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Effects of low-frequency thalamic deep brain stimulation in essential tremor patients

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ABSTRACT

Background: Essential tremor (ET) patients may present with postural and/or intentional tremor. But despite high-frequency thalamic deep brain stimulation (DBS) effectively suppressing both, the emergence of intentional tremor has been attributed to a higher extent to cerebellar dysfunction. Therefore, we hypothesized thalamic 10 Hz-stimulation, which is known to worsen motor functions, having more impact on intentional tremor than on postural tremor.

Methods: In sixteen ET-patients with bilateral thalamic-DBS, tremor rating scale (TRS) and ultrasound-based tremor-amplitude measurements were analyzed by sequentially applying three DBS-settings in a randomized order: i) low-frequency stimulation (LFS), ii) DBS being turned off (DBS-OFF) and iii) high-frequency stimulation (HFS). Repeated measures analyses of variance for TRS and for the quotients of tremor-amplitudes during DBS-OFF and LFS for intentional (q_{int}) and postural tasks (q_{post}) were calculated. Finally, electrode localization and the abovementioned quotients were put into relation by Pearson's correlation coefficient.

Results: HFS reduced TRS significantly compared to DBS-OFF and LFS (ps < .001), while the latter two also differed significantly with TRS being the worst during LFS ($p < .05$). Additionally, intentional tremor-amplitude appeared to be strongly influenced by LFS than postural tremor-amplitude ($p < .05$). Furthermore, a lower placement of the electrodes caused worse intentional tremor-amplitude during LFS ($r = .517$, $p > .05$), while postural tremor-amplitude was unrelated to electrode localization (ps < .05).

Conclusions: During LFS in ET-patients, there is a more severe exacerbation of intentional tremor compared to postural tremor. Possibly, there are two different mechanisms responsible for both tremor entities, making more refined stimulation regimes feasible in the future.

Introduction

Essential tremor is a common disease, typically expressing as postural tremor of the upper limbs. Nevertheless, some patients additionally suffer from intentional tremor which is often the predominant source of disability (Liu et al., 1997; Tranchant et al., 1995). Patients with intentional tremor resemble those suffering from cerebellar dysfunction. Therefore, underlying pathomechanisms in intentional tremor have been suspected in the alterations of cerebello-thalamic connections (Britton et al., 1994; Deuschl et al., 2000; Koster et al., 2002).

The cerebellar role in ET is further emphasized by clinical observations such as the impairment of the blink-reflex (Kronenbuerger et al., 2007), ataxia during tandem gait (Stolze et al., 2001) and cognitive and affective deficits (Bermejo-Pareja, 2011; Gasparini et al., 2001; Lombardi et al., 2001; Tröster et al., 2002) resembling those in the 'cerebellar cognitive affective syndrome' as introduced by Schmahmann and colleagues (Schmahmann and Sherman, 1998). Otherwise, cerebellar irregularities in ET-patients undergoing autopsy (Louis et al., 2007) could not be consistently proven (Rajput et al., 2010).

This lack of concept for the pathomechanisms of ET has contributed to only sparse therapy options (Deuschl et al., 2011); yet, medically refractory cases might be treated by high-frequency thalamic-DBS (Deuschl et al., 2011; Dick, 2003). For this purpose, electrodes are placed into the ventrolateral thalamus (classically the *pars posterior* of the *nucleus ventralis lateralis*, VLp). The mechanisms of action of DBS are likewise unclear and might imply the alteration of cortical activity by blockade of thalamic projections (McIntyre et al., 2004) or the prevention of thalamic tremor propagation (Anderson et al., 2006). However, thalamic stimulation in ET has recently been challenged by electrode placement in the posterior subthalamic area (PSA). This brain region is supposed to account for a significant

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proportion of cerebellothalamic connections (Blomstedt et al., 2009; Herzog et al., 2007). Thus, the modification of this pathway appears to substantially influence tremor-therapy. Nevertheless, interactions between other brain areas are also responsible for some forms of tremor such as in Parkinson's disease (PD). In this context, it has been speculated that the basal ganglia serve as a trigger producing tremor, while again cerebellothalamo-cortical pathways rather account for the tremor-amplitude (Helmich et al., 2012). Hence, it is conceivable that tremor-amplitude in ET might be modified as well by interference in this pathway. Accordingly, thalamic-LFS has proven to worsen tremor in different diseases such as spinocerebellar ataxia (Barnikol et al., 2008) or ET (Kuncel et al., 2007) and it appears as if 10 Hz-stimulation induces synchronized activity in many brain areas (Florin et al., 2008). Taken together, different tremor manifestations might reflect affection in closely related but yet different neuronal sub-systems (Deuschl et al., 2000).

Ultimately, clinical experience emphasizes the notion of distinct origins of different tremor-manifestations. Thus, effective HFS for postural tremor is not always accompanied by the same efficiency for intentional tremor, and vice versa. Besides, patients with cerebellar dysfunction may suffer from intentional tremor without substantial postural tremor or patients with PD at times present with postural tremor but no obvious cerebellar dysfunction. It is therefore imaginable that intentional tremor has a stronger affiliation with cerebellothalamic pathways. We therefore hypothesized that i) intentional tremor is more likely to be affected by LFS and ii) stimulation in the cerebellothalamic pathways modulates intentional tremor to a higher degree compared to postural tremor. Accordingly, we investigated 16 ET-patients by clinical evaluation and ultrasound kinematic tremor-analysis under different stimulation conditions and put this into relation with electrode localization.

Methods and materials

Subjects

Sixteen ET-patients (5 females and 11 males, average disease duration: 25.5 ± 13.3 years) participated in this study after providing informed consent. All patients were treated at our center with bilateral thalamic-DBS or DBS in areas directly below (average time since electrode implantation: 4.2 ± 3.1 years) due to medically refractory ET, according to the diagnostic criteria (Deuschl et al., 1998).

The subjects were recruited from consecutive routine visits at the University Hospital of Cologne. Inclusion criteria were an age between 18 and 80 years and the absence of relevant depression and anxiety as well as neurological comorbidities. The study was approved by the local ethics committee (study no. 11-336) and carried out in accordance with the Declaration of Helsinki. All patients gave their written informed consent prior to participating and the study was registered in the German Clinical Trials Register (Main ID: DRKS00004210).

Table 1 shows participants' mean demographic and disease characteristics; additionally, in the supplemental data Table 4 illustrates patients' individual clinical data.

Clinical evaluation

First, HFS-parameters were optimized if requested by patients. In the second step, stimulation was changed in randomized order between i) LFS with 10 Hz, ii) HFS with 120–150 Hz and iii) DBS-OFF. For HFS and LFS, only the stimulation frequency differed, i.e. DBS was kept constant with respect to pulse width, voltage and active contacts. A computer-generated block randomization schedule was used to sequentially assign the subjects to different stimulation sequences. This alternating testing sequence aimed at avoiding potential systematic carryover effects of stimulation and the assignment to the different groups was performed before the subjects were enrolled. The randomization list was kept by an investigator not evaluating motor functions (M.A.) and patients and raters were blinded for applied stimulation-frequency.

Ten minutes following stimulation changes, motor function was videotaped. After the completion of all tests, tremor severity was analyzed under double-blinded conditions by two experienced raters (D.P. and C.E.) using the Fahn–Tolosa–Marin tremor rating scale (TRS) (Fahn et al., 1993). An interrater-reliability analysis applying the weighted Kappa statistic was performed to determine consistency among raters.

Table 1
Patients' demographic and general stimulation data (individual data in supplemental data).

Demographic and stimulation data		Mean ± SD
Demographic measures		
	Number of included patients	16
	Gender (♀:♂)	5:11
	Age (years)	62.29 ± 14.29
	Disease duration (years)	25.51 ± 13.30
	Duration DBS (years)	4.2 ± 3.1
Active electrode location		
	x-coordinates[a] (mm lateral to AC-PC-line)	12.2 ± 1.3
	y-coordinates (mm behind the middle of AC)	17.5 ± 1.3
	z-coordinates (mm above AC-PC-line)	0.9 ± 1.8
Stimulation parameters		
	Amplitude (volt)	2.47 ± 1.11
	Pulse width (microseconds)	76.88 ± 23.80
	Frequency (hertz)	128.13 ± 8.54

[a] Contacts located on the left hemisphere are negative per definition. For this study, all contacts were converted to positive values for a better visualization.

Electrode localization

Each active contact used for stimulation was calculated in postoperative high-resolution computed tomography scans and/or intraoperative stereotactic skull X-ray radiographies (anterioposterior and lateral). Subsequently, we re-imported these images into the planning software (STP and STVX, Stryker Corp, Duisburg, Germany) for superimposition on preoperative MRI, eventually resulting in stereotactic coordinates. These coordinates were transformed with reference to the length of the intercommissural line (ICL) and hemispheral width, thus yielding standard brain measurements. For better visualization, all 25 standard brain coordinates of active electrodes were plotted on coronal slices[5] of the Atlas of the HUMAN BRAIN™ (Mai et al., 2008) in Fig. 2.

Finally, if patients had more than one active contact, the average of the coordinates of active electrodes was computed for further analysis. General data of mean electrode coordinates and stimulation settings can be found in Table 1 and in the supplemental data in Table 4.

Ultrasound kinematic tremor-analysis

The differential effects of distinct DBS-settings on postural and intentional tremor were further measured by a 3D-ultrasound kinematic analysis tool (CMS 20S, Zebris medical GmbH, Isny, Germany). The recording procedure was similar to previously published studies of our group (Barbe et al., 2011). Briefly, patients were comfortably seated in front of a table with their backs supported. The shoulder was in a neutral position and the elbow flexed at 90°. Ultrasound markers were placed at the tip and the base of the index finger and the wrist of the more severely affected hand (see Fig. 1A). The two used paradigms consisted of i) lifting the arm from the table and

[5] Note, that coronal slices of the Atlas of the HUMAN BRAIN™ are not entirely available in 1 mm sections, making the rounding of y-coordinate values necessary in some cases.