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/hydroxyzine 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 inter-hemispheric 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.

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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, Miočinović 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 QUEST2 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

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

Funding agencies: This study was supported by the Hungarian Brain Research Program (2017-1.2.1-NKP-2017-00002), NKFIH EFOP-3.6.2-16-2017-00008, and NKFIH SNN125143 government-based funds. Our research was partly financed by the Higher Education Institutional Excellence Program of the Ministry of Human Capacities in Hungary, within the framework of the 5th thematic program of the University of Pécs, Hungary (207653/2018/FEKUSTRAT).

Received: 21 November 2018; Revised: 19 January 2019; Accepted: 14 February 2019

Published online 2 April 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27660
Finally, 895 paired examinations were included. The baseline characteristics of the study cohort in the therapy during the follow-up period are presented as Supplementary Tables S1 and S2. The median number of return visits was 3, with a median intervisit interval of 6 months. A statistically significant ordinal logistic regression model could be developed between the PGI-I scale (anchor) and the changes in the QUEST-SI (Nagelkerke pseudo-$R^2$; 0.421; $P < 0.01$). Both anchor- and distribution-based methods were applied for determining the MCID thresholds.3,4 The mean changes, the effect size, the results of receiver operating characteristic analyses, and the calculated MCID values are shown in Table S3. The threshold values for minimal yet clinically meaningful changes slightly varied across ET severity stages (Table 1).

Previous studies investigating pharmacotherapy5 and surgical treatments6,7 for ET evaluated changes in the QUEST-SI only from a statistical point of view (Table S4). However, statistical significance does not necessarily imply clinical relevance, as small but significant improvement may be clinically negligible. Therefore, the simultaneous judging of the statistical significance and MCID thresholds may allow a more reliable interpretation of outcomes in clinical trials. Enrolling a high number of patients representing a wide range of disease severity and using well-established methods,3,4 we found that any improvement greater than 4.47 or any worsening greater than 4.98 in the QUEST-SI indicates a minimal yet clinically relevant change in the HRQoL.

Although MCID values may highly depend on the study population, the establishment of distinct MCID thresholds for different disease severity stages may help the wider applicability of our results. Our MCID thresholds may also be a good base for the planning of clinical studies, calculating sample power, and judging the outcomes of clinical trials.

**Table 1.** Minimal clinically important difference threshold (MCID) values for the overall population and each disease severity stage

| Instrument | PGI-I | Mild | Moderate | Severe | Overall MCID |
|------------|-------|------|----------|--------|--------------|
| QUEST-SI   | 3     | -4.11| -4.53    | -4.59  | -4.47        |
|            | 4     | -0.12| -0.01    | 0.02   | -0.05        |
|            | 5     | 4.78 | 4.89     | 4.98   |              |

Disease severity was determined by the QUEST score as described by Kovacs et al.3 Threshold for mild severity is ≤11.25, whereas for moderate and severe 11.26-20.35 and >20.35, respectively.3 MCID, minimal clinically important difference threshold; PGI-I, Patient-rated Global Impression of Improvement; QUEST-SI, #of the Quality of Life in Essential Tremor Questionnaire.

**References**

1. Troster AI, Pahwa R, Fields JA, Tanner CM, Lyons KE. Quality of life in Essential Tremor Questionnaire (QUEST): development and initial validation. Parkinsonism Relat Disord 2005;11(6): 367-373.

2. Kovacs M, Makkos A, Janszky J, Kovacs N. Independent validation of the Quality of Life in Essential Tremor Questionnaire (QUEST). Ideggyogy Sz 2017;70(5-6):193-202.

3. Horvath K, Aschermann Z, Kovacs M, et al. Minimal clinically important differences for the experiences of daily living parts of movement disorder society-sponsored unified Parkinson’s disease rating scale. Mov Disord 2017;32(5):789-793.

4. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol 2008;61(2):102-109.

5. Samotus O, Kumar N, Rizek P, Jog M. Botulinum toxin type A injections as monotherapy for upper limb essential tremor using kinematics. Can J Neurol Sci 2018;45(1):11-22.

6. Rezaei Haddad A, Samuel M, Hulse N, Lin HY, Ashkan K. Long-term efficacy of constant current deep brain stimulation in essential tremor. Neuromodulation 2017;20(5):437-443.

7. Elias WJ, Lipsman N, Ondo WG, et al. A randomized trial of focused ultrasound thalamotomy for essential tremor. N Engl J Med 2016; 375(8):730-739.

**Supporting Data**

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