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Optical Measurements during Asleep Deep Brain Stimulation Surgery along Vim-Zi Trajectories

Peter Zsigmond[a] Karin Wårdell[b]

[a]Departments of Neurosurgery and Clinical and Experimental Medicine, Linköping University, Linköping, Sweden;
[b]Department of Biomedical Engineering, Linköping University, Linköping, Sweden

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Deep brain stimulation · Laser Doppler flowmetry · Microcirculation · Intraoperative recordings · Essential tremor · Posterior subthalamic area · Anesthesia

Abstract
Background: Optics can be used for guidance in deep brain stimulation (DBS) surgery. The aim was to use laser Doppler flowmetry (LDF) to investigate the intraoperative optical trajectory along the ventral intermediate nucleus (VIM) and zona incerta (Zi) regions in patients with essential tremor during asleep DBS surgery, and whether the Zi region could be identified. ***Methods:*** A forward-looking LDF guide was used for creation of the trajectory for the DBS lead, and the microcirculation and tissue greyness, i.e., total light intensity (TLI) was measured along 13 trajectories. TLI trajectories and the number of high-perfusion spots were investigated at 0.5-mm resolution in the last 25 mm from the targets. ***Results:*** All implantations were done without complications and with significant improvement of tremor ($p < 0.01$). Out of 798 measurements, 12 tissue spots showed high blood flow. The blood flow was significantly higher in VIM than in Zi ($p < 0.001$). The normalized mean TLI curve showed a significant ($p < 0.001$) lower TLI in the VIM region than in the Zi region. ***Conclusion:*** Zi DBS performed asleep appears to be safe and effective. LDF monitoring provides direct in vivo measurement of the microvascular blood flow in front of the probe, which can help reduce the risk of hemorrhage. LDF can differentiate between the grey substance in the thalamus and the transmission border entering the posterior subthalamic area where the tissue consists of more white matter tracts.

Introduction

Essential tremor (ET) is the most common tremor disorder, and is likely to be complex with multiple genes involved in combination with environmental factors [1]. Deep brain stimulation (DBS) alleviates tremor. After the introduction of DBS in the ventral intermediate nucleus (VIM) of the thalamus by Benabid et al. [2] in 1987, the VIM has become the most selected target worldwide for DBS surgical treatment of tremor. In recent years, the posterior subthalamic area (PSA) has become more popular as a target in ET. The PSA, including the zona in-

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karger@karger.com
www.karger.com/sfn

Peter Zsigmond
Department of Neurosurgery
Linköping University Hospital
SE–581 85 Linköping (Sweden)
peter.zsigmond@regionostergotland.se

Table 1. Patients' data and assessment of ETRS score before surgery and 3 months postoperatively

Patient No.	Unilateral/ bilateral	ETRS before surgery	ETRS after surgery	Improvement
1	unilateral	18	4	14
2	unilateral	21	5	16
3	unilateral	14	0	14
4	bilateral	30	8	22
5	unilateral	16	2	14
6	bilateral	16	4	12
7	unilateral	21	7	14
8	unilateral	14	3	11
9	unilateral	22	2	20
10	bilateral	20	1	19

ET was evaluated on the contralateral side. ETRS, Essential Tremor Rating Scale.

certa (Zi) and the prelemniscal radiation (Raprl), was introduced as a target for ET. In 1965, Mundinger [3] reported good results by making lesions in the subthalamic region for the control of ET. DBS of the PSA aims to target the dentatorubrothalamic tract where the fibers are confined to a small volume before fanning out in the VIM [4–6]. Advancing a somewhat medially placed VIM electrode below the AC-PC line usually results in the Zi in the PSA being reached [7].

Traditionally, DBS procedures are performed awake, thereby allowing for feedback from the patient regarding the clinical effect of the inserted electrodes. Microelectrode recording (MER) is frequently used in awake DBS to verify that the location within the target structure is optimal. The use of MER can be associated with longer theater times and may increase the risk of hemorrhagic complications [8]. Another consideration with DBS is the fear of being awake during surgery, which is a deterrent for many candidates although most patients do well. In recent years, there has been a trend among neurosurgeons toward utilizing general anesthesia during DBS implantation, and studies have not shown any disadvantages with asleep DBS surgery [9]. At the Department of Neurosurgery in Linköping, general anesthesia without MER recording has been the routine since 2010 during DBS implantation in the subthalamic nucleus (STN) and Zi. In patients with ET, we only target the Zi, enabling us to rely on direct anatomical targeting. Since the patients are asleep, we cannot monitor them clinically and so intraoperative methods that also function under these circumstances would be preferable.

It is known that optical techniques, based on diffuse reflectance spectroscopy [10, 11] and laser Doppler flowmetry (LDF) [12], can be used to intraoperatively distinguish grey-white matter tissue with a high degree of precision along the intraoperative DBS trajectories. LDF has the added advantage to combine the grey-white matter tissue-mapping with microvascular blood flow measurements. In the stereotactic surgical setting, this is done with a forward-looking probe which also acts as a guide for the DBS lead to be implanted. The method has been evaluated in more than 130 DBS implantations towards different DBS targets [13], and typical curves ("barcodes") from the cortex toward the VIM and the STN have been statistically defined [14, 15], and the safety aspects reviewed [13]. In this study, the aim was to investigate the intraoperative optical trajectory along the VIM and Zi in the PSA region during asleep DBS surgery, and to investigate if the Zi region can be identified. An additional aim was to study the microvascular blood flow along the same trajectory. A successful outcome will help surgeons to identify preplanned targets, also in anesthetized patients, and alert them to potential vessel structures in the vicinity of the probe tip.

Material and Methods

Patients

Ten right-handed patients (6 females and 4 males) aged between 41 and 74 years (mean ± SD: 64 ± 11 years) with ET were included in the study (Table 1). They were referred for unilateral ($n = 7$) or bilateral ($n = 3$) DBS implantation in the Zi at the Department of Neurosurgery at Linköping University Hospital, Linköping, Sweden. All patients were evaluated on the contralateral treated extremity with the Essential Tremor Rating Scale (ETRS) score before and 3 months after surgery. ETRS item 5 in part A and items 10–14 in part B were evaluated (maximum score = 32 points). Only the active contact (ON) was evaluated postoperatively.

Imaging and Surgery

Following positioning of the Leksell stereotactic system® (LSS, Model G, Elekta Instrument AB, Sweden) to the skull, MRI with gadolinium contrast was done for direct anatomical targeting using a 3-T scanner (Gd-T1 and T2, voxel size [0.49 × 0.49 × 2.0] mm^3, TE = 80 ms, TR = 8,000 ms, Ingenia, Philips Healthcare, The Netherlands). Using these settings, the STN and red nucleus were hypointense (Fig. 1a). Planning of the trajectories was performed in Leksell® SurgiPlan (Elekta Instrument AB). The target was identified on transaxial T2-weighted images slightly posterior-medial to the STN at the level of the maximal diameter of the red nucleus as described by Blomstedt et al. [16]. The trajectories chosen passed along the medial parts of the VIM and then entered the Zi in the PSA region (Fig. 1b). The transition zone between the base of the VIM and the PSA was the AC-PC line. After skull trep-

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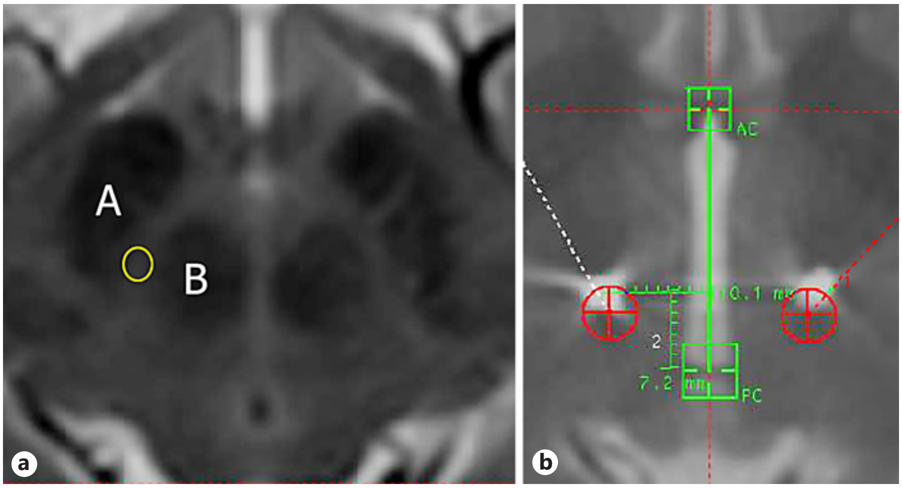

Fig. 1. **a** The Zi target area is shown by a yellow circle. The PSA including the Zi starts at the bottom of the VIM nucleus at the AC-PC plane. The Zi target area where we intend to place the most distal contact is around 4 mm below the AC-PC line. A, STN; B, red nucleus. **b** Postoperative CT/MRI fusion of a 41-year-old female with bilateral severe tremor, implanted with Medtronic leads 3389 in the Zi-PSA region. Contacts 0 and 1 are below the AC-PC line. The electrode on the right side on the AC-PC plane is situated in the medial parts of the VIM nucleus, approximately 10 mm lateral of the midline and 7 mm anterior to the posterior commissure.

anation, a trajectory was created with the optical probe which replaced the conventional guide. Details of the optical measuring sequence is presented in the next section. The DBS lead (3389, Medtronic Inc., USA) was implanted and the position verified with intraoperative fluoroscopic guidance (Philips BV Pulsera, Philips Medical Systems, The Netherlands). The patients underwent the procedure as 1 stage under general anesthesia. The total time including positioning of the LSS, MRI, planning, optical measurement, and DBS implantation was around 4–5 h. After a change of draping, the impulse generator was implanted. A postoperative CT scan (slice thickness 1 mm, GE Lightspeed Ultra, GE Healthcare, UK) was performed within 24 h of implantation. It was used to evaluate the lead position and exclude hemorrhage. More information about the surgical procedure can be found in Zsigmond et al. [13].

Intraoperative Optical Measurements

LDF (PF 5000, Perimed AB Sweden) was used for taking intraoperative optical measurements [17–19]. LDF uses a 780-nm laser with an output power of 1 mW to illuminate the tissue through an optical fiber incorporated along the forward-looking measurement probe. A receiving fiber collects back-scattered light and processes it to a perfusion value (0–999 arbitrary units [AU]) and a total light intensity (TLI) (0–10 AU) representing the grey-white matter tissue values.

The perfusion and TLI signals were sampled, processed and visualized in real time in the operating room with software in LabVIEW (National Instruments, Inc., TX, USA). The optical probe was constructed to comply with the LSS and then inserted by the surgeon from the cortex towards the precalculated target with a hand-driven mechanical device. Before surgery, the perfusion and TLI levels were checked in Motility Standard (Perimed AB). Thereafter, the probe was cleaned and sterilized according to the STERRAD® protocol. A full description of the measurement system and probe can be found in Wårdell et al. [14].

During surgery, optical measurements were performed along the predefined trajectories ($n = 13$) at the following positions: cortex (–60 mm from the target), internal capsule (–40 mm from the target). Thereafter, measurements were done every 0.5 mm towards the predefined target (0 mm), starting at –25 mm for the first 5 trajectories, and –30 mm for the remaining 8. Recordings were also done up to +2 mm beyond the target along 11 of the trajectories. At each position, the LDF recording lasted long enough (approx. 10 s) to verify the blood flow (also called "perfusion") level. This was communicated between the engineer and the neurosurgeon for each measurement position. At a few sites, where pulsatile and higher perfusion was found, the recording was extended to 30 s to certify a stable perfusion level before proceeding to the next site. Recordings were done at 798 tissue positions.

Data Analysis

ETRS score was statistically evaluated by applying a single-sided Wilcoxon signed rank sum test. A significance level of $p < 0.05$ was used. During insertion of the optical probe, the hand-controlled mechanical device produced a movement artifact clearly visible in the perfusion signal. As shown previously [14], this artifact is used as a position reference for the data analysis. Between such artifacts, a time interval of approximately 5 s was used for the calculation of perfusion (mean ± SD, peak-to-peak) and TLI at each measurement position. The TLI values were normalized against the respective signal captured in the internal capsule region. The individual curves of perfusion and TLI were plotted, starting from –25 mm, towards the target region, and were related to the respective individual planned trajectory after coregistration in SurgiPlan of the preoperative MRI and postoperative CT. SurgiPlan was also used to find the AC-PC plane, i.e., the bottom of the VIM for all individual trajectories. After adjustment to the AC-PC line, from –6 to –4 mm, for 3 of the optical trajectories, a mean TLI curve ($n_{traj} = 12$) including values from –23 to 0 mm ($n_{sites} = 564$) was calculated. The following positions were marked in the respective optical curves: thalamus VIM, AC-PC plane, and Zi.

Average perfusion and TLI were calculated in the center of the VIM (–7 ± 1 mm) and Zi by including the target ±1 mm (0 ± 1 mm) per recording when available. Tissue sites with increased perfusion (>100 AU) were searched for according to the previous definition [13, 14] where perfusion is presented in the range of 101–250 AU at the A level, 251–500 AU at the B level, and >500 AU at the C level. The double-sided Wilcoxon signed rank sum test was used to compare TLI and perfusion in the VIM and STN. $p < 0.05$ was considered significant.

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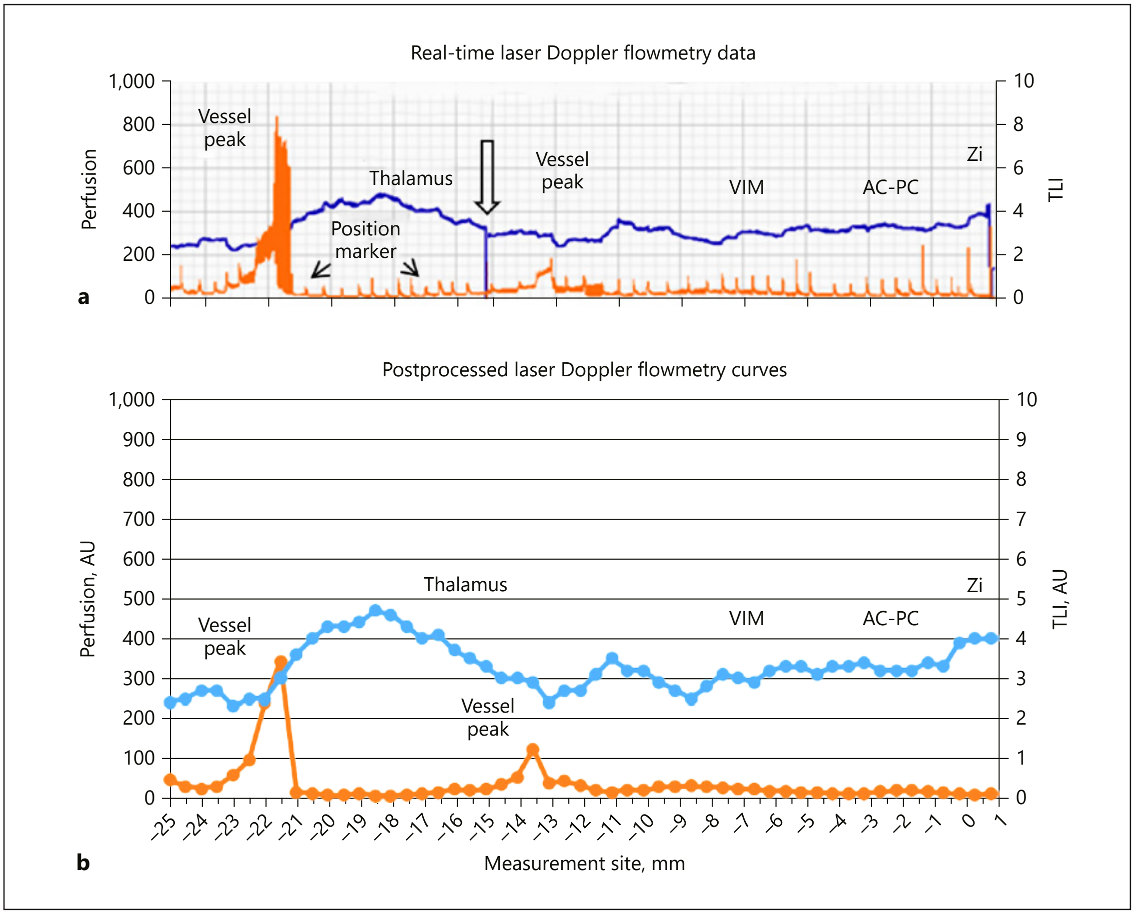

Fig. 2. a Data as presented in real-time in the operating room. Microvascular perfusion (orange) and tissue greyness, i.e., total light intensity (TLI, blue). Pulsative blood flow with a large peak-to-peak is visible at 21.5 mm from the target (Zi). The large arrow marks a section removed due to a short disconnection of the LDF system. This part was not included in the analysis and presentation in **b** which shows the postoperative processed curves of the perfusion and TLI values. Each plot corresponds to an average of the recordings (of 5–10 s) between the position markers shown in **a**.

Results

All implantations were done without complications. The postoperative CT verified that there were no hemorrhages, and that the 2 distal leads were positioned in the PSA and the 2 proximal leads in the lower medial part of the VIM nucleus (approx. 10–12 mm from the midline). Contacts below the AC-PC line were considered to be in the PSA including the Zi. The average postoperative deviation of the electrodes was 0.7 mm medially and no deviation occurred in the anterior-posterior direction. One of the 2 distal contacts in the Zi region was used for the final monopolar programing. The average current was 1.4 V after 3 months of stimulation. Tremor measured on the ETRS was significantly reduced in all patients ($p < 0.01$; Table 1), with an average of 192 preoperatively and 35 postoperatively.

In general, the microcirculation was very low (<100 AU), with an average of 26.8 ± 24.0 AU ($n = 798$). The mean perfusion in the VIM and Zi was 31.5 ± 23.7 ($n = 60$) and 17.7 ± 5.3 ($n = 57$) AU, respectively. This difference was significant ($p < 0.001$). Out of the 798 measurement sites, 12 high blood flow spots (1.5 %) were detected. Seven of the high blood flow spots were in the VIM region and none in the PSA/Zi region. Ten of the spots were within the A range and 2 in the B range when considering the average calculated perfusion, and 1 was a C peak when studying the peak-to-peak (814 AU, at the most). This measurement example of the microcirculation (perfusion) and the TLI, as displayed in the OR, is presented

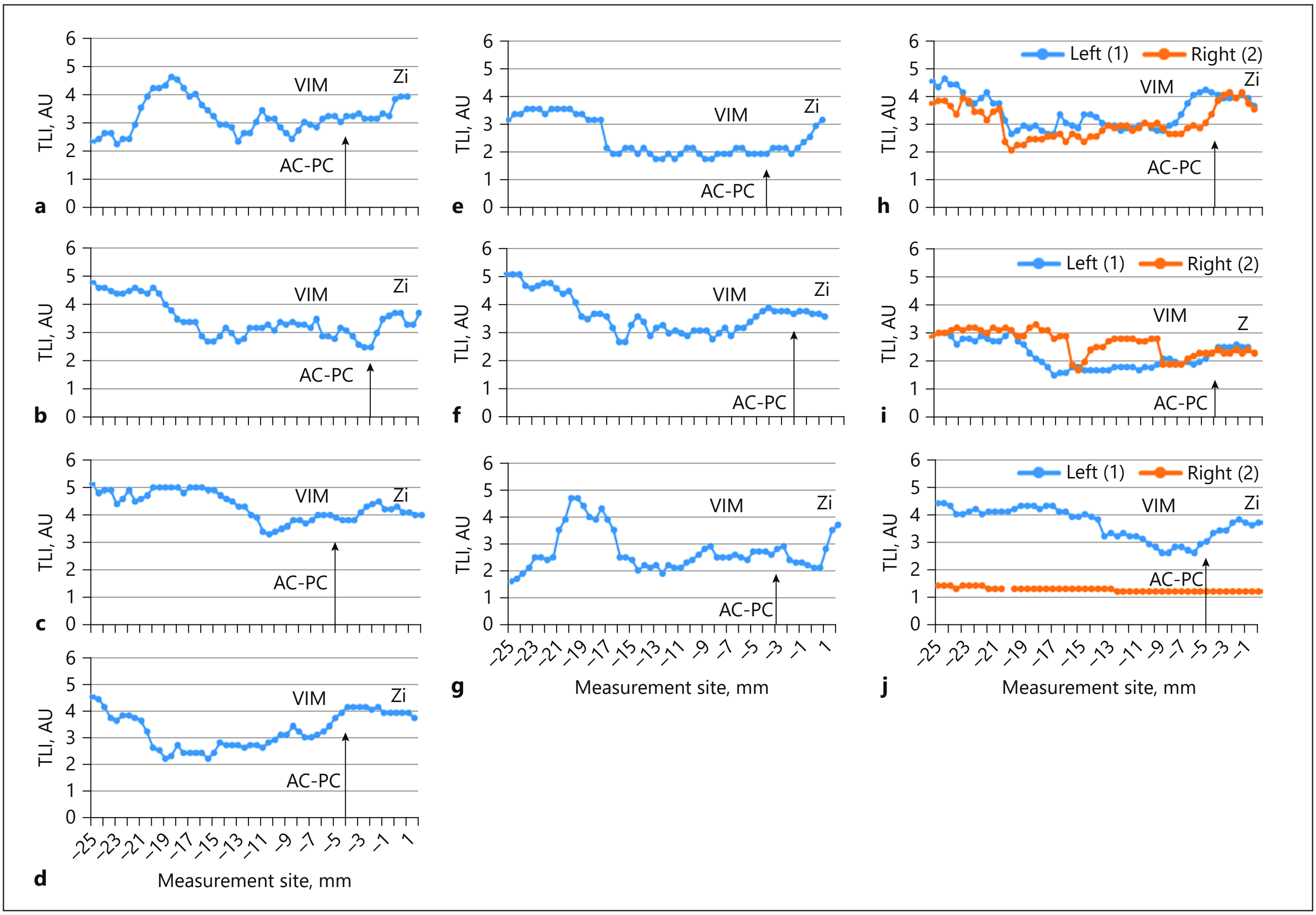

Fig. 3. Individual total light intensity (TLI) curves representing tissue greyness changes when passing from the thalamus through the VIM and towards the Zi. Unilateral (**a–g**) and bilateral (**h–j**) optical measurements during DBS implantations. The respective AC-PC planes, i.e., the lower part of VIM, are marked with an arrow. **h** The second implantation curve has a very similar shape to the first, but with a small shift.

in Figure 2a. The high-flow C peak is visible at –22.0 to –21.5 mm from the Zi target. A small A peak is also visible –13.5 mm from the Zi, i.e., in the VIM region. In the case of high-flow peaks preoperatively, the downward movement of the optical probe was paused for a few seconds until the perfusion normalized. The corresponding postoperatively processed curves representing the average perfusion and TLI are displayed in Figure 2b. Individual TLI curves are presented in Figure 3, with the respective AC-PC plane marked. When entering the Zi region, there was a small increase in the TLI. This indicates a slightly greater content of white matter compared to the in the VIM/thalamus. The normalized mean TLI curve ($n = 12$), after adjustment to the AC-PC line, is presented in Figure 4. In this curve, the outlier seen in Figure 3j was excluded. The average normalized TLI for VIM and Zi was 0.60 ± 0.11 and 0.72 ± 0.15, respectively. This difference was significant ($p < 0.001$). It should be pointed out that the optical trajectories only present about a third of the total path when starting in the cortex, and that the steps between the measurement sites were 0.5 mm, i.e., the real length of each optical trajectory was around 25 mm.

Discussion

In this study, we extended the optical measurement portfolio, previously used for the STN and VIM [12–15], to a detailed analysis of the trajectory towards the Zi. In order to give the postoperative programming more pos-

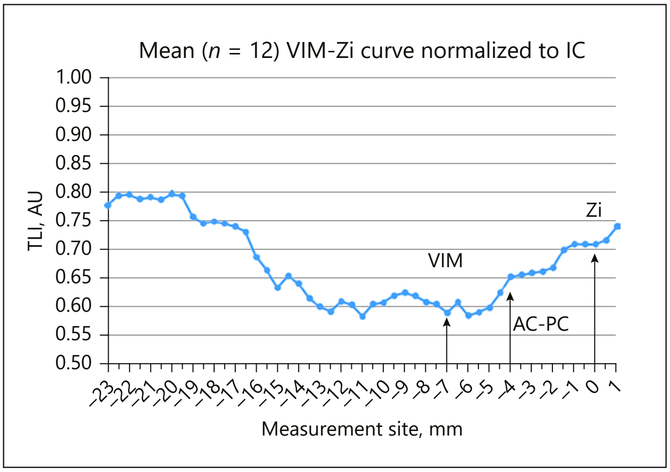

Fig. 4. Mean curve from 12 individual TLI trajectories after adjustment to the AC-PC line. IC, internal capsule.

sibilities, the trajectories were planned along the medial VIM nucleus towards the Zi. Zi as a target of DBS for ET patients with medically refractory tremor performed asleep without MER appears to be safe and effective. The surgical procedure aims to increase quality of life and at the same time reduce possible surgical complications associated with the procedure, such as deviation of the electrode and intracerebral hemorrhage. Since there is no established possibility of patient hemorrhage assessment perioperatively, there is a need for in vivo monitoring tools. With LDF monitoring, we were able to take in vivo measurements of the microvascular blood circulation in front of the probe, thereby reducing the risk of adverse events like hemorrhage. LDF can also differentiate between the grey matter in the thalamus and the transmission border entering the PSA where the tissue consists of more white matter tracts (Fig. 4). It is not time-consuming; the required time for a unilateral measurement is approximately 7 min, and during this time the burr hole is sealed with fibrogen glue. We experienced a reduced incidence of intracranial air during electrode implantation compared to in awake surgery as described by Ko et al. [20].

Despite the effort to reduce CSF loss with tissue glue-sealing, head elevation and the short operation time, there appeared to be a small brain shift when 2 leads were implanted in 1 of the patients (Fig. 3h). Similar deviations were found by Giller et al. [10], when processing spectroscopic data captured in relation to DBS surgery. In all TLI curves (Fig. 3), a small increase is found, i.e., the tissue is slightly whiter when the probe reaches the PSA. When averaging all normalized TLI curves and adjusting them to the respective AC-PC, this increase is more obvious (Fig. 4). This is in agreement with intraoperative reflectance spectrometric measurements previously done by us [11]. The advantage with the current method is that measurements can be done with a 0.5-mm precision and thus data be linked to the stereotactic MRI. An additional advantage is the dual function of the LDF system, which also includes the microvascular blood flow and can thus act as a “vessel alarm” [13]. In this investigation, all high-perfusion spots appeared above the VIM and in the VIM region. This is in agreement with previous investigations at our clinic where it was found that mainly the VIM trajectories showed increased blood flow, together with regions close to the ventricles and sulci. The findings also agree with the hemorrhage incidents reported in relation to MER [8, 21]. In this study, all surgeries were completed without incidents of hemorrhage. However, a total of 1.5% of the recorded sites had increased blood flow; one, 20 mm from the target, showed high pulsatile perfusion and this should be considered as a high-risk spot (Fig. 2). This percentage of high-risk tissue sites is lower than in our previous investigation. A main reason for this is that the measurements in the cortical region were excluded in the analysis.

Conclusion

From the Linköping perspective, LDF is a method that can support the surgeon in monitoring regions with increased blood flow and indicate “bar-codes”, i.e., grey-white tissue changes along the trajectory towards the target region. These measurements can be done with general anesthesia, which shortens the operation time and is preferable for the patient and the clinical outcome.

Statement of Ethics

The studies were approved by the local ethics committee at the University Hospital Linköping (No. M182–04, T54–09) and conducted in accordance with the World Medical Association Declaration of Helsinki. Informed written consent was received from the patients.

Disclosure Statement

K.W. has stocks in the spin-off company Fluolink AB and is the inventor of a patent owned by the company. There are no other potential conflicts of interest or company involvements. P.Z. has no conflicts of interest to declare.

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Author Contributions

Both authors planned and performed the study, analyzed the data, and wrote the paper.

References

1 Louis ED. Essential tremor then and now: how views of the most common tremor diathesis have changed over time. Parkinsonism Relat Disord. 2018 Jan;46 Suppl 1:S70–4.

2 Benabid AL, Pollak P, Louveau A, Henry S, de Rougemont J. Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. Appl Neurophysiol. 1987;50(1-6):344–6.

3 Mundinger F. Stereotaxic interventions on the zona incerta area for treatment of extrapyramidal motor disturbances and their results. Confin Neurol. 1965;26(3):222–30.

4 Coenen VA, Allert N, Paus S, Kronenbürger M, Urbach H, Mädler B. Modulation of the cerebello-thalamo-cortical network in thalamic deep brain stimulation for tremor: a diffusion tensor imaging study. Neurosurgery. 2014 Dec;75(6):657–69.

5 Nowacki A, Schlaier J, Debove I, Pollo C. Validation of diffusion tensor imaging tractography to visualize the dentatorubrothalamic tract for surgical planning. J Neurosurg. 2018 Mar;130(1):99–108.

6 Nordin T, Zsigmond P, Pujol S, Westin CF, Wårdell K. White matter tracing combined with electric field simulation - A patient-specific approach for deep brain stimulation. Neuroimage Clin. 2019;24:102026.

7 Blomstedt P, Sandvik U, Linder J, Fredricks A, Forsgren L, Hariz MI. Deep brain stimulation of the subthalamic nucleus versus the zona incerta in the treatment of essential tremor. Acta Neurochir (Wien). 2011 Dec;153(12):2329–35.

8 Gorgulho A, De Salles AA, Frighetto L, Behnke E. Incidence of hemorrhage associated with electrophysiological studies performed using macroelectrodes and microelectrodes in functional neurosurgery. J Neurosurg. 2005 May;102(5):888–96.

9 LaHue SC, Ostrem JL, Galifianakis NB, San Luciano M, Ziman N, Wang S, et al. Parkinson's disease patient preference and experience with various methods of DBS lead placement. Parkinsonism Relat Disord. 2017 Aug;41:25–30.

10 Giller CA, Liu H, German DC, Kashyap D, Dewey RB. A stereotactic near-infrared probe for localization during functional neurosurgical procedures: further experience. J Neurosurg. 2009 Feb;110(2):263–73.

11 Johansson JD, Blomstedt P, Haj-Hosseini N, Bergenheim AT, Eriksson O, Wårdell K. Combined diffuse light reflectance and electrical impedance measurements as a navigation aid in deep brain surgery. Stereotact Funct Neurosurg. 2009;87(2):105–13.

12 Wårdell K, Blomstedt P, Richter J, Antonsson J, Eriksson O, Zsigmond P, et al. Intracerebral microvascular measurements during deep brain stimulation implantation using laser Doppler perfusion monitoring. Stereotact Funct Neurosurg. 2007;85(6):279–86.

13 Zsigmond P, Hemm-Ode S, Wårdell K. Optical measurements during deep brain stimulation lead implantation: safety aspects. Stereotact Funct Neurosurg. 2017;95(6):392–9.

14 Wårdell K, Zsigmond P, Richter J, Hemm S. Relationship between laser Doppler signals and anatomy during deep brain stimulation electrode implantation toward the ventral intermediate nucleus and subthalamic nucleus. Neurosurgery. 2013;72(2 Suppl Operative): ons127–40.

15 Wårdell K, Hemm-Ode S, Rejmstad P, Zsigmond P. High-Resolution Laser Doppler Measurements of Microcirculation in the Deep Brain Structures: A Method for Potential Vessel Tracking. Stereotact Funct Neurosurg. 2016;94(1):1–9.

16 Blomstedt P, Sandvik U, Tisch S. Deep brain stimulation in the posterior subthalamic area in the treatment of essential tremor. Mov Disord. 2010 Jul;25(10):1350–6.

17 Nilsson GE, Tenland T, Öberg PA. Evaluation of a laser Doppler flowmeter for measurement of tissue blood flow. IEEE Trans Biomed Eng. 1980 Oct;27(10):597–604.

18 Wårdell K, Fors C, Antonsson J, Eriksson O. A laser Doppler system for intracerebral measurements during stereotactic neurosurgery. Conf Proc IEEE Eng Med Biol Soc. 2007;2007: 4083–6.

19 Strömberg T, Wårdell K, Larsson M, Salerud S. Laser Doppler monitoring and imaging techniques. In: Vo-Dinh T, editor. Biomedical Photonics Handbook, vol 1. Boca Raton: CRC Press; 2014. pp. 435–59.

20 Ko AL, Magown P, Ozpinar A, Hamzaoglu V, Burchiel KJ. Asleep Deep Brain Stimulation Reduces Incidence of Intracranial Air during Electrode Implantation. Stereotact Funct Neurosurg. 2018;96(2):83–90.

21 Zrinzo L, Foltynie T, Limousin P, Hariz MI. Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. J Neurosurg. 2012 Jan;116(1):84–94.

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