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Involuntary eyelid closure after STN-DBS: evidence for different pathophysiological entities

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Abstract

Objective: Involuntary eyelid closure (IEC) may occur after deep brain stimulation of the subthalamic nucleus (STN-DBS) in Parkinson's disease (PD) and is often categorised as apraxia of lid opening (ALO), albeit the appropriateness of this term is under debate. To gain insight into the hitherto undefined pathophysiology of IEC after STN-DBS we performed a comprehensive clinical and electrophysiological characterisation of lid function in a total of six PD patients.

Methods: The study was carried out in six PD patients who developed IEC after STN-DBS. They underwent neurological examination and electromyography recording of activity in the orbicularis oculi muscle (OO) upon varying stimulation patterns. Intraoperative studies were performed in one patient.

Results: Increasing STN-DBS intensity induced IEC in four patients, whereas it improved the condition in two. Needle EMG showed tonic hyperactivity of the OO in STN-DBS induced IEC, while variable patterns of OO activity (irregular and tonic) were seen in patients with STN-DBS relieved IEC. Intraoperative analysis in one patient showed evidence for IEC being induced by activation of corticobulbar fibres.

Conclusions: We identified two groups of IEC after STN-DBS based on clinical and EMG patterns: (i) STN-DBS induced IEC associated with tonic OO overactivity and (ii) STN-DBS relieved IEC presenting with variable EMG patterns. Our findings provide relevant information on pathophysiology of STN-DBS related IEC and implications for its therapeutic management.

Introduction

Therapeutic deep brain stimulation of the subthalamic nucleus (STN-DBS) provides an effective evidence-based symptomatic treatment for advanced Parkinson's disease (PD)¹⁻³. Optimal hardware programming can be challenging in some cases, as side effects may interfere with stimulation parameters required for sufficient control of motor symptoms⁴. A common and limiting side effect is involuntary eyelid closure (IEC) sometimes referred to as apraxia of lid opening (ALO). This specific symptom has been reported in 1.8 to 30 % followed up after STN-DBS^{1,4,5}.

Goldstein and Cogan defined ALO in 1965 as the patient's inability to voluntarily initiate opening of eyelids⁶. ALO was specified clinically as an IEC without ongoing visible contraction of the orbicularis oculi muscle (OO) and without oculomotor nerve dysfunction or ocular, myopathic or myasthenic signs. Enhanced activation of the frontalis muscle during periods of inability to open the eyes voluntarily has been observed presumably indicating insufficient compensatory attempts of activating neighbouring cranial muscles^{6,7}. However, the terminology of ALO is under debate, as some authors do not consider it as "true apraxia" but rather as a form of focal dystonia⁸. Recent systematic EMG studies show failure of voluntary activation of the levator palpebrae superioris (LPS) during periods of eye closure⁹⁻¹². Replacement of ALO by the terms "inhibition of levator palpebrae superioris muscle" or "blepharocolysis" has been suggested accordingly. Tonic activity of the OO and inhibition of LPS even co-occurred within a single patient due to impaired antagonistic inhibition^{9,11}.

Here, we present a case series of six PD patients exhibiting clinical features of IEC in the postoperative management of STN-DBS. The rationale for our study was to define electrophysiological signatures in these patients and to investigate whether IEC after STN-DBS

matched the clinical criteria of previously described ALO or blepharospasm upon clinical and electrophysiological characterization. Additionally, testing of different stimulation parameters in correlation with surgery protocols including intraoperative test stimulation and microelectrode recordings, as well as testing of response to levodopa, allowed us to define pathophysiological and topographical characteristics of IEC. These findings were supported by one additional case with intraoperative analysis of stimulation induced IEC. Our results enable to categorise IEC in PD patients after STN-DBS into different groups with direct implications for its therapeutic management.

Patients and methods

General information on patients

We reviewed 83 consecutive records of PD patients treated with STN-DBS in Tübingen. IEC was reported in 9.6 % (n = 8). Six of these eight PD patients (PD1 – PD6; six male; mean age 65.7 ± 6.0 years; mean duration of disease 17.9 ± 4.9 ; preoperative Hoehn & Yahr stage ranging from 4 to 5) were available for further clinical evaluation (clinical details in table 1). In one patient (PD4), only data from stimulation through the right hemisphere electrodes were used for the analysis because of intraoperative bleeding at the left hemisphere electrode location. All six patients (PD1-PD6) experienced IEC after bilateral implant of STN-DBS electrodes leading to intermittent functional blindness. They were scheduled for a systematic clinical examination and specific electrophysiological tests (see below).

In addition, we recorded intraoperative data in one patient (PD7), who displayed IEC during intraoperative test stimulation of the right STN area allowing a comprehensive topographic mapping of potentially involved neural structures.

Surgical procedure

Patients underwent bilateral electrode implantation into the STN using the CRW stereotactic frame (Radionics, Burlington, MA) between 2003 and 2009. The target point was located 12 mm lateral, 3-4 mm posterior and 4-5 mm inferior to MCP. The trajectories had an double-oblique orientation entering the STN from antero-lateral. Postoperative imaging confirmed the location of the active contacts within the STN. The orientation of the contact that modulated IEC at lowest stimulation intensity was determined in comparison to the target point (supplemental table 1). All patients were operated with local anaesthesia,

only one patient (PD2) was subjected to general anaesthesia at the beginning of the surgical procedure due to severe clinical symptoms of levodopa discontinuation and thus was tested for direct side effects of test stimulation.

Electrophysiological exploration of the targeted brain area was performed using three microrecording / macrostimulation electrodes (FHC, Bowdoinham, ME). Clinical testing along trajectories for therapeutic and side effects was performed afterwards. The quadripolar electrode (type 3389, Medtronic, Minneapolis, MN) was inserted into each STN along the trajectory that yielded best results in electrophysiological exploration and test stimulation and connected to an implantable pulse generator (Kinetra, Medtronic, Minneapolis, MN) (supplemental table 1). All patients received post-operative MRI (T1, 1.5 Tesla-Scanner, Siemens Sonata, Erlangen, Germany) according to the manufacturers guidelines (Medtronic, USA; SAR < 0.1 W/kg) to ensure correct electrode placement one day after bilateral implantation of chronic electrodes.

Clinical and electrophysiological features

We used clinical and electrophysiological tests to characterise IEC in our patients. We specifically assessed (i) the effects of STN-DBS on IEC (induction vs. reversal) and (ii) the pattern of OO-EMG activity associated with IEC.

Clinical testing for the effects of changing STN-DBS parameters on IEC

Stimulation parameters were tested systematically. Every cathodal monopolar contact was tested with standard parameters (pulse width: 60 μ s; frequency: 130 Hz) with contralateral STN contacts set to 0 V. Voltage was subsequently increased in intervals of 0.5 V and beneficial

effects as well as stimulation-induced side effects were recorded by a neurologist specialised in DBS (DW). The thresholds for elicitation of IEC for all electrode contacts in each patient were determined to specify the spatial representation of this side effect. Electrodes were labelled according to the consensus nomenclature for Kinetra[®] stimulators (0-3: left STN; 4-7: right STN). 0 and 4 indicated the most distal, 3 and 7 the most proximal contacts of electrodes on the left and right side, respectively.

Electromyographic testing of the orbicularis oculi muscle (OO)

In patients PD1 to PD6, we performed needle electromyography testing of the orbicular part of the right lower OO using concentric electromyography needles (25 mm length, 0.3 mm diameter, Ambu Neuroline, Ballerup, Denmark). The localisation of the needle was controlled by voluntary forceful eyelid closure resulting in tonic OO discharge in all of the patients. The OO-EMG was recorded with stimulators on and off with straight forward gaze resulting in two recording conditions in each patient: A) StraightOFF, B) StraightON. EMG recordings were performed with NeuroScreen plus (Jaeger-Toennies, Würzburg, Germany) and sampled at 9615 Hz. To allow data evaluation in the stimulator 'on' condition, all data were exported to Matlab 7.0 and band-pass filtered from 10-120 Hz resulting in adequate reduction of stimulation artefacts. Innervation patterns were determined after filtering.

Data analysis

Filtered OO-EMG data were inspected and categorised among discharge patterns in direct comparison of inner subject data with and without IEC (background activity, tonic overactivity, irregular overactivity). Subsequently, amplitudes of the OO-EMG activity were quantified by root mean square analysis according to equation 1.

$$R(x) = \sqrt{\sum_{i=1}^n x_i^2} \quad (\text{eq. 1})$$

Results

Clinical testing for the effects of stimulation

Clinical testing could differentiate two groups: (i) group 1 (n=4; PD1-PD4) in which bilateral IEC could be induced by unilateral STN-DBS, and (ii) group 2 (n=2; PD5, PD6) in which IEC was reversed by STN-DBS. Individual parameters of all patients when IEC occurred for the first time and the parameters that improved IEC are listed in detail below (supplemental table 2).

IEC induced by stimulation

The first documentation of IEC induced by STN-DBS in patients PD1 to PD4 ranged from a few days to one year after STN-DBS surgery. As indicated in the methods section, a total of seven electrodes were available for testing in these four patients. Unilateral stimulation on monopolar contacts was capable to induce bilateral IEC in all of these patients. Threshold amplitudes varied from 1.0 – 6.5 V on standard parameters among patients, electrode contact and STN-sides (table 2). In five out of seven electrodes tested, IEC was elicited with lower thresholds on the more distal contacts with a mean gradient of -2.3 V (SD = 1.3 V). Stimulation thresholds for typical side effects due to activation of capsular fibres (i.e. visible muscular contraction) were evoked at comparable intensity as IEC (with a mean difference of less than 1.0 V) and showed similar rostro-caudal distribution of threshold amplitudes (table 2).

IEC was preceded in two patients by increased rates of involuntary blinks (PD1 and PD3), and in one patient by prolonged involuntary blinks (PD2) at stimulation intensities that were subthreshold for onset of permanent IEC. In PD4, no such premonitory clinical signs were observed.

IEC improved by stimulation

Patients PD5-PD6 showed a reversal of IEC when increasing STN-DBS intensity.

In patient PD5, IEC first appeared after reduction of dopaminergic medication post surgery (44% reduction of levodopa equivalent dose compared to preoperative baseline) and worsened over time in line with a decrease in the intensity of STN-DBS. In episodes with IEC eyelids could be opened passively by the physician and only closed with onset of the next involuntary or voluntary eye blink. The patient described that IEC was milder, if environment or situation required attention. In contrast, gazing into light provoked IEC. Clinically, compensatory contractions of the frontalis muscle were observed when the patient tried to open his eyelids voluntarily in episodes of IEC. IEC was completely reversed within seconds after onset of unilateral STN-DBS and reappeared within a minute after switching off the stimulus. Contacts (1, 5, 6) were the most effective for improvement of IEC (table 2).

IEC in PD6 first occurred when the STN-DBS accidentally switched off three years after surgery. IEC appeared within a few minutes and resulted in visible tonic contractions of the OO and in great difficulties for passively moving the eyelids. IEC completely resolved within seconds after switching on the stimulator with contacts 2 and 6 being most effective (table 2).

The most beneficial contacts for improvement of IEC in all of the two patients had also proven beneficial for the control of motor symptoms in postoperative management and therapeutic efficacy of stimulation was documented by UPDRS III scores in PD5 (MedOff/StimOff: 42, MedOff/StimOn: 29) and PD6 (MedOff/StimOff: 57, MedOff/StimOn: 22). A further increase of amplitude on the respective contacts elicited dyskinesias and confirmed proper electrode localisation taken together with postoperative MRI.

In all patients with IEC improved by stimulation (PD5, PD6), additionally the influence of oral application of levodopa (200 mg) on IEC was tested. Therefore, all dopaminergic medication was

withdrawn over night (at least 12 hours) and STN-DBS was turned off at least 30 minutes before. Medical testing was performed after 30 - 60 minutes of application and clinical symptoms were rated using the UPDRS III. In PD5, IEC completely reversed 40 minutes after the single dose and dopaminergic on-state was documented by UPDRS III scores (MedOff/StimOff: 42; MedOn/StimOff: 27). In PD6, levodopa reversed IEC completely within 30 minutes after intake (UPDRS III MedOff/StimOff: 57; MedOn/StimOff 25). IEC reappeared 2.5 – 3 h after oral application of levodopa related to subsequent wearing-off.

Electromyographic recording from the OO

EMG recordings defined different electrophysiological groups.

In four of the six patients (PD1-PD4) background activity of the OO was present during stimulator off. A tonic interference pattern of the OO occurred in presence of IEC during stimulation (see supplemental figure 1). Consistently, root mean square analysis indicated an increase of activity upon stimulation (table 3).

In PD5, irregular discharge of the OO was observed during IEC in the stimulator off condition (see supplemental figure 2). Activity significantly decreased between single bursts of the OO.

Despite of the transient reduction of OO-EMG discharge, the patient was not able to open eyelids voluntarily. This irregular pattern remained unchanged if the patient was advised to forcefully try to open his eyes during IEC. Stimulation completely reversed the irregular overactivity of the OO and allowed voluntary eyelid opening. In correlation, the root mean square analysis demonstrated a decrease of OO activity during stimulation (table 3).

In PD6, OO-EMG revealed a tonic interference pattern with increased amplitudes during IEC in the stimulator off condition. Subsequent stimulation reversed IEC completely (see supplemental figure 3) and OO-EMG amplitudes decreased (table 3). OO-EMG pattern in this patient was inverse to the pattern observed in patients PD1 to PD4.

IEC during intraoperative test stimulation

In PD7, bilateral IEC occurred during intraoperative test stimulation of the right STN and could be induced at 2.0 mA (pulse width: 60 μ s, frequency: 130 Hz) on the central trajectory on the anatomic target point. Test stimulation on the medial trajectory induced IEC at 4.0 mA (see video). Further clinical signs for stimulation of capsular fibres included dysarthria at 1.5 mA (central trajectory) and at 3.5 mA (medial trajectory) (detailed information on intraoperative effects from test stimulation are available in supplemental table 3).

Discussion

The present study for the first time correlates clinical observations with electromyographic patterns in patients with IEC after STN-DBS. Our results indicate that IEC in PD patients after STN-DBS might have a complex pathophysiology and that the previously applied term ALO, referred to non-paralytic motor abnormality, falls short of the clinical heterogeneity in these patients. Our results underline the relevance of proper clinical and electrophysiological categorisation to initiate adequate therapeutic management.

Detailed analyses of clinical data allowed the definition of two groups: (i) group 1 with IEC induced by stimulation, and (ii) group 2 with IEC improved by stimulation or levodopa. All subjects of group 1 showed a tonic interference EMG pattern and increase of OO-EMG activity during IEC as commonly observed in blepharospasm, either idiopathic or secondary¹¹. In contrast, patients of group 2 presented with variable electrophysiological features: PD5 displayed irregular overactivity of the OO. Instead, PD6 showed an inverse pattern with respect to patients of group 1, with tonic OO discharge during IEC that was clinically and electrophysiologically reversed by stimulation or levodopa.

IEC induced by STN-DBS showed a characteristic distribution of threshold intensities with caudal contacts eliciting IEC at lower stimulation intensities than rostral ones. Caudal electrode contacts are located in general more medial but also closer to the capsula interna that descends and approaches laterally to the STN. Therefore, we speculate on corticobulbar tracts as the neuroanatomical substrates of the observed activation of the OO muscle. This is in line with previous studies showing that STN-DBS can activate cortico-bulbar and other neighbouring tracts: single pulse STN-DBS caused facilitation of the R1- and inhibition of the R2-components of the blink reflex to trigeminal nerve stimulation due to prepulse conditioning, presumably

because of activation of fibres in the pallido-pedunculopontine tract¹³. Unilateral single-pulse STN-DBS and transcranial magnetic stimulation (TMS) induced bilateral activation of cranial nerve innervated muscles including OO, suggesting that fibres to both ipsi- and contralateral motor nuclei descended together at the level of the STN^{14, 15}. In our patients, unilateral stimulation caused bilateral IEC due to tonic overactivity of the OO. Therefore, the dorsal intermedial facial nucleus innervating the OO could be the structure mediating our findings, as it receives bilateral projections from the capsula interna. Unintended activation of descending cortico-bulbar fibre tracts might cause either direct depolarisation of the nuclei or facilitation of excitatory postsynaptic potentials generated in the motoneurons from other concomitant inputs. Especially, the lower stimulation threshold for bilateral IEC on the more lateral trajectory in PD7 and similar thresholds for side effects mediated through stimulation of the capsula interna in PD1-PD4 would be compatible with this hypothesis. A further intraoperative case report by Shields and colleagues also reported bilateral IEC from stimulation but speculated on a premotor inhibition of the central caudal nucleus (innervating LPS) mediated by trigeminothalamic fibre tracts¹⁶. However, tonic overactivity of the OO in our study would not comply with this explanation. Current spreading to structures medial from the STN electrode could also interfere with premotor control of lid function. Perirubral fields were identified to be connected to the OO as revealed from tracer experiments in rats¹⁷ and might be entrained easily by STN-DBS. Interstitial nucleus of Cajal (InC), rostral intermedial longitudinal fascicle (riMLF), and the m-group also participate in premotor control of the eyelid but are rather related to LPS function and upgaze than to tonic innervation of the OO^{18, 19}.

IEC in PD5 and PD6 was completely reversed with dopaminergic medication or STN-DBS. Overactivity of the OO was evident in these two patients and IEC presented with irregular (PD5) or tonic (PD6) contractions. Yet, responsiveness of IEC on levodopa, coincident contraction of

frontalis muscle, and the ability to passively retract eyelids in PD5 provide evidence for possible LPS inhibition^{9, 20-22} or more likely disturbed antagonistic inhibition^{9, 11, 12}. Although no electrophysiological data were presented in previously published similar cases²⁰⁻²⁴, we think that the cases reported by these authors would be similar to those of PD5 and PD6 of our series because of their response to levodopa or stimulation.

Premotor control of lid-eye coordination by extrapyramidal and mesencephalic circuitries has been suggested and dopaminergic involvement was further substantiated by analysis of blinking rates in patients with PD and schizophrenia. Dyskinetic PD patients and untreated schizophrenic patients displayed increased blinking rates, whereas the opposite occurred in hypodopaminergic states²⁵. Excitability of reflex blinking was increased in dopaminergic off-state²⁶ and decreased after apomorphin administration²⁷. The present data add further evidence for nigro-striatal contribution to premotor control of lid-eye coordination, as stimulation effects on improvement of IEC already appeared at low stimulus intensities together with motor improvement. Side effects due to involvement of the capsula interna occurred with far higher stimulus intensities (table 2).

Alternatively, a stimulation-induced entrainment of premotor fibres of the central caudal oculomotor nucleus located in the vicinity of STN may be involved. As it innervates LPS and receives complex premotor afferents from basal ganglia including riMLF and InC, these fibres could be entrained in restoration of tonic LPS activity. However, the absence of oculomotor side effects and synergistic effects of levodopa argue in favor of effects mediated through nigro-striatal pathways.

In conclusion, IEC in PD after STN-DBS may occur as a direct side effect from stimulation and, therefore, respond to adequate stimulation programming, or as a direct correlate of the underlying

neurodegeneration of dopaminergic neurons and, therefore, respond to STN-DBS or levodopa administration.

Systematic clinical and electromyographic characterisation may help in identifying the differences between the two forms of IEC seen after STN-DBS. In patients with IEC induced by STN-DBS, low intensity stimulation was necessary to avoid current spreading to neighbouring structures, which could also be avoided by bipolar stimulation. If no sufficient control of motor symptoms can be achieved without induction of IEC, botulinum toxin injections into the orbicular portion of the OO should be considered with generally good to excellent response.

Consideration of neuroanatomical correlates might argue in favor of a stimulus-related activation of corticobulbar fibres in the capsula interna in this group. This was further strengthened by the intraoperative observation that allowed an estimate of the localisation of this symptom.

A second group of patients showed IEC responsive to stimulation or levodopa intake, revealing an impairment of nigro-striatal premotor control of lid function. Co-contraction of frontalis muscle and the ability to passively retract eyelids were suggestive of concomitant inhibition of LPS or disturbed antagonistic inhibition. Our findings imply clues for therapeutic management of IEC after STN-DBS. Strategies for DBS programming and dopaminergic medical therapy can be diametrically opposed in regard to the pathophysiological mechanisms of IEC, and their appropriate allocation is necessary to achieve favorable clinical outcome.

Tables and figures

Table 1: Clinical characteristics

patient	age	sex	H&Y	disease duration [years]	uncontrolled motor symptoms prior to STN-DBS surgery	DBS-surgery [month/year]	LED [mg] before/after STN-DBS	UPDRS III [StimOff/StimOn]
PD1	59	male	5	26	peak-dose dyskinesias wearing off (end of dose) sudden offs	02/2008	1450 / 970	43 / 16

					freezing of gait (dopa-sensitive)			
PD2	57	male	5	18	wearing off (end of dose)	12/2007	1325 / 800	40 / 18
					limb tremor			
PD3	64	male	4	20	peak-dose dyskinesias	10/2003	590 / 300	41 / 25
					wearing off (end of dose)			
PD4	68	male	4	17	wearing off (end of dose)	12/2007	1660 / 850	63 / 29
					freezing of gait (dopa-sensitive)			
					off-dystonias			
PD5	71	male	4	13	wearing off (end of dose)	07/2007	1200 / 675	42 / 27
PD6	73	male	4	20	wearing off (end of dose)	11/2005	1280 / 765	57 / 25
					peak-dose dyskinesias			
					freezing of gait (dopa-sensitive)			
PD7*	68	female	5	11	wearing off (end of dose)	03/2009	1460 / 700	57 / 30
					limb tremor			
					freezing of gait (dopa-sensitive)			

Clinical characteristics. Abbreviations: H&Y = Hoehn & Yahr stage before surgery. LED = levodopa equivalent dose in [mg]. *Patient seen in the operating room because of IEC induced by intraoperative test stimulation

Table 2: Threshold amplitudes for induction or reversal of IEC and visible capsular side effects

	left STN	threshold in [V]	threshold CI [V]	right STN	threshold in [V]	threshold CI [V]
		<u>induction</u> of IEC (PD1-PD4)	(side effect)		<u>induction</u> of IEC (PD1-PD4)	(side effect)
		<u>reversal</u> of IEC (PD5, PD6)			<u>reversal</u> of IEC (PD5, PD6)	
PD1	3	4.0	3.0 (d)	7	n	1.5 (cf, ca)
	2	3.0	3.0 (d)	6	1.6	n

	1	3.0	3.0 (d)	5	2.0	n
	0	2.5	2.5 (ca)	4	n	2.2 (cf, ca)
PD2	3	5.0	n	7	4.5	5.0 (cf)
	2	4.0	n	6	4.5	5.5 (cf)
	1	2.0	n	5	2.5	3.0 (cf, ca)
	0	1.0	n	4	1.5	nt
PD3	3	6.5	5.0 (d)	7	5.0	5.0 (cf)
	2	5.5	4.0 (d)	6	5.0	4.0 (d)
	1	3.0	2.0 (d)	5	4.5	4.5 (cf)
	0	3.0	2.0 (d)	4	4.0	4.5 (cf)
PD4	3	e	e	7	n	2.5 (cf)
	2	e	e	6	2.0	2.0 (cf)
	1	e	e	5	3.0	1.0 (cf)
	0	e	e	4	3.5	2.5 (cf)
PD5	3	n	n	7	n	4.5 (d)
	2	contact deficient	contact deficient	6	2.5	4.0 (d)
	1	2.5	5.5 (cf)	5	2.5	3.5 (cf)
	0	n	5.0 (cf)	4	n	4.5 (cf)
PD6	3	4.0	n	7	2.5	n
	2	2.5	n	6	3.0	n
	1	3.0	n	5	n	4.0 (cf)
	0	n	n	4	n	3.0 (cf)
PD7	3	n	5.0 (p)	7	n	3.5 (veg)
	2	n	3.5 (p/d)	6	n	3.5 (d)
	1	n	2.5 (p)	5	n	3.0 (d)
	0	n	1.0 (p)	4	n	2.5 (d)

Threshold amplitudes in [V] (i) for IEC induced by stimulation (PD1-PD4) and IEC reversed by stimulation (PD5, PD6), and (ii) visible capsular side effects were documented for each monopolar contact connected with the generator casing on standard parameters [60 μ s, 130Hz]. In PD7, no IEC could be induced after surgery.

Abbreviations: CI = capsular interna; d = dysarthria; cf = contraction face; ca = contraction arm; p = paraesthesia; veg = vegetative; n = not present; nt = not tolerated; e = excluded from analysis

Table 3: Results from clinical testing and analysis of OO-EMG

patient	onset of IEC after STN-DBS [months]	effect of stimulation	effect of levodopa	OO-EMG pattern StraightOFF / StraightON	root mean square [μV] StraightOFF / StraightON
PD1	0	induction of IEC	nt	background / tonic overactivity	33 / 281
PD2	6	induction of IEC	nt	background / tonic overactivity	291 / 1300
PD3	12	induction of IEC	nt	background / tonic overactivity	214 / 711
PD4	6	induction of IEC	nt	background/ tonic overactivity	82 / 670
PD5	3	reversal of IEC	reversal of IEC	irregular overactivity / background	642 / 229

PD6	36	reversal of IEC	reversal of IEC	tonic overactivity / background	2300 / 748
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Results from clinical testing and analysis of OO-EMG. Onset of IEC after STN-DBS [months] describes the time point of the first documented onset of IEC after STN-DBS. Root mean square of OO-EMG after bandpass-filtering in [μ v]. Abbreviations: nt = not tested; StraightOFF = straight forward gaze with stimulator off; StraightON = straight forward gaze with stimulator on

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Competing interests

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