Rest Tremor Pattern Predicts DaTscan (123I-Io fluopane) Result in Tremulous Disorders

Rest tremor (RT) is typical of Parkinson’s disease (PD) but can occur in other tremulous disorders, such as essential tremor (ET) plus dystonic tremor, drug-induced tremor, ET-PD syndrome, and scans without evidence of dopaminergic deficit (SWEDD). Differentiating RT disorders clinically may be challenging and often requires DaTscan (123I-Io fluopane), an expensive and time-consuming procedure not widely available and rarely used in routine diagnosis of tremulous disorders. Thus, there is an urgent need for new reliable and cost-effective biomarkers to reveal striatal dopaminergic deficit in tremulous patients in the absence of DaTscan.

A few studies investigated the electrophysiological features of RT, suggesting the possible usefulness of tremor pattern for differentiating PD from other tremulous disorders. These studies, however, were conducted in small patient series and focused on differentiation between the diseases rather than on the association between tremor pattern and DaTscan.

In our study, we enrolled 205 consecutive patients with RT and assessed the performance of tremor features (pattern, frequency, amplitude, burst duration, coherence) in differentiating patients with abnormal DaTscan (DaT+) from those with normal DaTscan (DaT−) (see Methods in Supporting Information Appendix S1).

A total of 123 patients with RT had DaT+, while 82 patients had DaT−. Clinical characteristics of these patients with RT are shown in Supporting Information Table S1. The pattern (alternating or synchronous, Fig. 1A) was the RT feature that performed the best in distinguishing patients with striatal dopaminergic deficit from those with integrity of striatal dopaminergic neurons (Fig. 1B,C; Supporting Information Table S2). Random Forest feature selection and multivariate logistic regression model did not significantly improve the classification of DaT+ and DaT− patients compared with using RT pattern alone (Fig. 1D), suggesting that this tremor feature, which balances simplicity and accuracy, may represent the best option in clinical practice.

The alternating pattern of RT is a powerful, low-cost, and widely available biomarker of striatal dopaminergic deficit in tremulous patients. The evaluation of tremor pattern could help clinicians distinguish parkinsonian RT associated with dopaminergic deficit from non-parkinsonian RT with intact dopaminergic neurons and guide the decision making in clinical practice.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Key Words: rest tremor; tremor pattern; Parkinson’s disease; DaTscan; clinical practice

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**FIG. 1.** (A) Electromyographic recordings from the extensor carpi radialis and flexor carpi ulnaris muscles of a patient with alternating pattern and a patient with synchronous pattern of rest tremor (RT). (B) Receiving operating characteristic (ROC) curves for assessing the classification performance of RT pattern (red) (area under the curve [AUC], 0.86; 95% confidence interval [CI], 0.81–0.91), amplitude (green) (AUC, 0.77; 95% CI, 0.69–0.84), frequency (blue) (AUC, 0.70; 95% CI, 0.62–0.78), burst duration (gray) (AUC, 0.54; 95% CI, 0.46–0.62), and coherence (black) (AUC, 0.49; 95% CI, 0.38–0.59) in differentiating patients with RT with abnormal DaTscan (DaT+) from those with normal DaTscan (DaT–). (C) ROC curves for assessing the classification performance of RT pattern (red) (AUC, 0.86; 95% CI, 0.81–0.91) and bradykinesia score (blue) (AUC, 0.68; 95% CI, 0.61–0.75) in differentiating patients with RT with DaT+ from those with DaT–. The bradykinesia score was calculated as the mean of the scores of the Unified Parkinson’s Disease Rating Scale motor, Part III items 23 (finger tapping), 24 (hand movements), and 25 (pronation-supination movements) in the most affected upper limb with RT. (D) ROC curves for assessing the classification performance of RT pattern (red) (AUC, 0.86; 95% CI, 0.81–0.91) and multivariate logistic regression model with Random Forest feature selection (blue) (AUC, 0.90; 95% CI, 0.84–0.95) in differentiating patients with RT with DaT+ from those with DaT–. The performances of both classifiers are compared using DeLong’s test (P = 0.27). The variables selected using Random Forest were pattern (importance = 5.61), amplitude (importance = 4.83), frequency (importance = 4.07), and burst duration (importance = 3.14). The cohort included 123 DaT+ and 82 DaT– patients.
Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.

Low-Frequency Oscillations at The Limbic Globus Pallidus Internus Seem to Be Associated With Premonitory Urges in Tourette’s Syndrome

Tourette’s syndrome (GTS) is a neurodevelopmental disorder characterized by multiple motor and phonic tics, which can be highly disabling. Tic-preceding urge sensations have been reported in more than 90% of patients with GTS. In this study, we attempted to analyze electrophysiological correlates of the urge sensation.

We studied a 17-year-old girl diagnosed with GTS who regularly experienced an urge preceding each tic and who also underwent bilateral GPi-DBS surgery. Local field potentials, accelerometric analysis of movements, and video were simultaneously recorded and rated in a free-to-tic condition (Supporting Information).

To disentangle the urge-to-tic-related activity, we selected a 10-second pre-tic window, based on a previous clinical study showing premonitory urges during this time frame.1 To separate urge from motor-related activity, we independently analyzed the 2-second window before movement/tic, because this is the average interval during which neural preparatory mechanisms are activated2 (Supporting Information).

Only left globus pallidus internus (GPi) local field potential recordings from 27 tics were available for analysis (flowchart in Supporting Information). We identified a significant increase in 4- to 10-Hz power activity in the limbic portion of the GPi during the 10-second period preceding tic onset, compared with resting state (P = 0.003) and voluntary movement (P = 0.013). This disappeared 2 seconds before tic onset, during premotor activation, and was absent during the 10 seconds preceding voluntary movements (Fig. 1). The timing suggests this band activity, mediated by limbic activation, could be linked to the urge sensation.

A slight increase in the beta band was also present in the 10-second pre-tic (11–30 Hz), compared with resting state (P = 0.005) and pre-movement (P = 0.019). Activity in the 11- to 30-Hz band showed significant dampening in the 2-second window before both tics and voluntary movement. Beta-band activity preceding voluntary movement, in contrast, showed a steeper decrease than pre-tic activity (P = 0.002) (Fig. 1).

Our finding is consistent with the hypothesis that low-frequency peaks correlate with the urge to tic. Other studies are in line with these assumptions. One group showed 3- to 12-Hz bursts in patients with GTS at rest, both in GPi and thalamus, and that burst duration correlated with disease severity.3 Another study showed that low-frequency oscillations seen during rest shift to beta-band activity during tic activity.4 A recent study showed a 3- to 10-Hz power increase in the thalamus at or immediately after tic onset, but absent in the second before tic.5 Our results, however hypothetical, have added a temporal frame to these findings.

Current understanding of the mechanism underlying urge sensation suggests the presence of an urge-to-tic network involving the limbic circuit in line with our findings that low-frequency power increment was maximal in the limbic portion of the nucleus. Abnormal power in the 4- to 10-Hz band within segregated basal ganglia circuits has been found to be associated with tremor, levodopa-induced dyskinesias, impulse-control disorders in patients with PD, and here in the rostral GPi in GTS. Each of these abnormalities probably is related to a similar basic neurophysiological signaling pathway, but gives rise to different symptoms depending on discrete subcircuits involved in motor, cognitive, and emotional control. Our findings add to the growing idea of using closed-loop approaches for DBS: in this case, targeting the urge sensation to control clinical manifestations in GTS.

Data Availability Statement

Data are available upon reasonable request.

Miguel Wilken, MD,1,2* Daniel Cerquetti, Eng,1 Malco Rossi, MD, PhD1,3 José A. Obeso, MD, PhD4,5 and Marcelo Merello, MD, PhD1,3

1Movement Disorders Service, Neurology Department, FLENI, Buenos Aires, Argentina, 2Clinical Neurophysiology, Neurology Department, FLENI, Buenos Aires, Argentina, 3Argentine National Scientific and Technological Research Council (CONICET), Buenos Aires, Argentina, 4HM CINAC (Centro Integral de Neurociencias Abarca Campal), Hospital Universitario HM Puerta del Sur, HM Hospitales, Madrid, Spain, and 5Medical School, CEU-San Pablo University, CIBERNE, Instituto Carlos III, Madrid, Spain

*Correspondence to: Dr. Miguel Wilken, Movement Disorders Service, Neurology Department, Raúl Carrea Institute for Neurological Research (FLENI), Montañeses 2325, Buenos Aires C1428AQK, Argentina; E-mail: mwilken@fleni.org.ar

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