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Deep brain stimulation of the ventral intermediate nucleus in patients with essential tremor: Stimulation below intercommissural line is more efficient but equally effective as stimulation above

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ABSTRACT

Background: The posterior subthalamic area (PSA), ventral to the intercommissural line (ICL) and the ventral intermediate nucleus (VIM), has been suggested as a promising target for deep brain stimulation (DBS) in patients suffering from essential tremor (ET). In this study the clinical benefit of VIM and PSA DBS on postural tremor suppression was systematically evaluated in a two step approach with a 3D ultrasound kinematic analysis tool.

Methods: We defined the exact position of 40 VIM-DBS-electrodes from 21 ET patients. In a first experiment with a subgroup of electrodes we subsequently activated a thalamic and a contact below ICL (sub-ICL) with equal parameter settings for within subject comparison. In a second step, we divided all electrodes into two groups, i.e. one group with activated thalamic and the other group with activated contacts below ICL and performed a group comparison under patients' individual stimulation parameters. Here, the corrected amplitude required for tremor suppression was analyzed separately for both groups.

Results: Within subject comparison with equal parameter settings revealed a significant improvement of sub-ICL compared to thalamic stimulation. In contrast, group comparison under patients' individual stimulation did not show any significant difference in tremor suppression between VIM and PSA DBS. Although higher corrected stimulation amplitude was needed in the thalamic group this difference was not significant.

Conclusion: The data suggest that sub-ICL stimulation may be more *efficient* compared to thalamic stimulation but equally *effective* when patients' individual stimulation parameters are used.

Introduction

The ventral intermediate nucleus (VIM) of the thalamus is the classic target for deep brain stimulation (DBS) in patients suffering from essential tremor (ET). The stereotactic coordinates of the VIM in a standard brain are defined as 12 mm lateral, 5 mm posterior, and 0 mm below the midcommissural point (MCP). (Papavassiliou, et al., 2004) The tremor suppressing effect (Benabid, et al., 1996; Limousin, et al., 1999) and safety (Flora et al., 2010) of DBS in this brain region have been confirmed in a variety of studies.

However, in the last years, several case studies and articles supported the idea that the area ventral to the VIM, the so-called posterior subthalamic area (PSA), might constitute a promising target for treatment of posttraumatic (Andy, 1983; Hooper, et al., 2001), MS (Nandi and Aziz, 2004; Brice and McLellan, 1980), dystonic (Kitagawa, et al., 2000), Parkinsonian (Velasco, et al., 2001) and essential tremor. (Kitagawa, et al., 2000; Plaha, et al., 2004; Blomstedt, et al., 2010) The PSA is composed of the zona incerta (ZI) and the radiatio prelemniscalis (RaPrl) containing dentato-thalamic fiber bundles (see Blomstedt, et al., 2009 for review). Initially, as for the VIM (Schuurman, et al., 2000), lesional surgery was performed in this

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brain region with good results (Krauss, et al., 1994; Mundinger, 1965), but was dropped after the introduction of DBS.

Herzog and co-workers were able to demonstrate that stimulation in tremor patients below the ventral border of the VIM is more efficient compared to stimulation in the VIM itself. (Herzog, et al., 2007) Consistent with this observation, at our center we often observed better clinical tremor suppression intraoperatively during test-stimulation below the standard VIM coordinates. If side effects were mild and tolerable, the electrode could therefore be implanted below the intercommissural line (sub-ICL) in some cases.

Although the concept of potentially advantageous effects of sub-ICL stimulation for ET has been discussed and explored in the field, to date no study has demonstrated that patients with electrodes implanted below ICL in fact benefit further from a more ventral stimulation when patients' individual stimulation parameters are used. In this retrospective study, we therefore systematically analyzed whether sub-ICL stimulation results in a better clinical outcome of postural tremor suppression, measured with a 3D ultrasound kinematic analysis tool. We have located the exact position of 40 electrodes from 21 ET patients treated with DBS and followed a two step approach. In a first step, if an electrode position revealed both, a thalamic and a sub-ICL contact, we subsequently stimulated on both contacts with equal stimulation parameters in a randomized fashion. The aim of this first experiment was to test whether postural tremor suppression at the sub-ICL contact is more *efficient* (i.e. postural tremor suppressing effect dependent on the amount of stimulation amplitude) consistent with the results reported by Herzog, et al. (2007).

In a second step, we divided the electrodes into two groups according to their location, i.e. one group with the most ventral activated contact located below and another group with the most ventral contact located above ICL. Here the effect on postural tremor suppression was assessed under individual stimulation parameters. The aim of this second experiment was to test if postural tremor suppression is more *effective* in the sub-ICL group (i.e. postural tremor suppressing effect independent of the amount of amplitude). In our opinion, the combination of these two experiments in the same cohort of ET patients could make a contribution to the current debate on the optimal anatomical target for DBS in ET patients.

Since PSA and VIM are located in close vicinity, stimulation with high amplitudes in the VIM could either spread to the PSA or affect a higher portion of the VIM thereby eliminating a possible difference between the two groups in the second experiment. Therefore, our third hypothesis was that if there was no significant difference between the two groups under individual stimulation parameters, a higher amount of current might be needed in the thalamic group to achieve a similar tremor suppressing effect.

Materials and methods

Subjects

For this study we systematically contacted all ET patients who had been implanted at our center between 1998 and 2009. Twenty-one ET patients with 40 DBS electrodes implanted in the VIM were included into the study (19 bilateral and 2 unilateral). The testing was performed postoperatively at least 3 months after electrode implantation to avoid any significant microlesional effects. Thalamotomy prior to DBS was an exclusion criterion. Each contact on every electrode was tested from 0–5 V in 1 V increments for effects and side effects. The contact with the best clinical effect (i.e. tremor reduction) and lowest side effect (e.g. dysarthria and ataxia) was activated and stimulation parameters were optimized on the following 2 days as reported before (Barbe, et al., 2010). At the time of testing and stimulation parameter optimization the physician in charge (M.T.B.) was blinded for the exact position of the electrode-contacts (i.e. above or below ICL).

Localization of the electrode-contacts

The exact stereotactic coordinates of the center of each contact were obtained from intraoperative stereotactic skull X-rays (anterior-posterior and lateral) and/or postoperative high resolution CCT scans for each single patient. We imported the images into the planning softwares (STP and STVX, Leibinger-Stryker, Freiburg, Germany) for superposition on preoperative MRI yielding stereotactic coordinates. (Sauner, et al., 2010) These coordinates were transformed with reference to the length of the ICL and hemispheral width, thus attaining standard brain measurements (according to the Brain Atlas of Schaltenbrand and Wahren (Nowinski and Belov, 2003)). For visualization, standard brain coordinates were plotted on coronal sections of the Brain Atlas of Schaltenbrand and Wahren. Note that the coronal slices of the Brain Atlas of Schaltenbrand and Wahren are not entirely available in 1 mm sections so that the values of the y-coordinates had to be rounded in some cases.

Tremor-analysis

To characterize the effect of DBS on postural tremor we used a 3D ultrasound kinematic analysis tool (CMS 20S, Zebris, Isny, Germany). This system localizes ultrasound markers within a 1-mm spatial and high temporal resolution (sampling rate 66 Hz with three markers) by evaluation of transmission time and triangulation of marker position. Similar to accelerometer measures, this system helps to objectively determine tremor amplitude and frequency. For the analysis, patients were comfortably seated in front of a table. Three ultrasound markers were placed at the tip of the index finger, the thumb, and the wrist contralateral to the electrode tested. As a measure for tremor severity the total travel-distance of each marker was analyzed with 3DAWin analysis software Version 1.20 (MedCom Software). Total travel-distance accommodates frequency and amplitude shifts and was therefore chosen as a consistent parameter reflecting the effect of DBS on postural tremor. Patients were asked to lift their arm from the table and hold it in a stretched position, with fingers stretched and the wrist slightly bended. Instructions were given with the help of a video clip in order to keep them standardized for each patient. All patients had a training session before the measurement was started. There were resting intervals between each measurement. Data was recorded 10 times for 12 s each in every condition. Ten seconds from the middle of each trial were analyzed. The mean of the travel-distance of the marker from the index finger of the 10 trials was used for further analysis. For the overall tremor suppressing effect, we compared tremor suppression with active stimulation under optimized settings versus tremor during the no-stimulation paradigm. We divided the average “on-travel-distance” by the average “off-travel-distance” to yield a ratio reflecting the amount of tremor suppression for each electrode-contact. Patients were randomized for ‘stimulation-on’ and ‘stimulation-off’ mode as well as for right and left body side. Stimulation-off and stimulation-on were defined as a measurement at least 1 h after stimulation was turned off or on respectively.

For the within-subject comparison between thalamic and sub-ICL stimulation we subsequently activated contacts positioned above and below ICL (21 electrodes from 13 patients, i.e. 21 contacts above and 21 contacts below ICL) and stimulated with equal stimulation settings (3 V, 60 μsec and 130 Hz). If side effects occurred through one of the activated contacts the amplitude was reduced on both contacts in 0.5 V— increments by the physician until the side effects resolved. For the sake of comparison (*efficiency*, i.e. postural tremor suppressing effect dependent on the amount of amplitude), the same amplitude was used for each contact (thalamic or sub-ICL) within the same electrode to keep the effect comparable. In this sub-experiment the ultimate goal was therefore not the maximal therapeutic effect but rather the controlled comparison between the two areas of stimulation. The off-, on-thalamic-, and on-sub-ICL paradigm was tested in a