus processing and task performance, possibly

through the remaining sub-networks. Potentially, with disease progression, this mechanism will no longer suffice and cognitive function will likely deteriorate, unmasking the difference reported in previous studies (Shiner et al., 2021) of more severe cognitive decline in *GBA*-DLB patients.

The main limitation of this pilot cross-sectional study is its small sample size; therefore, the replication of results in an independent and larger sample is required to show their generalisability. We did not sequence the entire *GBA* gene and looked only at the *AJ* mutations. Furthermore, all patients were on medication at the time of assessment, which could impact the results. Nevertheless, despite these limitations, our study provides, for the first time, evidence of differential event-related activity in DLB patients with *GBA* mutations.

References

- Bonanni L, Franciotti R, Onofrij V, Anzellotti F, Mancino E, Monaco D, Gambi F, Manzoli L, Thomas A, Onofrij M. (2010) Revisiting P300 cognitive studies for dementia diagnosis: early dementia with Lewy bodies (DLB) and Alzheimer disease (AD). *Clin Neurophysiol* 40(5-6):255-65. <https://doi.org/10.1016/j.neucli.2010.08.001>
- Cohen MX (2014) Analyzing neural time series data: theory and practice, MIT press.
- Güntekin B, Başar E (2016) Review of evoked and event-related delta responses in the human brain, *Int J Psychophysiol* 103:43-52. <https://doi.org/10.1016/j.ijpsycho.2015.02.001>
- Harmony T (2013) The functional significance of delta oscillations in cognitive processing. *Front Integr Neuroscience* 5:7-83. <https://doi.org/10.3389/fnint.2013.00083>
- McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, Weintraub D et al (2017) Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* 89:88-100. <https://doi.org/10.1212/WNL.0000000000004058>
- Rosenblum Y, Maidan I, Fahoum F, Giladi N, Bregman N, Shiner T, Mirelman A (2020) Differential changes in visual and auditory event-related oscillations in dementia with Lewy bodies. *Clin Neurophysiol* 131:2357–2366. <https://doi.org/10.1016/j.clinph.2020.06.029>
- Rosenblum Y, Bregman N, Giladi N, Mirelman A, Shiner T (2021) Associations between visual hallucinations and impaired visuo-spatial abilities in dementia with Lewy bodies. *Neuropsychol.* 35:276. <https://doi.org/10.1037/neu0000728>
- Shiner T, Mirelman A, Rosenblum Y, Kavé G, Weisz MG, Bar-Shira A, Goldstein, Thaler A, Gurevich T, Orr-Urtreger A, Giladi N, Bregman N (2021) The frequency and clinical effect of *GBA* mutations and *APOE* ϵ 4 polymorphisms on Dementia with Lewy Bodies among Ashkenazi Jews. *J. Alz. Dis.* 4:1–9. <https://doi.org/10.3233/JAD-201295>
- Shiner T, Mirelman A, Weisz MG, Bar-Shira A, Ash E, Cialic R, Nevler N, Gurevich T, Bregman N, Orr-Urtreger A, Giladi N (2016) High frequency of *GBA* gene mutations in dementia with Lewy bodies among Ashkenazi Jews. *JAMA Neurol.* 73:1448-1453. <https://doi.org/10.1001/jamaneurol.2016.1593>

Declarations

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Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Availability of data and material

Data will be made available on reasonable request.

Code availability

Custom codes will be made available on request.

Authors' contributions

Study concept and design: TS, YR, AM.

Data acquisition: YR, TS.

Data analysis and interpretation: YR.

Drafting the article: YR, TS.

Equipment: AM.

Critical revision of the manuscript for important intellectual content: YR, TS, AM, AOU, NG, NB, IM, OG, MGW.

All authors approved the final version.

Ethics approval

The study was approved by the local ethical committee and performed according to the Principles of the Declaration of Helsinki.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

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