before that was followed by a progressive insomnia, also associated with behavioral and mood lability.

General physical examination, laboratory tests, fundoscopic analysis, brain CT scan, and MRI were unremarkable. The EEG showed only a diffuse slowing, mainly on anterior regions, with preserved posterior alpha rhythm on eye closure. On admission, facial dyskinesias and choreo-athetoid movements of the limbs (Video, Segment 1) were observed. These hyperkinesias were later seen during periods of unresponsiveness resembling sleep. The epileptic nature of these episodes was ruled out by means of video-EEG recordings, that documented a concomitant EEG pattern intermediate between sleep and wakefulness suggestive of a "Status Dissociatus" (Video, Segment 2).[4] A short-stepped gait, characterized by festination and freezing of gait (FOG), was also noticed (Video, Segment 3).

CSF and serum analysis revealed the presence of anti-NMDAR antibodies. Intravenous and oral steroids combined with repeated intravenous immunoglobulin led to a gradual normalization of clinical and EEG abnormalities. Repeated laboratory and radiological screening for neoplasms as well as neurological and cognitive follow-up did not reveal any abnormalities in the following 3 years.

Anti-NMDAR encephalitis constitutes one of the most common causes of encephalitis in children, in whom it can present with a broad spectrum of movement disorders.[3] Gait disorders have been reported particularly in children, also as a presenting sign, and have been characterized by the presence of ataxia, unilateral weakness with circumduction or spasticity.[3,5,6] Our case presented the typical sequence effect of step length noted in adults with FOG and probably represents the youngest case of such phenomena.[7]

Because anti-NMDAR encephalitis can present with vague symptoms, diagnosis and treatment are often delayed. Our case highlights that gait disturbance should raise the concern for anti-NMDAR encephalitis in young children, particularly when observed in the setting of other neurological abnormalities.

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References

1. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25–36.
2. Dalmau J. NMDA receptor encephalitis and other antibody-mediated disorders of the synapse: The 2016 Cotzias Lecture. Neurology 2016; 87:2471–2482.
3. Goldberg EM, Titulaer M, de Blank PM, Sievert A, Ryan N. Anti-N-methyl-D-aspartate receptor-mediated encephalitis in infants and toddlers: case report and review of the literature. Pediatr Neurol 2014;50:181–184.
4. Stamelou M, Plazzi G, Lugaresi E, Edwards MJ, Bhatia KP. The distinct movement disorder in anti-NMDA receptor encephalitis may be related to Status Dissociatus: a hypothesis. Mov Disord 2012;27:1360–1363.
5. Yeshokumar AK, Sun LR, Klein JL, Baranano KW, Pardo CA. Gait disturbance as the presenting symptom in young children with anti-NMDA receptor encephalitis. Pediatrics 2016;138:e20160901.
6. Janmohamed M, Knezevic W, Needham M, Salman S. Primary lateral sclerosis-like picture in a patient with a remote history of anti-N-methyl-D- aspartate receptor (anti-NMDAR) antibody encephalitis. BMJ Case Rep 2018;2018:bcr-2017-224060.
7. Fasano A, Bloem BR. Gait disorders. Continuum (Minneap Minn) 2013;19:1344–1382.

Supporting Data

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

Monitoring Subthalamic Oscillations for 24 Hours in a Freely Moving Parkinson's Disease Patient

Adaptive deep brain stimulation (DBS) devices aim to personalize stimulation delivery by following the current state of symptom-specific neural signals during different activities of daily living (walking, sleeping, etc.). This approach is not yet suitable for clinical practice, and groundwork is needed. The first essential steps for establishing adaptive DBS comprise the capacity for measurements in chronically implanted patients (to avoid the "stunning effect")[1] and for prolonged recordings not corrupted by artifacts.[2,3]

Our centers teamed up to address these challenges and were able to successfully record the bilateral subthalamic local field potentials for 24 hours in 1 patient chronically implanted for Parkinson's disease (ClinicalTrials.gov: NCT03422757). The recordings were performed in a 55-year-old woman suffering

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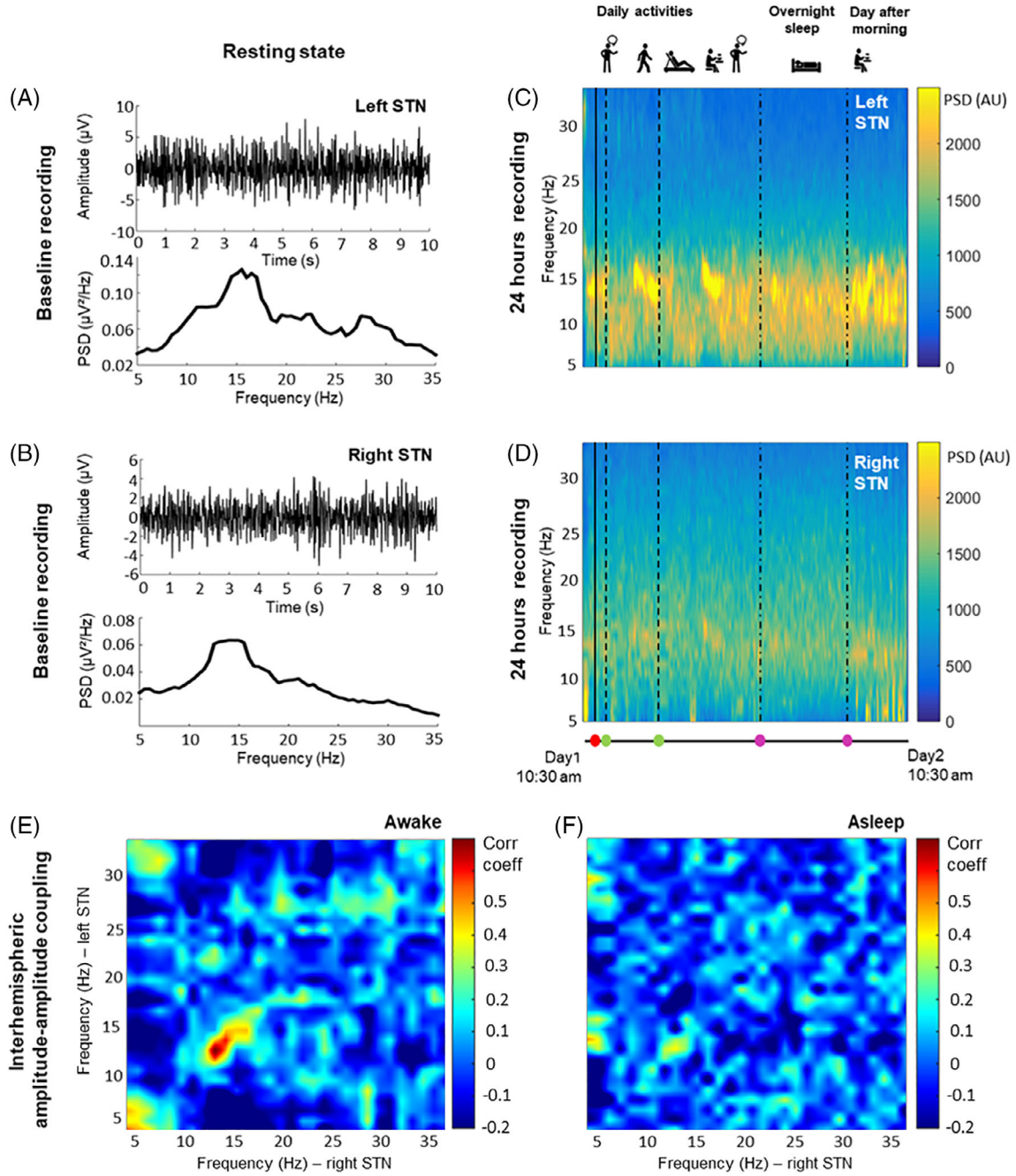

FIG. 1. Time plot (upper row) and power spectral density (lower row) of local field potentials (LFPs) recorded in the left (A) and the right (B) subthalamic nucleus (STN) in baseline condition. Time-frequency plot of LFPs in the range 5-35 Hz recorded in the left (C) and the right (D) STN during 24 hours of cDBS. Red dot indicates when deep brain stimulation was activated and green dots the intake of levodopa. Nighttime sleep is shown between the 2 pink dots. Interhemispheric subthalamic cross-frequency amplitude-amplitude coupling during daytime (E) and nighttime sleep (F).

from akinetic-rigid PD for 8 years and admitted to the hospital for battery replacement after 4 years of subthalamic DBS (Activa PC, lead model 3389; Medtronic). After 30-minute recordings (baseline) in stim-off/meds-off condition (overnight pausing of all dopaminergic medication), we set the new AlphaDBS device (Newronika Srl)[1] to the chronically active parameters (left: 3-C+, 4.8 V, 60 μs, 170 Hz; right: 11-C+, 5.5 V, 60 μs, 170 Hz). Recordings lasted for 24 hours continuously over 2 days, during which the patient freely performed everyday life activities and had approximately 6 hours of sleep at night. Recordings were performed during active stimulation in a differential configuration (left: contacts 0-1; right: contacts 8-9) and stored on the device.[1] We chose these contacts as they showed the highest peak in the β-frequency range. Despite active stimulation, we observed clear modulation of the low β-frequency range (13-20 Hz) following levodopa intake.[4] In this band, we recorded the highest interhemispheric subthalamic cross-frequency amplitude-amplitude coupling ($r = 0.62$, $P < 0.0001$) during the daytime, which diminished during night sleep (Fig. 1). The clinical efficacy of DBS was maintained throughout the experiment, with stable improvement ranging between 30% and 37% (with respect to the baseline MDS-UPDRS part III

score of 39/108), which was similar to that experienced by the patient at home (36% improvement in stim-on/meds-off at enrollment visit). During the study, the patient continued the home medication regimen and took 1 pill of fast-acting oral levodopa/benserazide 100/25 mg on 2 occasions. Levodopa improved parkinsonian symptoms by 5 points on the MDS-UPDRS part III score, without adverse events (i.e., dyskinesias). No adverse events or complaints by the patient were reported. The Ethical Committee approved the study, and all patients gave written informed consent.

Our results prove the feasibility of prolonged recordings (up to 24 hours) in freely moving, chronically stimulated patients. They further corroborate the hypothesis that oscillations in the β-frequency range might be used as a levodopa-related biomarker for adaptive DBS paradigms, as they are present during active stimulation and years after surgery. We also provide for the first time preliminary evidence that interhemispheric subthalamic coupling changes between wakefulness and sleep can be monitored and possibly serve as an additional behavior-specific biomarker. These findings pave the way for testing different adaptive stimulation paradigms for STN-DBS and prompt a more accurate definition of symptom-related and behavior-specific biomarkers in PD.[5]

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References

1. Arlotti M, Marceglia S, Foffani G, et al. Eight-hours adaptive deep brain stimulation in patients with Parkinson disease. Neurology 2018;90:e971-e976.
2. Canessa A, Pozzi NG, Arnulfo G, et al. Striatal dopaminergic innervation regulates subthalamic beta-oscillations and cortical-subcortical coupling during movements: Preliminary evidence in subjects with Parkinson's disease. Front Hum Neurosci 2016;10:611.
3. Arnulfo G, Pozzi NG, Palmisano C, et al. Phase matters: A role for the subthalamic network during gait. PLoS One 2018;13:1-19.
4. Priori A, Foffani G, Pesenti A, et al. Rhythm-specific pharmacological modulation of subthalamic activity in Parkinson's disease. Exp Neurol 2004;189:369-379.
5. Swann NC, de Hemptinne C, Miocinovic S, et al. Gamma oscillations in the hyperkinetic state detected with chronic human brain recordings in Parkinson's disease. J Neurosci 2016;36:6445-6458.

Minimal Clinically Important Difference for the Quality of Life in Essential Tremor Questionnaire

Essential tremor (ET) can considerably impair health-related quality of life (HRQoL). Disability and impairment, related to motor and nonmotor symptoms of the disease, can be specifically captured by the Quality of Life in Essential Tremor Questionnaire (QUEST).[1] Although this instrument is increasingly used in clinical practice and research, its minimal clinically important difference (MCID) has not yet been established. We therefore aimed to determine these threshold values that may provide guidance on judging the clinical relevance of changes associated with both disease progression and various treatment options.

A total of 248 consecutive patients with ET attending the Department of Neurology, Pécs, Hungary, between June 2013 and December 2018 were enrolled. In addition to demographic, medication, and disease-related data, the validated Hungarian version of the QUEST[2] was assessed at baseline. Disease severity was determined by the QUEST Summary Index (QUEST-SI) as mild (≤11.25), moderate (11.26-20.35), and severe (>20.35).[2] The major neurocognitive disorder was an exclusion criterion (Montreal Cognitive Assessment score <20.5). At follow-up visits, the QUEST-SI was reassessed, and patients rated the perceived changes in ET-related difficulties since the last visit on the Patient-rated Global Impression of Improvement (PGI-I) scale. The methods for calculating MCID were previously described in full detail elsewhere.[3]

Key Words: essential tremor, health-related quality of life, minimal but clinically relevant differences, minimal clinically important change, Quality of Life in Essential Tremor Questionnaire

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