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Resting-state functional magnetic resonance imaging of the subthalamic microlesion and stimulation effects in Parkinson's disease: Indications of a principal role of the brainstem

Brainstem — central to Parkinson's disease

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ABSTRACT

During implantation of deep-brain stimulation (DBS) electrodes in the target structure, neurosurgeons and neurologists commonly observe a "microlesion effect" (MLE), which occurs well before initiating subthalamic DBS. This phenomenon typically leads to a transitory improvement of motor symptoms of patients suffering from Parkinson's disease (PD). Mechanisms behind MLE remain poorly understood. In this work, we exploited the notion of ranking to assess spontaneous brain activity in PD patients examined by resting-state functional magnetic resonance imaging in response to penetration of DBS electrodes in the subthalamic nucleus. In particular, we employed a hypothesis-free method, eigenvector centrality (EC), to reveal motor-communication-hubs of the highest rank and their reorganization following the surgery; providing a unique opportunity to evaluate the direct impact of disrupting the PD motor circuitry *in vivo* without prior assumptions. Penetration of electrodes was associated with increased EC of functional connectivity in the brainstem. Changes in connectivity were quantitatively related to motor improvement, which further emphasizes the clinical importance of the functional integrity of the brainstem. Surprisingly, MLE and DBS were associated with anatomically different EC maps despite their similar clinical benefit on motor functions. The DBS solely caused an increase in connectivity of the left premotor region suggesting separate pathophysiological mechanisms of both interventions. While the DBS acts at the cortical level suggesting compensatory activation of less affected motor regions, the MLE affects more fundamental circuitry as the dysfunctional brainstem predominates in the beginning of PD. These findings invigorate the overlooked brainstem perspective in the understanding of PD and support the current trend towards its early diagnosis.

1. Introduction

Deep-brain stimulation (DBS) is a rapidly evolving surgical strategy, in which one or more electrodes are implanted in specific brain regions to treat a variety of disabling neurological and psychiatric conditions. Externally-generated electrical currents applied to the electrodes then stimulate the surrounding brain tissue and eventually alleviate the patients' debilitating symptoms. While new applications and brain targets for DBS continue to emerge (Hariz et al., 2013), DBS of the subthalamic nucleus (STN) or globus pallidus (GP) interna have – over the past two decades (Miocinovic et al., 2013) – become well-established treatment options for movement symptoms associated with Parkinson's disease (PD).

Abbreviations: BOLD, blood-oxygenation-level dependent; DBS, deep-brain stimulation; EC, eigenvector centrality; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; FDG-PET, fluorodeoxyglucose positron emission tomography; FWE, family-wise error; GP, globus pallidus; ICA, independent component analysis; MLE, microlesion effect; MNI, Montreal Neurological Institute; PD, Parkinson's disease; PPN, pedunculopontine nucleus; rm-ANOVA, repeated measures analysis of variance; rs-fMRI, resting-state fMRI; SD, standard deviation; STN, subthalamic nucleus; UPDRS-III, motor part of the Unified Parkinson's Disease Rating Scale..

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Neurosurgeons and neurologists frequently observe an intriguing phenomenon, already in the operating room while implanting the DBS electrodes. Shortly after insertion of electrodes into the target structure, and well before the actual DBS pulse-generator is switched on, motor symptoms of many PD patients improve markedly. Such improvement remains noticeable for a certain period after implantation (Derrey et al., 2010; Koop et al., 2006; Singh et al., 2012), in some cases even months (Kondziolka and Lee, 2004; Mann et al., 2009). A general term, known as the "microlesion effect" (MLE), has been established to designate this phenomenon. Based on prevailing schemes of functional organization of the basal ganglia (DeLong, 1990), the MLE could be attributed to the reduction of abnormal basal ganglia output by disruption of cells and/or fibers in the STN and GP, that is, a mechanism similar to targeted ablative lesioning therapy. In fact, pallidotomy and subthalamotomy have been considered favored therapeutic approaches for patients with advanced PD in countries incapable of providing DBS treatment due to economical or technological limitations (Alvarez et al., 2005). However, in contrast to the permanent and irreversible impact of ablative surgery, DBS is considered a less destructive and more adaptable method (Haberler et al., 2000). Above all, the action of the MLE associated with implantation of the DBS electrodes is transient and gradually fades within days or weeks. This suggests that apart from the destruction of brain tissue within the electrode track, it reflects other transient posttraumatic tissue reaction along or close to the electrode. In particular, sharp leakage of neurotransmitters caused by damaged synapses influencing the surrounding unaffected neurons and post-operative collateral edema of brain matter around the electrode is thought to play an important role in the MLE (Jech et al., 2012). Appearance of the MLE is remarkably beneficial — is considered as an evident immediate sign of good placement of the DBS electrode within the particular portion of the target structure (Maltete et al., 2008). Yet, the mechanisms behind the MLE have not been understood.

We hypothesized that penetration of DBS electrodes in the STN has a substantial impact on the low-frequency blood-oxygenation-level dependent (BOLD) fluctuations in the resting-state (rs)-fMRI signal, which have been shown to be altered by PD (Jech et al., 2013; Kahan et al., 2014; Mueller et al., 2013). Specifically, the invasive intervention in combination with the utilization of a novel hypothesis-free analytical method gave us a unique opportunity to assess the direct impact of the physically disrupted STN on the rest of the abnormal motor circuitry *in vivo* without prior assumptions. This approach could identify novel anatomo-functional correlations accountable for improvement of motor symptoms related to the MLE and, subsequently, provide new insights into the functional organization of the human brain affected by PD.

2. Materials and methods

2.1. Subjects

Thirteen patients suffering from an akinetic-rigid variant of PD (11 males/2 females, age: 52 ± 7 years (mean ± standard deviation), disease duration since the first symptoms: 13 ± 3 years, duration of levodopa treatment: 9 ± 3 years) participated in the study after giving their written informed consent. All patients had a sporadic type of disease including five patients with beginning of symptoms before 40 years of age. None of these young-onset PD patients was positive for common genetic mutations potentially related to PD. All experimental procedures conformed to the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the General University Hospital in Prague, Czech Republic. All patients met the United Kingdom Brain Bank Criteria for diagnosis of PD and were classified into the akinetic-rigid subtype of PD (Schiess et al., 2000), and suffered from motor fluctuations and/or disabling dyskinesias associated with long-term levodopa treatment. Further, all patients were referred for STN DBS therapy and thereby underwent the implantation of both DBS electrodes and the internal pulse generator.

Patients expressing signs of dementia and/or depression based on a standard psychiatric examination and neuropsychological testing (Mini-mental State Examination, Mattis Dementia Rating, Beck Depression Inventory) were excluded from the study. One further patient was excluded due to excessive involuntary movements extending to the head during the scanning session, which was evaluated post-hoc by analyzing realignment parameters of the data during the fMRI preprocessing procedure. A detailed demographic and clinical description of patients involved in the study is summarized in Table 1 and Supplementary Table S1.

2.2. Surgical procedure

Implantation of the DBS apparatus consisted of two separate surgery sessions: Insertion of the permanent quadripolar stimulation electrodes (3386 Medtronic, Minneapolis, MN, USA) into the STN bilaterally and implantation of the connection leads and the internal pulse generator to the subclavical region. This study focused exclusively on the time points preceding and immediately succeeding the first surgery session (*i.e.*, pre-/post-implantation of electrodes), while the MLE was still identifiable.

The methodology associated with implanting the DBS electrodes and the internal pulse generator was identical to the one thoroughly described elsewhere (Jech et al., 2012).

2.3. Magnetic resonance imaging

All MRI investigations were performed at 1.5 T on a Magnetom Symphony scanner (Siemens, Erlangen, Germany). fMRI was collected in a 10-min session with 200 volumes of functional brain images collected using a T_2*-weighted, gradient-echo-planar imaging (EPI) sequence (flip angle, $FA = 90°$; repetition time, $TR = 3000$ ms; echo time, $TE = 51$ ms, 31 axial slices, nominal in-plane resolution 3×3 mm^2, slice thickness at 4 mm) sensitive to the BOLD effect. For display and registration purposes, high-resolution three-dimensional T_1-weighted structural data were acquired using a magnetization-prepared rapid acquisition gradient-echo (MP-RAGE) sequence ($FA = 15°$; $TR = 2140$ ms; inversion time, $TI = 1100$ ms; $TE = 3.93$ ms). In Session 2 (*i.e.*, 0–3 days post-implantation), T_2-weighted images were additionally collected using a turbo spin-echo sequence ($TR = 5520$ ms; $TE = 86$ ms; slice thickness 4 mm) for evaluating the grade of the collateral edema caused by the DBS electrode penetration. This particular imaging sequence markedly intensifies the contrast of edema (appearing as hyperintensities in resulting images; Fig. 1), which considerably eases its detection and evaluation.

All safety risks related to potential interference of the static magnetic field, radio-frequency pulses, or magnetic field gradient pulses and the implanted metallic DBS hardware were rigorously assessed, and associated technical precautions were diligently adhered to. The underlying safety standards employed for this evaluation have been published in more detail elsewhere (Jech et al., 2012).

2.4. Experimental protocol

Patients were instructed to look at a fixation cross on a projector screen while remaining still in a supine position during scanning. Two MRI examinations were carried out: (*DBS OFF1*) pre-implantation of DBS electrodes ('Session 1'; 18 ± 17 days before implantation) and (*DBS OFF2*) post-implantation of DBS electrodes ('Session 2'; 1 patient scanned on the day of surgery, 11 patients one day after surgery, and 1 patient 3 days after surgery). In order to uncouple the effect of electrode penetration from the therapeutic effects of levodopa and DBS, anti-Parkinsonian medication was withdrawn at least 12 h before both measurement sessions and the chronic DBS was not yet initialized. In both sessions (pre- and post-implantation), resting-state fMRI data sets ('*DBS OFF1*' and '*DBS OFF2*', respectively) were acquired as