Rest Tremor Pattern Predicts DaTscan (^{123}I-Ioflupane) 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).[1] Differentiating RT disorders clinically may be challenging and often requires DaTscan (^{123}I-ioflupane),[2,3] 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.[4-7] 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. RT pattern and DaTscan were strongly associated with each other, supporting the usefulness of pattern for predicting DaTscan result (odds pattern DaT−/synchronous, 3.74; odds pattern DaT+/alternating, 9.45; odds ratio, 34.3; confidence interval, 14.9–86.1). In our cohort, the large majority (104/115, 90.4%) of alternating patients were DaT+, while 71/90 (78.9%) synchronous patients were DaT−. Eighty-five of 104 (81.7%) alternating DaT+ patients had parkinsonian tremor, while all DaT− synchronous patients were affected by non-parkinsonian RT disorders (Supporting Information Table S3). Our study has several strengths. First, we demonstrated the stability of RT pattern both in the short- and long-term periods (Supporting Information Results), which is necessary to use this biomarker in the diagnosis of tremulous syndromes. Second, patients were prospectively followed for 2 years to confirm clinical diagnosis. Third, the use of RT pattern for predicting DaTscan result can translate into economic advantages by reducing the need for expensive procedures for correct tremor diagnosis. A limitation to this study is that it was performed in a large cohort from a single center, and further validation in an independent international cohort is warranted.

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.

Andrea Quattrone, MD,[1] Rita Nisticò, MD,[2] Maurizio Morelli, MD,[1] Gennarina Arabia, MD,[1] Marianna Crasà, PhD,[3] Basilio Vescio, PhD,[4] Alessandro Mechelli, MD,[1] Giuseppe L. Cascini, MD,[5] and Aldo Quattrone, MD[2,3*]

[1]*Institute of Neurology, University "Magna Graecia", Catanzaro, Italy,* [2]*Institute of Molecular Bioimaging and Physiology, National Research Council (IBFM-CNR), Catanzaro, Italy,* [3]*Neuroscience Research Center, University "Magna Graecia", Catanzaro, Italy,* [4]*Biotecnomed S.C.aR.L., Catanzaro, Italy, and* [5]*Institute of Nuclear Medicine, University "Magna Graecia", Catanzaro, Italy*

References

1. Van de Wardt J, van der Stouwe AMM, Dirkx M, et al. Systematic clinical approach for diagnosing upper limb tremor. J Neurol Neurosurg Psychiatry 2020;91(8):822–830. https://doi.org/10.1136/jnnp-2019-322676
2. Bajaj N, Hauser RA, Grachev ID. Clinical utility of dopamine transporter single photon emission CT (DaT-SPECT) with (123I) ioflupane in diagnosis of parkinsonian syndromes. J Neurol Neurosurg Psychiatry 2013;84(11):1288–1295. https://doi.org/10.1136/jnnp-2012-304436

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

***Correspondence to:** Prof. Aldo Quattrone, Neuroscience Centre and Neuroimaging Research Unit, Institute of Molecular Bioimaging and Physiology, National Research Council, Magna Graecia University, Viale Europa, Catanzaro 88100, Italy; E-mail: quattrone@unicz.it

Relevant conflicts of interest/financial disclosures: Nothing to report.

Full financial disclosures and author roles may be found in the online version of this article.

Received: 24 August 2021; **Accepted:** 27 August 2021

Published online 28 September 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28797

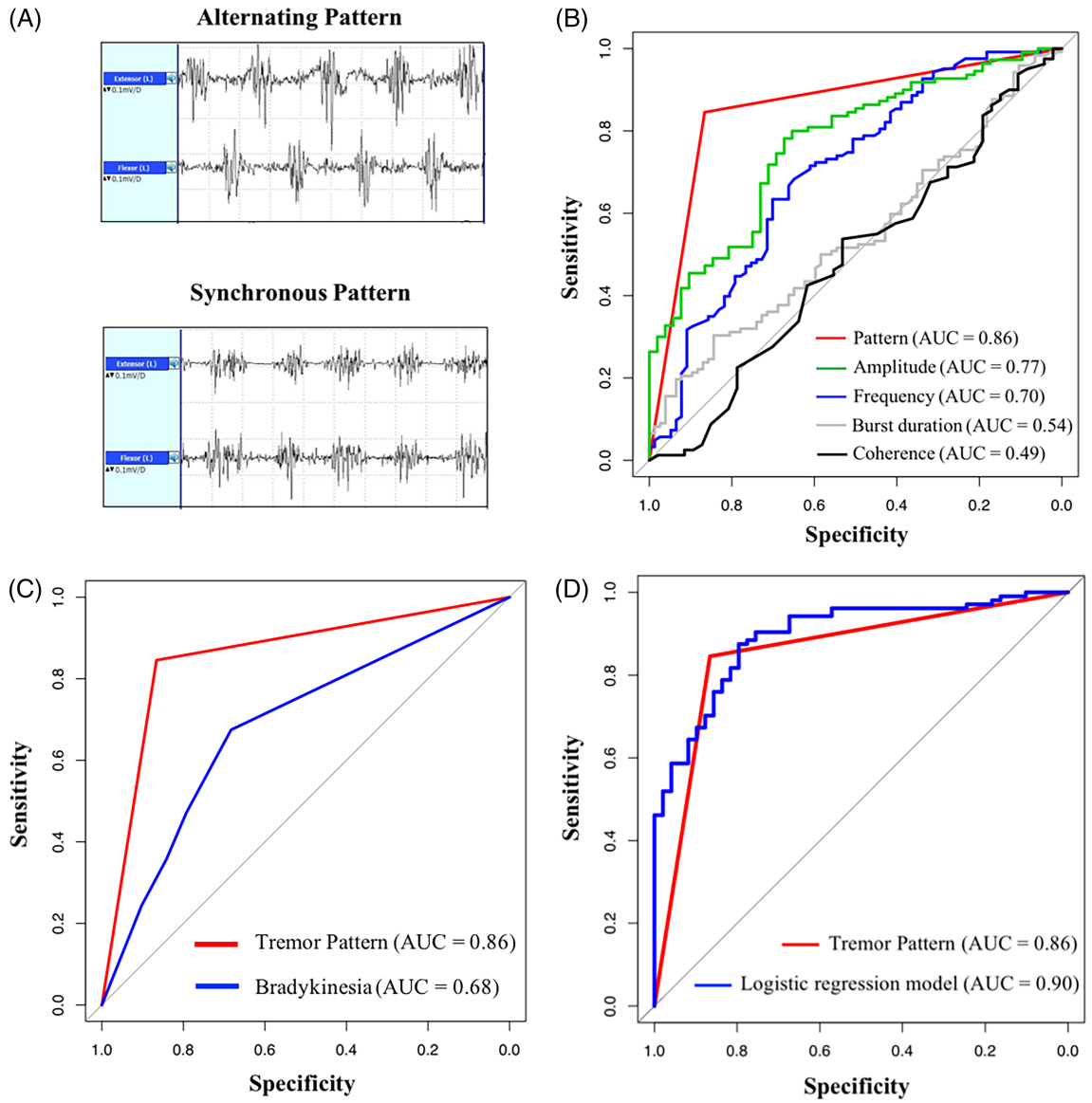

FIG. 1. (**A**) Electromyographic recordings from the extensor carpi radialis and flexor carpi ulnaris muscles of a patient with alternating pattern and a patient with synchronous pattern of rest tremor (RT). (**B**) Receiving operating characteristic (ROC) curves for assessing the classification performance 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.

3. Marshall V, Grosset DG. Role of dopamine transporter imaging in the diagnosis of atypical tremor disorders. Mov Disord 2003;18 (Suppl 7):S22–S27. https://doi.org/10.1002/mds.10574

4. Nisticò R, Pirritano D, Salsone M, et al. Synchronous pattern distinguishes resting tremor associated with essential tremor from rest tremor of Parkinson's disease. Parkinsonism Relat Disord 2011;17(1):30–33. https://doi.org/10.1016/j.parkreldis.2010.10.006

5. Nisticò R, Fratto A, Vescio B, et al. Tremor pattern differentiates drug-induced resting tremor from Parkinson disease. Parkinsonism Relat Disord 2016;25:100–103. https://doi.org/10.1016/j.parkreldis.2016.02.002

6. Arabia G, Lupo A, Manfredini LI, et al. Clinical, electrophysiological, and imaging study in essential tremor-Parkinson's disease syndrome. Parkinsonism Relat Disord 2018;56:20–26. https://doi.org/10.1016/j.parkreldis.2018.06.005

7. Zhang J, Xing Y, Ma X, Feng L. Differential diagnosis of Parkinson disease, essential tremor, and enhanced physiological tremor with the tremor analysis of EMG.

Parkinsons Dis 2017;2017:1597907. https://doi.org/10.1155/2017/1597907

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 activated[2] (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, PhD,[1,3] José A. Obeso, MD, PhD,[4,5] and Marcelo Merello, MD, PhD[1,3]

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

Relevant conflicts of interest/financial disclosures: M.W., D.C., and M.R. have nothing to disclose. J.A.O. has received honoraria for lecturing in meetings organized by BIAL in Spain, for serving as a member of Insighect's Advisory Board, and for serving as a member of the Adverse Event Committee for a Biogen randomized immunotherapy trial. He received honoraria for attending a one-session Advisory Meeting for Neurocrine and Roche in September 2019. He received grants from the Spanish Science and Education Ministry, Fundación La Caixa, and CIBERNED. M.M. has received consultation fees from TEVA and Lepetit. He has received research grants from Lepetit, Glaxo, St. Jude Medical, and Allergan and honoraria from Global Research. He serves as MDCP Chief Editor and receives royalties from Random House and Springer.

Received: 1 May 2021; **Revised:** 19 August 2021; **Accepted:** 23 August 2021

Published online 19 September 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28784