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ORIGINAL ARTICLE

Reduced alpha2 power is associated with slowed information processing speed in multiple sclerosis

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Abstract

Objective: Cognitive impairment is common in multiple sclerosis (MS), significantly impacts daily functioning, is time-consuming to assess, and is prone to practice effects. We examined whether the alpha band power measured with magnetoencephalography (MEG) is associated with the different cognitive domains affected by MS.

Methods: Sixty-eight MS patients and 47 healthy controls underwent MEG, T1- and FLAIR-weighted magnetic resonance imaging (MRI), and neuropsychological testing. Alpha power in the occipital cortex was quantified in the alpha1 (8–10 Hz) and alpha2 (10–12 Hz) bands. Next, we performed best subset regression to assess the added value of neurophysiological measures to commonly available MRI measures.

Results: Alpha2 power significantly correlated with information processing speed ($p < 0.001$) and was always retained in all multilinear models, whereas thalamic volume was retained in 80% of all models. Alpha1 power was correlated with visual memory ($p < 0.001$) but only retained in 38% of all models.

Conclusions: Alpha2 (10–12 Hz) power in rest is associated with IPS, independent of standard MRI parameters. This study stresses that a multimodal assessment, including structural and functional biomarkers, is likely required to characterize cognitive impairment in MS. Resting-state neurophysiology is thus a promising tool to understand and follow up changes in IPS.

KEYWORDS
alpha power, cognition, magnetoencephalography, multiple sclerosis, neurophysiology

INTRODUCTION

Cognitive impairment is a frequent symptom of multiple sclerosis (MS), affecting 34% to 65% of adult patients [1]. While multiple cognitive domains can be affected (e.g., attention, working, and verbal memory), information processing speed (IPS) is the first and most commonly affected cognitive domain [2]. A slowed IPS reduces the quality of life and participation in daily life [1, 3]. Neuropsychological tests for detecting cognitive dysfunction in MS exist but are time-consuming. Their results may be confounded by concomitant mood disorders, medication use, cognitive reserve, cultural differences, education, learning effect, and fatigue [1, 3]. Therefore, we need more objective markers that capture cognitive evolution and pick up treatment effects.

Currently, an objective, reproducible, and operator-independent estimator of cognitive impairment in MS is lacking. This hinders

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diagnosis, research, and treatment. Some correlations between cognition in MS and magnetic resonance imaging (MRI) structural brain parameters have been found. Whereas atrophy measures have elucidated early thalamic involvement in the pathophysiology, the correlations with cognitive scores are generally weak (correlation $r = -0.3$ between T2 lesion load and cognition) [4]. This is commonly described as the clinical–radiological paradox. [4, 5]. Functional MRI (fMRI) has also been employed in the search for a biomarker of cognitive impairment in MS. Yet, fMRI findings may be affected by reduced blood flow rather than reduced or reorganized neuronal activity, as hypothesized by Baijot et al. [6]. Both magnetoencephalography (MEG) and electroencephalography (EEG) provide a more direct measurement of neuronal activity and have – at the cost of a lower spatial resolution – a higher temporal resolution compared to fMRI, with MEG having a superior spatial resolution over EEG [7–10].

The peak alpha frequency measured by EEG and MEG is reproducible within subjects and can show individual differences in brain functioning [11, 12]. In standard conditions, the alpha peak frequency is individually determined, is independent of cognitive training, and functions as a reproducible marker for neurophysiological cognitive reserve [11, 13, 14]. In healthy subjects, the alpha band spectral power (8–12 Hz) during wake resting state correlates with cognitive performance [11, 12]. However, in several neurological illnesses such as Alzheimer's dementia, vascular dementia, and dementia with Lewy bodies, frequency power shifts are correlated with disease progression and may even be used to differentiate between conditions [11, 13, 15–22]. It stands to reason, therefore, that different pathophysiological conditions may be associated with specific neurophysiological changes.

In MS, we expect an association between cognitive scores and alpha power as production and modulation of alpha oscillations are heavily influenced by the thalamus, a structure known to be affected early in the disease course, and the atrophy of which is correlated with cognitive impairment in MS patients [23–25]. Alpha output is hypothesized to result from feed-forward mechanisms (from the thalamic alpha pacemaker and to a lesser extent from other alpha sources originating from the cortex), cortical–thalamocortical projections, and intracortical circuits [26]. Disrupted thalamocortical circuits cause deficits of higher order functioning, attentional deficits, loss of vigilance, and/or decreased processing speed [25, 27, 28]. Within the MS population, thalamic atrophy due to focal demyelination or from degeneration of thalamic nuclei secondary to disruption of thalamocortical circuits is associated with disease activity, reduced IPS, the transition from a clinically isolated syndrome (CIS) to definite MS, and with cognitive impairment in MS [25, 27, 29–31].

Both alpha power and thalamic volume correlate with MS patients' cognitive functioning [30, 32, 33]. Previous article examining the role of alpha power, however, do not correct for volumetric MRI parameters such as thalamic volume.

In summary, given the shifts in alpha frequency in other disorders with cognitive impairment, the stability of alpha frequency as a marker for cognitive reserve in healthy subjects, the primordial role of the thalamus in alpha generation, and the known link between thalamic integrity and cognition within the MS population, we hypothesized a link between alpha power and cognition in MS. Yet, it is unclear if alpha power is a marker of overall cognitive functioning or is specific to specific cognitive domains. In this article, we evaluate several cognitive screening tools, radiological parameters, and alpha power as possible predictors for cognitive functioning and aim to answer the question whether alpha spectral power improves the prediction of cognitive scores in addition to the known associations with MRI parameters.

PATIENTS AND METHODS

Participants

Data from 68 MS patients and 47 matched healthy controls were analyzed [34]. Patients included were diagnosed with MS according to the revised McDonald criteria with ages between 18 and 60 years. Patients with relapsing–remitting MS ($n = 59$), primary progressive MS ($n = 4$), secondary progressive MS ($n = 3$), and CIS ($n = 1$) and a score ≤6 on the Expanded Disability Status Scale (EDSS) were included as well as 47 age-matched healthy controls. Exclusion criteria were a recent relapse or treatment with corticosteroids in the 6 weeks before the study, pacemaker, dental wires, concomitant psychiatric disease (e.g., major depressive disorder), epilepsy, and benzodiazepine use. Participants underwent structural MRI, MEG recording, and cognitive testing.

Ethics

All subjects provided written informed consent. The study was approved by the local ethics committees of the University Hospital Brussels (Commissie Medische Ethiek UZ Brussel, B.U.N. 143,201,423,263, 2015/11) and the National MS Center Melsbroek (12 February 2015).

Data acquisition

Neuropsychological evaluation

The choice of tests was based on the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). IPS and working memory were tested by the Signal Digit Modalities Test (SDMT), verbal learning with the California Verbal Learning Test II (CVLT-II), visual learning and memory with the Brief Visuospatial Memory Test-Revised (BVMT-R). Verbal fluency was tested by performing the Controlled Oral Word Association Test (COWAT), a test which however is not included in the BICAMS. [1, 35] The Fatigue Scale for Motor and Cognitive Functions (FSMC) questions subjective experiences concerning cognitive and motor fatigue. [36]

MRI recordings

MRI was performed on a 3 Tesla Achieva scanner (Philips Medical Systems). The scanner protocol contained a three-dimensional (3D) T1-weighted imaging sequence with parameters: TR: 4.939 ms, FA 8, 230 × 230 mm^2 FOV, 310 sagittal slices, resulting in a 0.53 x 0.53 x 0.5 mm^3 resolution. This image was affinely coregistered to the MNI152 atlas.

The median delay between the MRI and MEG session across all subjects was 5 days with an interquartile range of 2–10 days. The maximal delay between MEG and MRI acquisition was 23 days.

As previously described, brain segmentation was done with the icobrain pipeline (version 3.1), which segments T1-weighted images into the cerebrospinal fluid, grey matter, and white matter. [37] White matter FLAIR (fluid-attenuated inversion recovery) hyperintensities are identified and included in white matter segmentation. After skull stripping and bias correction, the T1-weighted image is segmented using a probabilistic image intensity model. Lesion segmentation is done by the following loop until convergence: segmentation of the T1-weighted image, identification of intensity outliers on the FLAIR image, and supplementing the T1 image with these lesions. T1 hypointensities (black holes) are also obtained as a subsegmentation of the FLAIR lesions. Brain volumes (except for lesion load and black hole volume) are normalized for head size.

MEG data collection

MEG data were collected at the ULB Hôpital Erasme (Brussels, Belgium) on an Elekta Neuromag Vectorview scanner for the first 30 MS patients and 15 healthy controls and on an Elekta Neuromag Triux scanner for the remaining cohort (38 MS patients and 32 healthy controls) due to an upgrade. Both MEG scanners have a similar sensor layout (102 triple sensors consisting of one magnetometer and two orthogonal planar gradiometers) placed in a magnetically shielded room (Elekta Neuromag & Maxshield; Elekta Oy). No significant difference in power spectral density in any of the bands was detected between the original scanner and the upgraded scanner. During MEG data collection, subjects were asked to close their eyes and think of nothing specifically (eyes-closed resting state) for 10 min. MEG signals were recorded at a 1 kHz sampling rate with a 0.1–330 Hz pass-band filter. Subjects' head position, wakeful state, eye movements, and electrocardiogram were continuously monitored.

Data were preprocessed using MaxFilter software applying the temporal extension of signal space separation algorithm (default settings) and corrected for subject movement [38]. Further, data were filtered into the 0.1–40 Hz range, and artifacts were identified through independent component analysis and removed by comparing their time series to simultaneously acquired electrocardiograms and electrooculograms. Next, we applied a linearly constrained minimum variance beamformer to project on the source grid [39].

Time-series analyses and parcellation

The cerebral cortex was parcellated using a custom parcellation atlas to 42 parcels [34]. For each parcel, the first principal component of the time series within that parcel was used as that parcel's time series. Time series were analyzed by using a discrete fast Fourier transform to calculate the relative power for the MEG frequency bands (delta [0.5–4 Hz], theta [4–8 Hz], alpha1 [8–10 Hz], alpha2 [10–12 Hz], beta [12–30 Hz], and gamma [30–40 Hz]). Alpha power was divided into alpha1 (normalized power spectral density in the range 8–10 Hz) and alpha2 (normalized power spectral density in the range 10–12 Hz) in parallel with other studies examining the role of alpha power in cognition in MS [32, 40–42].

Based on the 3D location of the parcels and the parcellation atlas previously used while analyzing this dataset, the parcels were grouped into five brain regions [34]. Twelve parcels were assigned to the occipital region, ten parcels were assigned to the frontal region, six parcels were assigned to the central gyrus, six parcels were assigned to the parietal–temporal junction, and four parcels were assigned to the temporal region. Four parcels were excluded due to overlap with multiple regions. For each region, the average normalized spectral density was computed for frequencies 8–12 Hz within the alpha band. From all studied regions, the occipital region had a significantly higher average power spectral density. Predominant involvement of occipital regions in mild cognitive impairment due to other causes has been suggested in recent studies [18]. For these reasons, only this region was selected for further analysis. In the supplementary materials, a boxplot of the power spectral density of each region in the alpha band can be found (Figure S1).

Statistical analysis

Statistical analyses were performed with MATLAB. Differences in the study population were determined using Student's *t*-test. A set of chi-squared tests was performed to see if there were significant group differences between males and females, healthy controls and people with MS (pwMS), and scanner type. Pearson correlation tests were performed to check the correlation between the power spectrum, normalized brain volumes, and cognitive test scores.

Best subset regression was performed by including sets of possible predictors and creating all possible models [43, 44]. For each predictor a *t*-test was performed to see if it contributed significantly to the model. The selection ratio was the ratio of times a predictor attributed to a significant model divided by the number of significant models. Predictors included in more than half of the models were typically considered as contributing significant information on the outcome parameters. We preferred this search of all possible linear models as it avoids problems associated with traditional feature selection based on, for example, the Akaike Information Criterion. Indeed, a stepwise selection of parameters strongly depends on the order in which parameters were added [43, 44]. Finally, and next to each parameter's selection ratio, we report the contributions of the

predictors and their significance for the best-performing model. The latter was defined as the model with the highest adjusted R2 (i.e., the percentage of explained variance after correction by the number of predictors). By doing so, a larger model does not necessarily achieve a better score.

RESULTS

Patient characteristics

Sixty-eight MS patients and 47 healthy controls were included. Groups were matched for age and sex. MS patients had a lower education level (1.1 years difference). As expected, a significant difference between groups could be detected for each cognitive score, where the healthy control group systematically scored better than the pwMS group. Normalized brain volumes were significantly lower in the pwMS group compared to the control group.

The demographics and cognitive scores of our subjects are summarized in Table 1. In Figure S2, raincloud plots can be found.

In the pwMS group, 87% of the subjects were of the relapsing–remitting type, 3% were primary progressive, 6% were secondary progressive, and 4% were diagnosed with CIS. The EDSS values lie between 0 and 6.0 with a median EDSS of 2.5, with 76% of patients having an EDSS between 2 and 4.

Cognitive performance measures and patient variables

We have summarized the main patient characteristics (gender, age, and education), radiological parameters (normalized whole brain volume, normalized grey matter volume, normalized white matter volume, and normalized thalamus volume), MEG variables (spectral power in alpha1 and alpha2 in occipital regions), and the cognitive scores (SDMT, CVLT-II, COWAT, BVMT-R, and FSMC-Cog) in Table 1.

As seen in the 'corr' column in Table 2, age is negatively correlated with scores on the SDMT, CVLT-II, and BVMT. Education and alpha2 power correlates with all five cognitive measures. Radiological parameters correlate with cognitive measures (except with COWAT for all volumes and BVMT for normalized white matter volume).

Selection ratios, the 'ratio' column in Table 2, indicate the number of times a parameter significantly ($p < 0.05$) contributed to the multilinear model with respect to the number of possible models to which the parameter could contribute. If alpha2 power was included in the model, it was always retained (selection ratio of 100%) and

TABLE 1 Population characteristics.

Variable	All ($N = 115$)	HC ($N = 47$)	pwMS ($N = 68$)	*P* value
Sex (women)	68 (59)	28 (60)	40 (59)	0.936
Age (years)	48 (11)	47 (12)	48 (10)	0.542
Education (years)	15 (12)	15 (2)	14 (3)	**0.017**
Disease duration (years)	NA	NA	17 (10)	NA
Normalized whole brain volume	1502 (78)	1539 (69)	1477 (77)	**<0.001**
Normalized grey matter volume	881 (52)	898 (45)	868 (57)	**0.002**
Normalized white matter volume	621 (44)	640 (42)	607 (41)	**<0.001**
Normalized thalamus volume	17 (2)	18 (2)	16 (1)	**<0.001**
Occipital lower alpha	0.10 (0.04)	0.09 (0.05)	0.10 (0.04)	0.081
Occipital higher alpha	0.09 (0.04)	0.09 (0.04)	0.08 (0.03)	0.066
SDMT	50 (12)	54 (10)	48 (13)	**0.006**
CVLT-II	63 (10)	66 (7)	62 (11)	**0.022**
COWAT	9.7 (3.5)	11 (4)	9 (3)	**<0.001**
BVMT	27 (7)	29 (5)	25 (7)	**0.004**
FSMC-Cog	26 (10)	18 (6)	31 (10)	**<0.001**

Notes: Sex is indicated as *N* (%), and all the other parameters as mean (standard deviation). For sex, a chi-squared test was performed. For all other variables, a Student's *t*-test was performed. Education was quantified as the number of years of education (6 corresponds to primary school, 12 to high school, 15 to a bachelor's degree, and 17 to a master's degree). Bold type denotes significant outcomes ($p < 0.05$).

Abbreviations: BVMT-R, Brief Visuospatial Memory Test-Revised; CLVT-II, California Verbal Learning Test II; COWAT, Controlled Oral Word Association Test; FSMC-Cog, Fatigue Scale for Motor and Cognitive Functions-Cognitive subscore; HC, healthy controls; NA, not applicable; pwMS, people with multiple sclerosis; SDMT, Symbol Digit Modalities Test.

in the overall best model has a regression coefficient of 0.27 with a significance of $p < 0.01$ as seen in the 'regr' column of Table 2. This means that in every possible multilinear model that can be constructed, the alpha2 power always significantly contributed.

Higher education is linked to the SDMT, COWAT, CVLT-II, and FSMC-Cog (negative predictor). A higher thalamic volume is linked to the SDMT, BVMT, CVLT-II, and FSMC-Cog (negative predictor). Alpha2 power is predictive for the SDMT.

DISCUSSION

This study aimed to examine the potential of quantitative MEG analysis in the cognitive evaluation of MS patients. We observed a significant correlation between alpha2 power and different cognitive tests (a positive correlation in the case of SDMT, CVLT-II, COWAT, and BVMT-R, and a negative correlation for the FSMC). With a best subset regression approach, we could demonstrate that alpha2 power improved the prediction of IPS independently of more readily available MRI parameters. The latter was not the case for the other cognitive parameters considered.

Previous studies have already shown altered connectivity patterns in the alpha2 band in people with multiple sclerosis as compared to healthy controls. Tewarie et al. demonstrated lower functional connectivity in the alpha2 band in MS and demonstrated a correlation between cognitive functioning and functional connectivity in the beta band [41]. Similarly, Schoonheim et al. demonstrated an increased synchronization in the theta, lower alpha, and beta bands and a decreased synchronization in the upper alpha band [45]. Yet, these results did not correct for potential differences in power spectral density, nor did they correct for the use of benzodiazepines. Benzodiazepines are known to increase beta power strongly (and will thus via normalization affect other bands) and are frequently administered to treat sleep, anxiety, or tremor in people with MS. This study is one of the first to exclude people with MS treated with benzodiazepines because of the neurophysiological implications.

In this study, we also demonstrate the use of best subset regression to provide a reliable estimate of how important one particular parameter is among several (potentially correlated) parameters. We show that in multilinear models, including clinical parameters and traditionally used structural parameters, alpha2 power always significantly contributes to the SDMT model. This strongly corroborates the idea that alpha power contributes information to cognitive functioning in a way that is independent of more readily available clinical markers. To further assess the contribution of alpha power to the prediction of IPS, we reran the best subset regression without alpha power. We obtained a corrected R2 of 0.28 instead of 0.37. Including alpha2 power thus considerably increases the amount of explained variance.

Further, we also demonstrate that alpha2 power is mainly linked to IPS and only slightly contributes to other cognitive domains such as spatial and verbal working memory, cognitive fatigue, and verbal fluency. This may seem contradictive of the literature where alpha2 power is often linked to general cognitive decline. Here, it is important to remember that the SDMT is an excellent sentinel test for different cognitive domains [46] and may even predate decline in more specialized cognitive domains [47].

Neuropsychological screening tests are frequently influenced by education, learning effect, psychological well-being, or fatigue at the moment of taking the test; while in resting state neurophysiological recordings, no learning effects are present and could therefore provide a more objective assessment of cognitive functioning [12]. In clinical practice, a model incorporating patient characteristics (age, education), radiological parameters (such as thalamic volume), and neurophysiological data (alpha2 power density) could prove more robust to factors that affect cognitive test scores, but not the cognitive domains themselves.

In this study, longer time series of up to 5 min of resting-state eyes-closed MEG data were analyzed as opposed to epoch selection. Whereas epoching may provide cleaner data, it may fall victim to selection bias of manual selection of epochs and fail to incorporate intra-individual alpha-band oscillations that may also be associated with cognitive function, as is the case in other neurodegenerative diseases such as Alzheimer's dementia [20]. Further, alpha power may be affected by the frequency with which bursts of alpha oscillatory activity may be present. While this is not captured in epoch-selected analyses, a reduced occurrence of alpha power would lower the alpha peak and thus be reflected in our results. However, more advanced modeling (e.g., through the use of functional connectivity dynamics [34, 48]), may be necessary to fully capture the oscillatory dynamics [34].

One limitation of this study is a small but significant difference in education level at baseline. We also did not correct for disease-modifying treatments (DMTs) as we do not expect any effect of DMTs on neurophysiological functioning and alpha power. As our cohort contained seven people with progressive onset, we redid the analyses excluding those seven patients and observed no substantial changes. Whereas we considered it a strength to exclude symptomatic treatments that could affect neurophysiology (e.g., benzodiazepines) [34], it is important to realize that this choice also limits the generalizability of our results to patients not being treated with benzodiazepines. While MEG is not widely available in clinical practice, this study can act as a stepping stone for further research in which our findings could be extrapolated to widely available electroencephalography or to optically pumped magnetometer MEG sensors which might replace SQUID (superconducting quantum interference device) sensors in the future [49].

Finally, we assessed MEG during rest and specific tasks. As correctly pointed out by Khan et al. [40], the analysis of MEG data during different tasks is an essential future research avenue. One could expect stronger correlations for specific cognitive domains when people are scanned during specific tasks. Yet, one would also lose the generalizability that the resting-state condition brings.

TABLE 2 Regression outcome.

	SDMT			BVMT-R			COWAT			CVLT-II			FSMC-Cog		
Predictor	**corr**	**regr**	**ratio**	**corr**	**regr**	**ratio**	**corr**	**regr**	**ratio**	**corr**	**regr**	**ratio**	**corr**	**regr**	**ratio**
Age	**−0.43** ***	**−0.22***	**70%**	**−0.20***	0.00	2%	−0.06	0.00	0%	−0.18	0.14	1%	0.06	0.00	0%
Education	**0.34** ***	**0.23****	**100%**	**0.22***	0.17	6%	**0.30****	**0.29****	**100%**	**0.28****	0.18*	**52%**	**−0.24***	**−0.21***	**75%**
Normalized grey matter volume	**0.46** ***	0.00	44%	**0.26****	0.00	8%	0.12	0.00	0%	**0.37*****	0.25	29%	−0.16	0.17	0%
Normalized white matter volume	0.17	−0.20	17%	0.18	0.00	0%	0.11	0.00	0%	**0.24****	0.00	7%	**−0.25****	0.00	13%
Normalized whole brain volume	**0.41*****	0.00	23%	**0.27****	0.00	9%	0.13	0.00	0%	**0.40*****	0.00	30%	**−0.25***	0.00	13%
Normalized thalamus volume	**0.38*****	**0.33****	31%	**0.34*****	**0.26****	**68%**	0.14	0.05	0%	**0.41*****	0.25*	**55%**	**−0.32*****	**−0.35****	**91%**
Alpha1 (occipital)	−0.07	0.13	0%	**−0.24*****	−0.12	38%	−0.02	0.00	0%	**−0.23***	−0.13	20%	0.11	0.00	0%
Alpha2 (occipital)	**0.43*****	**0.34*****	**100%**	**0.19***	0.00	1%	0.18	0.14	0%	0.16	0.00	1%	**−0.21***	−0.15	4%
R2*		0.37			0.17			0.12			0.25			0.17	

Notes: In the left column predictors for performance on the SDMT, BVMT, CVLT-II, and FSMC-Cog are shown. For each cognitive test, the results of Pearson correlation are shown in the first column (corr). The second column shows the best multilinear model obtained through best subset regression (regr), and the final column shows the selection ratio (ratio) of all predictors across all models. Zero means the parameters were never retained, and 100% means it was retained in each possible model. As an example: in univariate models, the SDMT significantly correlates with age, education, normalized grey, white, whole, and thalamic volumes, and alpha2 power. In the multilinear model that explains most variance of the SDMT, age, education, normalized thalamic volume, and alpha2 power significantly contribute. Further, we also see that alpha2 always significantly contributes to every model predicting the SDMT. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Bold type denotes significant outcomes ($p < 0.05$) and ratios >50%. The latter means that these parameters significantly contributed to at least 50% of all multilinear models in which they were included. See section on Statistical Analysis for more details on best subset regression.

Abbreviations: BVMT-R, Brief Visuospatial Memory Test-Revised; CLVT-II, California Verbal Learning Test II; corr, correlation; COWAT, Controlled Oral Word Association Test; FSMC-Cog, Fatigue Scale for Motor and Cognitive Functions-Cognitive subscore; ratio, selection ratio; regr, regression; SDMT, Symbol Digit Modalities Test.

CONCLUSIONS

This study demonstrates that occipital upper alpha power is significantly associated with a subject's score on the SDMT, a test aimed at assessing IPS. The upper alpha power increased the explained variance from 27% to 38% in multilinear models, including clinical parameters and the typically assessed brain volumes. Our work corroborates the idea that the alpha band may be crucial for IPS [50].

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CONFLICT OF INTEREST STATEMENT

The authors hereby declare no conflicting interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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