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RESEARCH ARTICLE

Neural Circuits

Abnormally low sensorimotor α band nonlinearity serves as an effective EEG biomarker of Parkinson's disease

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Abstract

Biomarkers obtained from the neurophysiological signals of patients with Parkinson's disease (PD) have objective value in assessing their motor condition for effective diagnosis, monitoring, and clinical intervention. Prominent cortical biomarkers of PD have typically been derived from various β band wave features. This study approached the topic from an alternative perspective and attempted to estimate a recently suggested measure representing α band nonlinear autocorrelative memory from a publicly available EEG dataset that involves 15 patients with earlier-stage PD (dopaminergic medication OFF and ON states) and 16 age-matched healthy controls. The cortical nonlinearity was elevated for the PD ON state compared with the OFF state for bilateral sensorimotor channels C3 and C4 ($n = 26$; $P = 0.003$). A similar statistical difference was also identified between PD OFF state and healthy subjects ($n = 26$; $P = 0.049$). Analysis over all channels revealed that the α band nonlinearity induced upon medication was constrained to sensorimotor regions. The α nonlinearity measure was compared with a well-accepted cortical biomarker of β-γ phase-amplitude coupling (PAC). They were in moderate negative correlation ($r = –0.412$; $P = 0.036$) for only healthy subjects, but not for the patients. The nonlinearity measure was found to be insusceptible to the nonstationary variations within the particular data. Our study provides further evidence that the α band nonlinearity measure can serve as a promising cortical biomarker of PD. The suggested measure can be estimated from a noninvasive low-resolution single scalp EEG channel of patients with relatively early-stage PD, who did not yet need to undergo deep brain stimulation operation.

NEW & NOTEWORTHY This study suggests a nonlinearity measure that differentiates Parkinson's disease (PD) dopamine OFF-state scalp EEG data from those of dopamine ON-state patients and healthy subjects. Unlike typical PD cortical biomarkers based on β band activity, this metric shows elevation upon dopaminergic medication in the α band. We provide evidence supporting its potential as an early-stage promising PD biomarker that can be estimated from noninvasive EEG recordings with low resolution and SNR.

biomarker; dopamine; EEG; nonlinearity; Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) motor symptoms of tremor, rigidity, and akinesia are linked with the dopaminergic denervation of the striatum, leading to neural oscillatory abnormalities throughout the basal ganglia-thalamo-cortical, cortico-cortical, and cerebro-muscular networks (1). PD biomarkers indicative of the pathophysiology are most commonly obtained from invasive subcortical local field potential (LFP) recordings acquired from the electrode contacts, during or immediately after the deep brain stimulation (DBS) surgery, performed on advanced late-stage patients (2). These markers reflect the abnormality of the disease and hence are naturally expected to be modulated with dopaminergic medication, i.e., from medication OFF state to ON state. A desired property of a PD biomarker comes from its association with the motor symptom severity, typically quantified with the Unified Parkinson's Disease Rating Scale (UPDRS), which is unavoidably rather subjective, i.e., rater dependent (3). Thus, objective biomarkers are particularly desirable for early diagnosis, optimal treatment, and clinical improvement.

Neurophysiological biomarkers in PD literature have been overwhelmingly derived from the excessive subthalamic

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(STN) LFP β band (~13–35 Hz) activity (2), which is suppressed by dopaminergic administration (4) and coupled consistently with sensorimotor cortical regions (5). Beta band activity in the STN was shown to be phase coupled to the amplitudes of high-frequency oscillations (HFO) encompassing the frequency range of 200–400 Hz (6, 7). A following study (8) confirmed the occurrence of this phenomenon called phase-amplitude coupling (PAC) between β oscillations and HFO in the STN along with the correlation of PAC strength with the UPDRS akinesia-rigidity score. A recent review by van Wijk et al. (2) reports that the STN LFP β band activity-based features describe only ~17% of patient variability in symptom severity, hence contain limited informative power to explain the PD motor impairment. The ratio of slow HFO power (200–300 Hz) to fast HFO power (300–400 Hz) in the STN was proposed by Özkurt et al. (7). They showed that the STN HFO ratio could consistently distinguish the medication OFF state from the medication ON state and was correlated to the contralateral hemibody akinesia-rigidity score (7). The same study showed that HFO ratio and β peak power did not correlate with each other, whereas their combination had an elevated correlation with the akinesia-rigidity score, implying that β band and HFO activities had complementary contributions to the motor state. A PD tremor study conducted by Hirschmann et al. (9) demonstrated the increase of the HFO ratio could predict the emergence of tremors successfully and it outperformed other established biomarkers such as power at individual tremor frequency, β power, and low γ power.

The primary emphasis in the literature on PD biomarkers has centered on basal ganglia, especially the STN, local field potential (LFP) recordings. However, since cortical activities obtained through electroencephalography (EEG), magnetoencephalography (MEG), and subdural electrocorticography (ECoG) are integral components of the motor pathway, they also hold vital information related to the PD mechanisms. Besides cheap, noninvasive, safe, and mobile recordings, scalp EEG offers particular several other advantages such as the detection of early-stage Parkinsonian signatures (10), monitoring of disease progression and treatment response (11), and providing real-time feedback (12).

Unlike the consistency of abnormally high subcortical β activity for the medical OFF state, findings for the modification of cortical spectral β activity concerning dopaminergic medication have been rather ambiguous in the literature. Contrary to few studies concluding that dopaminergic medication increases the cortical β band activity in patients with PD (13, 14), many other cortical PD studies reported nonalteration of β band power due to medication (15–22). The nonalteration of β band power was also endorsed for the comparison between OFF state PD patients (with no medication) and healthy controls (20, 21). Moreover, accounting for the $1/f$ background activity did not affect the recent consensus that there was no significant variation in the cortical β band power between the medication OFF and ON states (22), which used the same publicly available EEG data set with the current study. Modification of cortical β band power seems also dubious for DBS studies, as Airaksinen et al. (23) reported elevated cortical β band power after DBS for some of the patients, while some others found suppression of the β power in the sensorimotor cortex by DBS (24, 25). Hence, although cortical β band power itself does not seem to be a reliable biomarker of PD motor impairment, a recent MEG study conducted by Vinding et al. (21) found out that the cortical β bursts are less frequent in the medication OFF state when compared with healthy controls. However, they could not identify the difference in burst rates when the PD medication OFF state is compared with the ON state instead of healthy controls.

One of the most promising cortical PD biomarkers reported is the excessive PAC strength between β and broadband γ band (50–200 Hz) activities, initially demonstrated by de Hemptinne et al. (18) via ECoG recordings placed over the primary motor cortex and confirmed by several other ECoG studies (26, 27). The PAC as a biomarker, which distinguished the PD OFF medication state from the ON medication and healthy control states, was also detectable when noninvasive scalp EEG is used (19). This finding was confirmed by Jackson et al. (28) using the same EEG data set, while they additionally concluded that the PAC strength correlated with another recent cortical PD biomarker, namely β band waveform shape asymmetry, which was initially demonstrated by Cole et al. (29) for ECoG data. They could show that the β band sharpness ratio indicating the waveform asymmetry was extremely correlated with β-γ PAC and could be reduced by DBS treatment.

Although analyses of the aforementioned two scalp EEG studies (19, 28) primarily focused on two lateral channels (C3 and C4) closest to sensorimotor cortex, they also demonstrated the specificity of these biomarkers (PAC and waveform asymmetry) to sensorimotor regions by evaluating them for all other remaining channels. Findings of another PD EEG study conducted by Miller et al. (20) were in general agreement with these studies, on the discriminative capability of β-γ PAC between medical states and its spatial specificity, in addition to the correlation of PAC with motor impairment scores. A high-density PD EEG study by Gong et al. (30) utilized the beamformer inverse method to investigate the β-γ PAC in the source level. Although the elevated PAC strength for the patients compared with healthy controls was located within the previously unidentified area of the dorsolateral prefrontal cortex as well as several sensorimotor regions, the correlation with motor impairment was nevertheless constrained solely to the latter, thus fundamentally agreeing with the earlier studies on the spatial specificity of PAC regarding the PD physiopathology.

Nonlinearity in the STN LFP recordings was notably identified within the β band range, such as the features derived from bispectrum (31) and burst duration (32). Both studies showed the evident nonlinearity observed within the β band range (OFF state) was suppressed by the administration of dopaminergic medication (ON state). It was reported by Camara et al. (33) that the nonlinearity increases for the STN LFP data episodes containing tremors. The presence of nonlinearity was also shown in the interspike interval series obtained from various subcortical regions (34).

Attempts for the identification of nonlinear dynamics within cortical data have been somewhat less common. The correlation dimension was utilized by Muller et al. (35) to identify the EEG channel-level topological differences for resting state and motor tasks. Model features based on delay differential equations were used by Lainscsek et al. (36) to

differentiate EEG data at the medication OFF state from the ON state. A recent study by Özkurt et al. (37) proposed a novel nonlinear measure based on higher-order autocorrelative memory. They applied this measure on the LFP-MEG data postoperatively acquired from the patients with advanced-stage PD that have undergone DBS operation and demonstrated that the nonlinearity is consistently inherent in the high β band (20–30 Hz) of the subcortical STN LFP, which dissolved upon the dopaminergic medication. While for the MEG source regions coherent with STN LFP activity being located at the proximity of the primary motor cortex, the nonlinearity was nonexistent but emerged only upon the administration of dopaminergic medication in the α band (8–12 Hz). The identified nonlinearities for subcortical β and cortical α bands were found to be respectively correlated with the UPDRS tremor and akinesia subscores.

In this study, we would like to investigate the previously proposed autocorrelative nonlinearity measure (37) for a cohort of patients with early-stage PD via a publicly available noninvasive scalp EEG data set, involving recordings from the patients with medication OFF and ON states as well as those from the age-matched healthy controls. We hypothesize that the α band nonlinearity induced by dopaminergic medication, as observed in the higher spatial resolution MEG cortical sources of patients with advanced-stage PD by Özkurt et al. (37), can similarly be inferred from EEG sensorimotor channels. Furthermore, this may enable the differentiation of medication states and consequently provide insights into the pathophysiology of earlier-stage PD using noninvasive, albeit low spatial resolution and low signal-to-noise ratio (SNR) EEG signals.

MATERIALS AND METHODS

Participants

We used a publicly available dataset (17) collected at the University of San Diego and curated by Alex Rockhill at the University of Oregon (https://openneuro.org/datasets/ds002778/versions/1.0.2). It comprises EEG resting state data acquired from 15 patients with PD (8 females, average age = 63.2 ± 8.2) for dopamine OFF and ON states, each lasting over 3 min (durations for OFF = 200.1 ± 26.5 s and ON = 199.9 ± 26.8 s). The data set also includes resting-state data with a similar duration for 16 healthy controls that are sex- and age matched (9 females, average age = 63.5 ± 9.6, data duration = 191.9 ± 5.9 s). All participants were right-handed and provided written consent in line with the Institutional Review Board of the University of California, San Diego, and the Declaration of Helsinki. For further details, please see Ref. 17. The same PD EEG data set has been used multiple times by several other studies (such as in Refs. 19, 22, 28, 38, and 39).

Procedure

Recordings were conducted on two separate days for OFF and ON medication sessions, the order of which was counterbalanced across patients. They were asked to abstain from taking medication for a minimum of 12 h before the medication OFF session. Data for healthy controls were collected in just one session. EEG recordings were acquired via a 32-channel BioSemi ActiveTwo System with a sampling rate of 512 Hz. During the recordings, the participants were enabled to sit comfortably and were instructed to focus their attention on a cross displayed on the screen. Furthermore, the participants underwent a series of clinical assessments, which were reported by George et al. (17). The dopaminergic medication improved the motor condition of the patients bilaterally, as indicated by the hemibody left and right side UPDRS III scores being reduced from 14.57 ± 4.68 (OFF) to 12.3 ± 4.96 (ON), significantly ($n = 30$; $P < 0.001$).

Preprocessing

Data for two of the patients were labeled as preprocessed by an EEG software package (EEGLAB), whereas the data for the remaining 13 patients were raw. Since the nonlinearity analysis strictly requires no "hard preprocessing," we excluded two patients (*pd6*, *pd16*) with preprocessed data from the analysis. In particular, the presence of any gaps in the data will compromise the accuracy of the estimation of the nonlinearity measure, as relatively large, continuous uninterrupted data segments are required to reveal the autocorrelative memory, properly (see *Nonlinearity Measure*). To match the number of healthy subjects to the patients for a fair comparison, we excluded the last three ones (*hc31*, *hc32*, and *hc33*) arbitrarily.

Data analyses and visualization were performed using MATLAB version 2022a (MathWorks Inc., Natick, MA). We used Fieldtrip *ft_preprocessing* function (40) to bandpass filter with the cutoff frequencies 0.5 and 50 Hz and demean the data. With the same function, we rereferenced the data using the Laplacian spatial filter, as it is known to provide highlighted localized activity and minimize the volume conduction (41). As we predominantly selected C3 and C4 (assumed to be closest to the left and right sensorimotor cortices, respectively) for the analyses in this study, the Laplacian filter was used to increase spatial selectivity for sensorimotor sources. Please note that the focus of analysis on these two bilateral sensorimotor channels has been rather common in PD EEG literature (19, 20, 28). Since we observed some increased levels of noise toward the end of the data, the last 7 s of data were eliminated for all channels of all subjects.

Nonlinearity Measure

The nonlinearity measure was proposed and developed by Özkurt et al. (37). It essentially quantifies the nonlinear memory inherent within any time series, through the energy difference of second-order and higher-order autocorrelative sequences. These sequences are constructed from "average magnitude difference function" (AMDF), which was originally defined and used by the speech processing community to track the pitch period of voices (42). In their formulation, AMDF was computed as the first-order (L^1 norm) memory of the signal $x(n)$ with length N

$$D(\tau) = \frac{1}{N}\sum_{n=0}^{N-1} |x(n) - x(n-\tau)|,\ \tau = 0, \ldots,\ \tau_{\max},$$

where τ denotes the lag.

A generalized AMDF is defined by inserting the degree p into the formula and defining it in a statistical manner for a stochastic time series (37):

$$s_x(\tau,p) = \sqrt[p]{E\{|x(n)-x(n-\tau)|^p\}},$$

where E denotes the expectation operator. Hence, $D(\tau)$ is equivalent to an estimate of $s_x(\tau,1)$.

AMDF sequence $(\tau,2)$ (degree 2, L^2 norm) can be shown to reflect the autocorrelative memory of the signal, i.e., the linear correlation at two different time points of the signal, where τ represents the temporal distance between those points. When we remove the mean from the signal $x(n)$, it may be taken as zero-mean. Then, the second-order AMDF sequence becomes equivalent to:

$$s_x(\tau,2) = \sqrt{E(x^2(n)) + E(x^2(n-\tau)) - 2E(x(n)x(n-\tau))},$$

$$= \sqrt{2var(x) - 2r_x(\tau)},$$

where var and r_x denote the variance and the autocorrelation, respectively. As $x(n)$ is assumed to be stationary, the term of variance contributes only to the baseline, hence the autocorrelation sequence $r_x(\tau)$ determines the essential temporal pattern of $(\tau,2)$ with respect to τ. The linear character of a signal is extracted from measures of the first two statistical orders, such as the second-order autocorrelation sequence $r_x(\tau)$ and its Fourier transform, i.e., power spectrum. Hence, linear analysis methods may reveal the dominant rhythms occurring within the frequency range of the commonly known EEG spectral bands.

Contrary to the second-order $(\tau,2)$, $s_x(\tau,p)$ with $p > 2$ comprises combinations of "higher-order" (i.e., orders greater than two) autocorrelations with the lag τ:

$$E\left\{[x(n)-x(n-\tau)]^p\right\} = \sum_{k=0}^{p}(-1)^k\binom{p}{k}E\left[x(n)^k x(n-\tau)^{p-k}\right].$$

Hence it may indicate nonlinear temporal variations within the signal. Various forms of higher-order autocorrelations as a function of the lag have been exploited to analyze and identify the nonlinear characteristics of time series in domains such as simulated data from certain nonlinear difference equations (43), clinical respiratory (44), and plasma turbulence (45) measurements.

As $s_x(\tau,p)$ does only contain the linear properties of the signal, the proposed nonlinearity measure L aims to quantify the deviation of the higher-order AMDF sequence via the L^2 norm of the difference of $s_x(\tau,p)$ (with $p > 2$) from $s_x(\tau,2)$. Note that, to obtain this deviation, both sequences (τ,p) and $s_x(\tau,2)$ are normalized by being divided by their maximum amplitudes to be kept in a comparable level. If the normalized AMDF sequences are denoted by s_{pN} and s_{2N}, the nonlinearity measure may simply be defined as

$$L = ||s_{pN} - s_{2N}||.$$

A simple numerical example that involves a simulated time series is provided in Supplemental Fig. S1 to demonstrate how the nonlinear memory of a time series could be revealed by the suggested measure. Let x_L be a linear autoregressive (AR) process

$$x_L(n) = 0.5x_L(n-1) + 0.5x_L(n-5) + w(n)$$

and x_{NL} be a nonlinear AR process

$$x_{NL}(n) = 0.5x_{NL}(n-1) + 0.5x_{NL}(n-5) - 0.96\left(x_{NL}(n-1) - |x_{NL}(n-1)|^{1.5}\right) + 0.3875\left(x_{NL}(n-5) - |x_{NL}(n-5)|^{5}\right) + w(n),$$

both with additive white Gaussian noise $w(n)$. The latter simulated time-series $x_{NL}(n)$ was borrowed from the example given by Sammon and Curley (44), where they described it as arising from a structurally unstable dynamical system. Energies of both time series were dropped to unity by normalization. The sampling frequency was assumed 100 Hz and the data lengths were taken as 10,000, which corresponds to 100 s. Supplemental Fig. S1, *A* and *B*, respectively, exhibit the simulated time series and their corresponding normalized nsAMDF difference $[(\tau,5) - s_x(\tau,2)]$, whose norm, by definition, is equivalent to the nonlinearity measure L, which was found to be 0.05 for the linear process $x_L(n)$ and 0.97 for the nonlinear process $x_{NL}(n)$. This is how L may distinguish a linear AR process from a nonlinear one.

In our particular implementation for the current study (see Fig. 1 for the workflow), we estimate L by computing the L^2 norm difference of normalized s_2 and s_p which are AMDF sequences averaged over data segments. We took segments of 14 s with 50% overlap in length, the higher-order as $p = 7$ and the maximum lag $\tau_{max} = 1$ s as these input parameters proved to be effective enough for PD neural time-series data from the previous work (37). Note that the degree of the AMDF sequence as $p = 7$ includes correlations for lower orders less than p, thus choosing a high enough degree assures to be on the safe side to capture nonlinear memory inherent within the signal. In addition, we bandpass-filter (forward-backward two-pass 4th-order Butterworth filter) the AMDF sequences for the range (8–12 Hz) to capture specifically the α band nonlinearity. The reason we bandpass filter AMDF sequences (τ,p) is to emphasize solely the nonlinear α oscillatory part that was observed by Özkurt et al. (37) for MEG motor cortical sources. Filtering is especially essential to implement for scalp EEG signals, which reputably have low SNR and contain large amounts of mixed signals from other sources due to volume conduction. The MATLAB code to obtain the nonlinear measure from any time series can be accessed at https://github.com/tolgaozkurt/nonlinearity_measure.

Surrogate Data

Surrogates are generated to retain the linear characteristics of the signal in question while excluding its nonlinear components. Thus, the presence of nonlinearity can be tested with respect to the suggested metric's capability to distinguish the original data from its linear surrogate counterparts. Linear surrogates have been commonly produced through Fourier transform (46). This family of methods imposes the general idea of keeping the power spectrum (hence the 2nd-order autocorrelative characteristics) of the signal intact by preserving the Fourier coefficients, while the phase is randomized. An improved version of the Fourier transform based surrogate method called "iterated

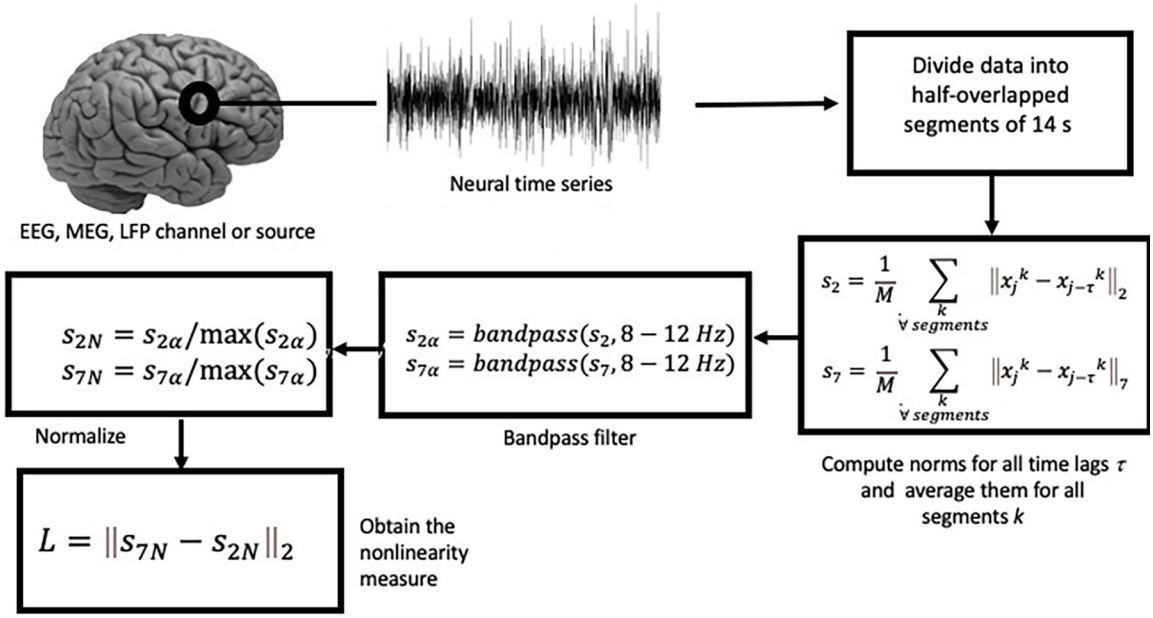

Figure 1. Extraction of the nonlinearity parameter L from a neurophysiological time-series: the nonlinear parameter is simply obtained as the energy difference between the normalized s_2 and s_7 computed over data segments. s_2 and s_7 indicate respective second-order and higher-order autocorrelative memories of the time series. For the cortical data used in this study, data segment length is chosen as 14 s, whereas s_2 and s_7 are bandpass filtered for the α band range (8–12 Hz). EEG, electroencephalography; LFP, local field potential; MEG, magnetoencephalography.

amplitude adjusted Fourier transform" (IAFFT) was suggested by Schreiber and Schmitz (47), which assures to preserve the probability distribution of the original signal as well as its autocorrelation. Nonetheless, as cautioned (32), IAFFT may confuse the nonlinearity with possible nonstationarity inherent in the neural time-series. As a remedy, another iterative surrogate method based on wavelet transform called "gradual wavelet reconstruction" (GWR) (48) is used. Apart from avoiding the trap of mistaking nonlinearity with nonstationarity, GWR allows surrogates along a continuum of a threshold parameter ρ ranging between 0 (equivalent to the standard IAAFT surrogate) and 1 (equivalent to the original signal). Wavelet coefficients of the original signal with an energy ratio corresponding to ρ are left out of the phase randomization process in the IAAFT. Hence, surrogates for about $\rho > 0.1$ (largest wavelet coefficients corresponding to low-frequency high scales) retain the fundamental nonstationary elements of the signal and are assumed to be on the safe side to be tested for nonlinearity (32).

Phase Amplitude Coupling

To quantify the well-established β-broadband γ PAC, we applied the normalized direct PAC method (49) by thresholding according to the analytical confidence limit derived by Özkurt (50). This method is an amplitude-normalized variant of the modulation index (51). It reduces the computational expense significantly, as it avoids the permutation test. The normalized direct PAC method has been commonly used for PAC estimation in neural signal literature and was added to open-source PAC toolboxes such as Tensorpac (52) and pacpy (https://github.com/voytekresearch/pacpy). The simple MATLAB routine used for this study can be accessed at https://github.com/tolgaozkurt/ndpac. Phase and amplitude frequencies were respectively determined within the β band (13–30 Hz) and γ band (50–150 Hz) ranges with bandwidths of 2 and 10 Hz. The confidence level was chosen as 0.95. If the PAC estimates were below the confidence limit threshold, which was computed from the explicit analytical formula given by Özkurt (50), then they were nullified. We determined the average PAC strength for each individual's sensorimotor EEG channels (C3 and C4) by dividing the sum of PAC values over the frequency region covered by β and γ band boundaries by the total number of nonzero PAC values. Please note that although comprehensive PAC findings for the same data were already published twice (19, 28), we repeated the PAC analysis, to search for any possible relation and biomarking performance comparison with the nonlinearity measure.

RESULTS

Alpha Band Nonlinearity

The induced α-band nonlinearity with dopamine was observed for the sensorimotor channels C3 and C4 of the patients with PD. Figure 2*A* depicts the difference $(s_7 - s_2)$ for an exemplary case of a representative patient's left sensorimotor channel (C3), where the medication ON conspicuous waves are absent for the state of OFF medication. This difference, which represents the nonlinear memory, diminished for the linear surrogate time-series obtained from the ON state signal using IAFFT. The surrogate ON and the medication OFF states both show similarly low levels of $(s_7 - s_2)$. The absence of the nonlinear memory for the OFF state and the surrogate ON data was also depicted in the frequency domain lying particularly on the α band range (Fig. 2*B*).

Group level analysis for all bilateral sensorimotor channels (C3 and C4) revealed that the nonlinearity measure L was significantly elevated for the PD patient's medication

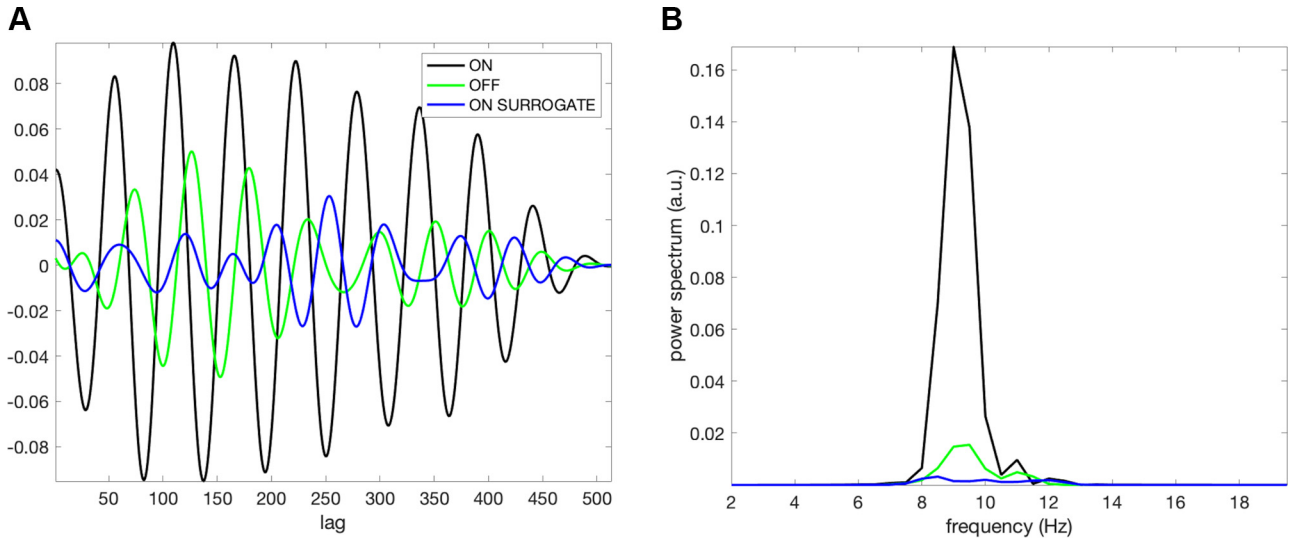

Figure 2. *A*: difference waveform between normalized s_2 and normalized s_7 for an arbitrary patient's left sensorimotor channel (C3) for ON state (black), OFF state (green), and ON state (blue) surrogate. *B*: power spectra of differences given by *A*. Dopamine increases the energy difference ($s_7 - s_2$) indicated by the single number, *L*. This difference lies specifically in the α band range 8–12 Hz. Surrogate ON state data is produced such that it has the exact second-order characteristics (autocorrelation and power spectrum) with ON state data, but lacks higher-order nonlinear features indicated by the decrease of *L* (*A*) similar to the level for OFF state data.

ON state compared with their medication OFF state (paired *t* test, $n = 26$; $P = 0.003$; Fig. 3). The nonlinearity measure was also higher for healthy controls when compared with patients at the medication OFF state (two-sample *t* test, $P = 0.049$). However, as presumed, there was no difference of the estimated nonlinearity measure between healthy controls and PD ON state (two-sample *t* test, $P = 0.8191$). As a reflection of the aforementioned statistical findings, Fig. 3 exhibits similar distributions of the nonlinearity for healthy controls and patients on dopamine (ON state) and how both deviate from that of patients without medication, i.e., PD OFF state. Thus, these findings did not only show that the cortical α band nonlinearity is indeed induced by dopaminergic medication and can be sensed by the suggested measure *L* from EEG channels without necessarily getting into the neural source level through an inverse method, but also that the absence of nonlinearity implies PD pathophysiology as an inference from the nonlinearity measure levels observed for the age-matched healthy subjects.

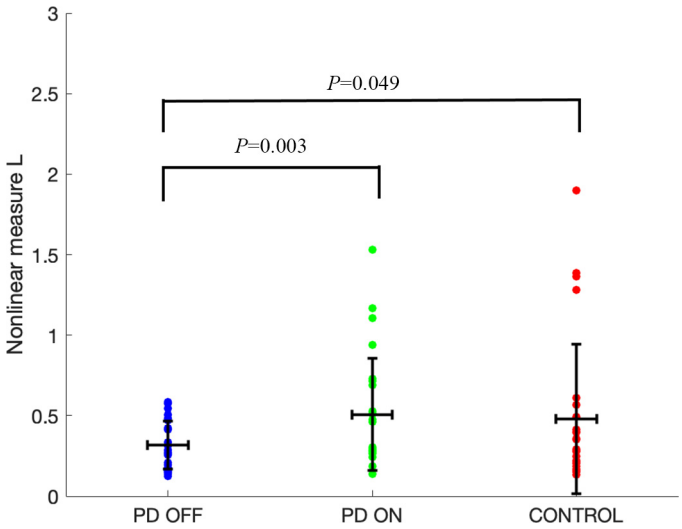

Figure 3. Distribution of the nonlinearity measure for medication OFF and medication ON states of the patients with Parkinson's disease (PD) along with the healthy controls for the bilateral somatosensory channels of C3 and C4. For the patients with PD, dopaminergic medication induces the nonlinearity and sets it to a similarly distributed level of the healthy controls. The nonlinearity is higher for the medication ON state compared with OFF state ($n = 26$; $P = 0.003$). Similarly, healthy controls have higher nonlinearity than the patients without medication ($n = 26$; $P = 0.049$).

GWR Surrogates

Figure 4*A* exhibits GWR surrogate time series for a representative patient's ON state left sensorimotor EEG channel data for $\rho = 0$, 0.1, 0.6. It is especially difficult to see a difference by the naked eye between the original data and its surrogate with $\rho = 0.6$, as the surrogate contains 60% energy (highest wavelet scales corresponding to low-frequency components) of the original, which was omitted from the phase randomization procedure.

We produced GWR surrogates for all EEG sensorimotor channels of ON state PD patients with the threshold ρ varying between 0 and 0.9 in steps of 0.1, to test whether the nonlinear measure is disturbed by the commonly observed nonstationary dynamics within EEG data. Accordingly, the nonlinearity measure *L* was computed for all these surrogates. The statistical comparison by a pair-wise *t* test showed that *L* was significantly greater for PD ON state channel data than their surrogates for all thresholds up to $\rho = 0.6$ with the exception $\rho = 0.1$ and $\rho = 0.3$, though the latter was marginally significant with $P = 0.061$ (Fig. 4*B*).

This implies that the suggested measure senses nonlinearity as such and it is not vulnerable to nonstationarity, for the EEG data set used in this study. As surrogate signals with $\rho = 0.2$, 0.3, 0.4, 0.5, and 0.6 look very much like the original data in a growing manner and hence retain the essential temporal variations within them, *L* still decreases significantly ($P <$

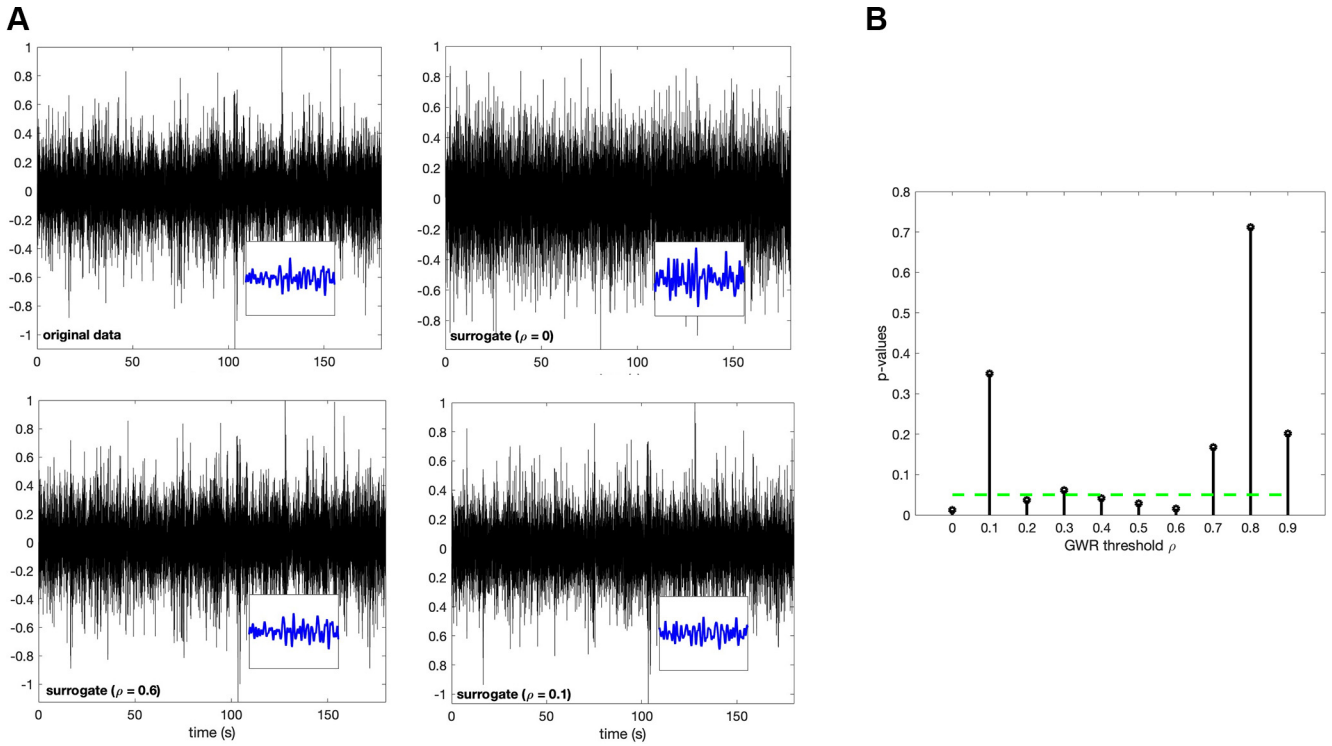

Figure 4. *A*: filtered ON state electroencephalography (EEG) channel C3 time-series for an arbitrary patient (no. 11) and its gradual wavelet reconstruction (GWR) surrogates for ρ = 0, 0.1, and 0.6. The *inset* plots depict a zoomed-in view for a duration of two arbitrary seconds (10–12 s). The GWR threshold ρ may be considered as a parameter gradually modifying similarity of the surrogates toward the original data. At the limits, the surrogate time series with ρ = 0 corresponds to iterated amplitude adjusted Fourier transform (IAAFT) surrogate phase-randomized time series, whereas the surrogate time-series with ρ = 1 corresponds to the original intact ON state time series. *B*: *P* values for the statistical comparison of the nonlinearity metric between ON state patients with Parkinson's disease (PD) cortical time-series and their GWR surrogates when the threshold ρ varies between 0 and 0.9 with steps of 0.1.

0.05) since even limited phase randomization is enough to cancel the nonlinearity mirrored by L. As for $\rho > 0.6$, the phase randomization is so tiny, and hence it resembles the original signal so much that the difference in nonlinearity cannot be discerned. This result is nearly in line with the study by Duchet et al. (32), where they found out significant difference also up to $\rho = 0.6$ between medication OFF and ON PD STN data for a measure derived from the averaged squared difference of β band burst durations between filtered original data and its GWR surrogates.

In our case, the reduction of the nonlinear measure for the surrogate signals with $\rho = 0.1$ was not statistically significant, despite these signals being less similar to the original data compared with those with $\rho = 0.6$. This could be because the nonlinear measure may particularly be sensitive to high scales that exclusively include low-frequency components within the α band range. In other words, it may show this sensitivity when only these components are retained, while all other scales are excluded.

Phase-Amplitude Coupling

Average β-γ PAC strength was found to be greater for the PD OFF state compared with the PD ON state (paired t test, $n = 26$; $P = 0.012$). However, there was no significant difference in the PAC strengths between PD OFF state and healthy controls. These findings are in line with those reported by Jackson et al. (28). Group-level statistical results indicated by P values of the t test along with Cohen's d effect sizes for both PAC and nonlinear measures are compared in Table 1.

We correlated PAC strength with the nonlinear measure even though they operate on totally different bands of the spectrum since the former is one of the most emphasized and prevalent biomarkers of recent "cortical" PD data studies as covered in INTRODUCTION. The Pearson correlation between PAC and L for the bilateral sensorimotor channels was not significant either for the OFF state ($r = -0.025$, $P = 0.913$) or for the ON state ($r = -0.254$; $P = 0.212$). However, PAC and L correlated significantly for the healthy subjects ($r = -0.412$; $P = 0.036$). Thus, the negative correlation between them tended to increase as the neuropathology is driven away.

Channel Topology of the Nonlinear Measure

To observe how spatially distributed the nonlinearity measure is, we constructed scalp topographies by averaging L

Table 1. *Comparison of nonlinear measure and PAC for all sensorimotor channels C3 and C4*

	PD OFF vs. PD ON State		PD OFF vs. Healthy Controls	
Metric	*P* Value	Effect Size	*P* Value	Effect Size
Nonlinear measure	0.003	0.695	0.049	0.417
PAC	0.012	0.496	0.493	0.094

Comparisons made between conditions by Student's t test along with Cohen's d effect size; $n = 26$. PAC, phase-amplitude coupling; PD, Parkinson's disease.

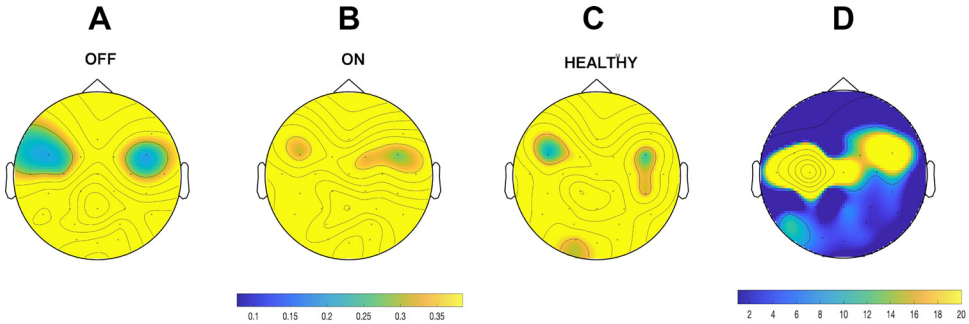

Figure 5. Scalp topography of the averaged nonlinearity measure for patients with Parkinson's disease (PD) for OFF state (*A*), ON state (*B*), and healthy individuals (*C*). Nonlinearity is constrained specifically to somatosensory regions for all states. *D:* depicts the reciprocal *P* values of the statistical comparison between nonlinearity measures of OFF and ON states, hence it indicates the statistical contrast between *A* and *B*, which is concentrated on the somatosensory channels.

over all subjects for all channels for the PD OFF state (Fig. 5*A*), PD ON state (Fig. 5*B*) along with healthy controls (Fig. 5*C*). Not only was *L* mainly specific to sensorimotor channels but also its level was lesser for the OFF state when compared with ON state as well as the healthy state. We also depicted the scalp topography of the statistical contrast (paired *t* test) between medication OFF and ON states as the reciprocal *P* values in Fig. 5*D*. A clear statistical distinction was evident in the sensorimotor channels, implying the spatial specificity of the pathology.

DISCUSSION

This study investigated the relevance of the α band nonlinearity measure *L* suggested by Özkurt et al. (37) for PD scalp EEG recordings. The patients with PD in that LFP-MEG study were inherently in their advanced stage as they had undergone DBS operation with an average disease duration of 11.43 ± 3.50 (14 patients). Although in the current study, the patients were without DBS electrodes and the average disease duration was 3.50 ± 2.64 (computed for 10 patients as the duration is not provided for 3 of them), i.e., they were at much earlier stages.

Apart from confirming the validity of the nonlinearity measure as a PD biomarker elevated by dopaminergic medication for cortical sources, the current study revealed several additional novel important findings that can be summed up as follows: *1*) *L* is effective for noninvasive scalp EEG channels over the primary motor cortex without the requirement to get into spatially high-resolved source-level. *2*) Not only does *L* distinguish the PD OFF state from the ON state, but it can also discriminate the PD OFF state from age-matched healthy subjects and hence indicates the PD pathophysiology. *3*) At least for the employed EEG data set, *L* is not found to be vulnerable to typical nonstationary variations of the neural time-series, hence it represents a genuine nonlinearity occurring within the analyzed data. *4*) *L* does not significantly correlate with the recently well-accepted cortical biomarker of β-γ PAC for patients with PD and may even outperform it in a statistical manner. *5*) Abundant nonlinearity quantified by *L* is spatially constrained to sensorimotor regions. *6*) *L* is potentially a promising biomarker for earlier-stage PD patients as well.

Some most popularly approved electrophysiological biomarkers of PD from cortical signals (EEG, MEG, ECoG) so far have been listed as β bursts, β coherence, β-broad γ band PAC, and β waveform asymmetry (19, 20, 28, 53). One reported drawback of β coherence as a biomarker is its requirement of multiple electrodes to be estimated properly (53), as it is practically extracted from all pair-wise combinations of all EEG channels (17, 20, 54). All these markers are essentially derived from β band oscillatory features, even though the cortical spectral power alone at the same frequency band is not reliable enough to discriminate PD data characteristics. Some of them were reported to be strongly correlated, such as PAC and waveform asymmetry (28, 29). In addition, PAC and the β waveform characteristics were shown to be dependent upon the bursting behavior of the β band (55), which implies that β band activity-derived markers, are intimately associated with each other, as they may all be assumed to quantify various aspects of the abnormal excessive oscillatory synchronization throughout the basal ganglia-thalamo-cortical loops.

Due to being operative at the α band for the sensorimotor cortical regions, the nonlinearity measure as a promising biomarker represents exclusive dynamics of the signal compared with the aforesaid measures. Besides, it shows an opposing behavior compared with the β-derived markers as it does not decrease but increases upon dopaminergic medication, i.e., the PD pathophysiology is connected with the absence of nonlinear autocorrelative memory, as observed for PD OFF state compared with medication ON and healthy states. There was no correlation between PCA and the nonlinear measure for the patients. However, some significant negative correlation ($r = -0.412$) was found for the healthy subjects. As the correlation is exclusive to healthy subjects and not that strong, one may safely consider the nonlinearity measure to be a biophysically unique marker of PD pathophysiology.

According to our statistical findings for the 13 patients (26 channels) used in this study, even though both *L* and PAC could discriminate PD EEG data for OFF and ON states, the nonlinearity measure *L* had a larger effect size and smaller *P* value compared to those of PAC (see Table 1). Furthermore, while *L* could discriminate PD OFF state from healthy controls, this was not the case for PAC. Hence, our empirical results favored *L* as a better describer of PD pathophysiological condition. Nevertheless, as these two measures (*L* and PAC) operate on different spectra (β and α) and dynamics (autocorrelative memory and oscillatory phase) of the data, they may well be considered to be complementary. This is also supported by our results showing a lack of correlation between them for the patient data and the presence of a relatively weak correlation for the controls.

Two separate studies (19, 28) using the same EEG data set with the current work reported somewhat initially inconsistent results when it comes to differentiating the PD OFF state from the controls via PAC. This discrepancy was shown by Jackson et al. (28) to be due to the sensitivity of the PAC measure to the rereferencing scheme and the applied PAC methodology. Thus, the parameter dependencies of the PD markers should be taken rather carefully. Likewise, the filter type and the selected threshold may impact the β burst measures considerably (53). On the other hand, the nonlinearity measure depends on a few parameters of segment length, lag, and degree. Once all these parameters are appropriately determined for the PD neural dynamics, one can readily apply the method to the data using the established settings. In this study, we maintained the identical parameters used in the previous LFP-MEG study (37), without requiring any adjustments or searching for optimal parameters specific to the EEG data at hand. Compared with the other markers, one critical methodological requirement to properly estimate the nonlinearity measure is to use longer segments (in our case ~14 s) as the nonlinear dynamics can accurately be inferred from relatively large durations.

Conventionally, any suggested measure's correlation with motor impairment scores (UPDRS) is naturally accepted to be desirable, as it is thereby supported to be a neurophysiological marker representative of medication-induced motor improvement. However, for the current EEG data set used by previous studies, no significant correlation with UPDRS has been reported either for PAC (19) or waveform asymmetry (28). Similarly, another study using the same dataset (22) did not attempt to carry out UPDRS correlations with network measures due to the forewarned uncertainty of the clinical scores. The data curator cautions that the UPDRS rating scales were "collected by laboratory personnel who had completed online training and not a board-certified neurologist" (https://openneuro.org/datasets/ds002778/versions/1.0.2). Nevertheless, to compare the UPDRS correlation result with that of Özkurt et al. (37), we assumed the scores labeled as "left UPDRS" and "right UPDRS" represent motor impairment with respect to the contralateral sensorimotor channel, labeled respectively as C4 (right-sided) and C3 (left-sided), in our analyses. There was no significant correlation between dopaminergic medication-induced change in the nonlinearity metric (ΔL) and the change in the contralateral hemibody motor impairment score (ΔUPDRS) for the electrodes ($r = 0.23$, $P = 0.22$; Supplemental Fig. S2*A*). Although this finding is not in disagreement with the aforesaid studies using the same EEG data, we think that it does not necessarily imply the absence of interrelation between motor impairment and nonlinearity measure. The absence can be due to the underlined uncertainty of the UPDRS as cautioned. Besides, the low SNR of EEG channels may be another important factor. More importantly, one should keep in mind the vulnerability of these correlation results. When we took only one channel out from the analysis, a significant correlation between ΔL and hemibody ΔUPDRS emerged ($r = 0.38$, $P = 0.04$; Supplemental Fig. S2*B*). Hence, the correlation output is very sensitive to any possible flaw occurring in the signal quality of the electrodes, motor score examination, or biomarker estimation and should be taken into account while interpreting the results.

There is a list of topics for further investigation to clarify the role of cortical α band nonlinearity in PD mechanisms. One such direction concerns the degree of specificity to PD rather than other movement disorders such as dystonia, essential tremor, and multiple sclerosis. The previous study (37) already showed that motor cortical α band nonlinearity tends to associate with akinesia and rigidity, whereas subcortical STN high β band (20–30 Hz) correlated with tremor severity. Nonlinear measures of both bands were uncorrelated with linear spectral power values in the cortex and the STN. Thus, their findings implied that α band nonlinearity is associated with akinesia and rigidity scores but how the nature of L varies with respect to other movement disorders is still an open question.

Several studies have reported increases in STN power within the α band range upon dopaminergic medication (56–58). So far, nonlinearity observed in PD electrophysiological recordings generally has been associated with increased neural complexity (61). The presence of nonlinearity was interpreted as a hallmark of obstruction of the information coding capacity of the basal ganglia-cortical network (32). Autocorrelative nonlinearity (37), burst duration-derived nonlinearity (32), and higher-order spectral amplitude (31) were all reported to be excessively present for the PD STN at the β band. On the other hand, our results in accordance with Özkurt et al. (37) show that cortical α band nonlinearity implies an opposite prokinetic tendency as it lacks in the sensorimotor regions in PD and hence requires a different line of interpretation other than reducing the coding capacity. To confidently establish the neurophysiological role of α band nonlinearity in PD, more extensive neural data analyses on a larger cohort of patients and computational neural models describing cortical data are required.

The current study showed that the cortical L estimated from a single-channel EEG persists to be a promising indicator of PD at even earlier stages. Nonetheless, the robustness of the nonlinearity measure as a PD biomarker should be tested further with patient data obtained via various neurophysiology modalities collected by multiple sites. How L spontaneously varies with the disease progress is another interesting issue that needs to be elaborated in future studies. Thanks to the recent upsurge of mobile and wireless EEG systems (59), it is possible to quantify and track cortical nonlinearity across temporal scales from minutes to years, through a smartphone in real time, which allows personalization of monitoring for effective clinical treatment. This also matters to accurately track the neural markers sensitive enough to be affected by hourly circadian events as well as specific days such as festive holidays, e.g., Christmas Day (60).

DATA AVAILABILITY

Data will be made available upon reasonable request.

SUPPLEMENTAL DATA

Supplemental Fig. S1: https://doi.org/10.6084/m9.figshare.24657255.v1.

Supplemental Fig. S2: https://doi.org/10.6084/m9.figshare.24657258.v1.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author.

AUTHOR CONTRIBUTIONS

T.E.Ö. conceived and designed research; performed experiments; analyzed data; interpreted results of experiments; prepared figures; drafted manuscript; edited and revised manuscript; approved final version of manuscript.

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