Identification of target areas for deep brain stimulation in human basal ganglia substructures based on median nerve sensory evoked potential criteria

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Objective: In the interventional treatment of movement disorders, the thalamic ventral intermediate nucleus (VIM) and the subthalamic nucleus (STN) are the most relevant electrode targets for deep brain stimulation (DBS). This study tested the value of somatosensory evoked potentials (SEP) for the functional identification of VIM and STN.

Methods: Median nerve SEP were recorded from the final stimulation electrodes targeted at STN and VIM. Throughout the stereotactic procedure SEP were recorded during short electrode stops above STN/VIM and within the presumed target areas. After digital filtering, high and low frequency SEP components were analysed separately to parameterise both the 1000 Hz SEP burst and low frequency (<100 Hz) components.

Results: SEP recorded in the VIM target region could unequivocally be distinguished from SEP recorded in STN. The 1000 Hz burst signal was significantly larger in VIM than in STN without any overlap of amplitude values. In the low frequency band, a primary high amplitude negativity was obtained in VIM, contrasting with a low amplitude positivity in STN. SEP waveshapes in recordings above target positions resembled SEP obtained in STN. When entering VIM, a sharp amplitude increase was observed over a few millimetres only.

Conclusions: Based on SEP criteria, the VIM target but not the STN region can be identified by typical SEP configuration changes, when penetrating the target zone. The approach is independent of the patient’s cooperation and vigilance and therefore feasible in general anaesthesia. It provides an easy, reliable, and robust tool for the final assessment of electrode positions at the last instance during electrode implantation when eventual electrode revisions can easily be performed.

Over the past decade, deep brain stimulation (DBS) has been established as an important therapeutic option for the treatment of various movement disorders, refractory to or complicated by medical treatment. Essential tremor and parkinsonian tremor can be ameliorated or even abolished by DBS of the ventral intermediate nucleus (VIM). In Parkinson’s disease (PD) DBS of the subthalamic nucleus (STN) reduces rigor, tremor, and hypokinesia. A prerequisite for a beneficial outcome of patients is the accurate identification of a chosen target nucleus so that special emphasis is to be put on procedural aspects of electrode placement. Besides brain imaging with ventriculography, CT or MRI, electrophysiological techniques, such as stimulation at and recording from presumed target sites are used intraoperatively as functional targeting devices.

Commonly accepted as the gold standard of recording, high resolution microelectrode derivations are performed to depict target specific neuronal discharge patterns of single units, before implanting the final stimulation electrode, with an ongoing debate on the clinical impact of this technique. Both the technical equipment and the personal expertise for microrecordings require high standards, which are not easily available.

As, by contrast, the recording of somatosensory evoked potentials (SEP) is electrophysiological routine, we tested intraoperative SEP from the four contact DBS electrode for their anatomical specificity with regard to the ventrolateral thalamus (VIM region) and the subthalamic nucleus (STN region).

METHODS

In 23 patients with movement disorders (14 Parkinson’s disease, six essential tremor, three tremors due to multiple sclerosis; 15 men, 8 women; 34–75 years), undergoing surgery for DBS, SEPs were recorded intraoperatively from the final electrode implant. Ten patients (six with essential tremor, three with multiple sclerosis related tremors, and one with tremor dominant Parkinson’s disease) were implanted in VIM, 11 in STN and, early in the series, two Parkinson’s disease patients with planned STN surgery in “intermediate” positions (see “Casual observations”). We analysed 29 target SEPs (two SEP per subjects in six bilateral STN implantations, otherwise one SEP per subject). The effect of surgery for patients with Parkinson’s disease was rated based on the motor score (part III) of the Unified Parkinson Disease Rating Scale and for tremor patients based on the Essential Tremor Rating Scale. All patients gave informed consent under a study protocol approved by the local ethics committee.

The stereotactical procedure was performed from a frontal bur hole. The trajectories to the target points were calculated by image fusion of the preoperative MRI scan and CT scan, the intraoperative ventriculography, and the Schaltenbrand-Wahren atlas. Targeted regions were accepted or rejected depending on stimulation effects via test micro-electrodes. When—putatively after repeated corrections—the proper target position had been defined, the macro-electrode (with its second but lowest contact) was inserted to this brain site and SEP were recorded during momentary stops 2 cm and 1 cm above and within the presumed target position. This means

Abbreviations: VIM, ventral intermediate nucleus; STN, subthalamic nucleus; DBS, deep brain stimulation; SEP, sensory evoked potential
that SEP were collected during the study but not used for targeting. Criteria were developed in a post hoc analysis of the data obtained.

The electrode model (Medtronic 3389) used consists of a shaft with four ring contacts with a width of 1.5 mm, each, spaced at distances of 0.5 mm. The three basal contacts (anodes) were referenced against the cranial one (cathode), resulting in three bipolar derivations over 4.5 mm, 2.5 mm, and 0.5 mm. In a fourth channel, the compound action potential was derived medially at the ipsilateral upper arm proving the constancy of nerval input throughout all recording steps.

The median nerve contralateral to the DBS electrode was stimulated at an intensity of twice motor threshold to guarantee saturated responses. Recordings were performed at the end of surgery under intravenous propofol controlled sedation. Electrical stimuli were applied at 8.1 Hz (constant current squarewave pulses of 0.1 ms width) and averaged over 1000 single sweeps. A wide bandpass (5 Hz–1500 Hz) was used for data acquisition (sampling rate 10 kHz). Offline digital high-pass and low-pass filters (corner frequency: 428 Hz; 24 dB/octave) were applied to separate high frequency from low frequency responses, which, therefore, could be analysed independently.

Amplitudes of the low frequency subcortical (P16) and cortical (N20) SEP components were determined baseline to peak in the 5 Hz–428 Hz bandpass. The duration and amplitude of the high frequency burst component, superimposed to the primary subcortical component and oscillating around 1000 Hz for about 5 ms–10 ms, was determined in the 428 Hz–1500 Hz bandpass. The burst power was determined as a root-mean-square (rms) value over the signal time window and corrected for the noise induced error that was calculated in a burst free time interval from 30 ms–45 ms. Amplitude values are given for the first recording channel (4.5 mm grid).

Statistical analyses were performed using two sided paired t tests. Results were considered statistically significant at p levels <0.01.

Electrode positions were determined in a three dimensional system, based on intraoperative radiographs with ventriculography. The anatomical coordinates refer to the position of the second but lowest electrode along the x axis (laterality), describing the lateral distance from ac-pc midline (line between anterior and posterior commissure), along the y axis (anteriority), defined as the sagittal distance from pc (posterior commissure), and along the z axis (depth), defined as the vertical distance from ac-pc (negative values indicating below ac-pc/positive values indicating above ac-pc).

RESULTS
SEP in the VIM region (n=10 of 10 subjects)
SEP recorded from planned VIM targets displayed a specific configuration, distinguishable from SEP waveforms obtained at any other recording site (fig 1). In the low frequency band (<100 Hz) the response is characterised by a single monophasic negative component, sharply rising to an amplitude of 6.9 (5.4) µV (mean (SD)) with a peak latency of 17.3 (2.2) ms. In the high frequency band the 1000 Hz burst signal exhibited an average rms amplitude of 0.43 (0.11) µV, with signal onset at 13.4 (1.2) ms and offset at 22.8 (1.6) ms.

The average coordinates for the VIM target were x=11.6 (2.2) mm, y=6.6 (1.5) mm, and z=−1.8 (1) mm. The z value indicates comparatively low positions. Electrodes targeted to VIM may therefore partially lap into the caudally bordering structure—that is, Zona incerta.

The clinical DBS efficiency was reflected by a decrease of the total tremor score (from 61 (19.1) preoperatively to 24 (18.8) postoperatively; p=5.7×10−5).
SEP in the STN region (n=16 of 11 subjects)
Low frequency SEP; recorded from planned STN targets, are
dominated by a positivity of 1.1 (0.4) µV peaking at 18.7 (1.4) ms. The 1000 Hz burst has an amplitude of 0.09 (0.02) µV with
an onset at 14.2 (1.3) ms and an offset at 22.6 (1.6) ms (fig 1).

The coordinates of the STN targeted electrodes were x=11 (1.4) mm, y=11.1 (1.7) mm, and z=−2.2 (1.6) mm.

The clinical DBS efficiency was reflected by a reduction on
the UPDRS motor scale (37.75 (17.43) preoperatively to 19.1 (16) postoperatively; p=4.6 \times 10^{-3}).

SEP along the trajectory to VIM (n=14 of 7 subjects)
and STN (n=32 of 11 subjects)
SEP recorded 1 cm and 2 cm above STN and VIM hardly dif-
fered from those obtained in STN. They were characterised by
a primary, monophasic positive potential of comparatively low
amplitude. When stepping down from 2 cm to 1 cm above
either target position, an increase in amplitude goes in paral-
el with a decrease in latency. 1 cm and 2 cm above VIM the
positive potentials peak at 18.7 (1.9) and 19 (2) ms with
amplitudes of 2.4 (1.5) and 1.4 (1) µV respectively. For the
STN trajectory the values are: 19.1 (1.6) and 19.8 (1.6) ms
with amplitudes of 1.1 (0.6) and 0.8 (0.2) µV4—that is, a con-
sistent increase in amplitude cannot be seen towards the tar-
get zone. Burst signals are of lower amplitude than in the
according target regions, most strikingly in the transition to
VIM. The rms amplitudes for high frequency SEP 1 and 2 cm
above VIM are 0.12 (0.03) and 0.04 (0.02) µV, above STN 0.06
(0.05), and 0.03 (0.01) µV, respectively (fig 1).

Comparison of VIM SEP and STN SEP
The SEP amplitudes of low and high frequency responses were
significantly different in STN compared with VIM (low
frequency responses: p=1.2 \times 10^{-7}/burst responses: p=2.06 \times 10^{-10}).
All low frequency SEP had negative polarity in VIM and positive
polarity in STN. High frequency amplitudes did not overlap
between targets. Burst responses recorded in VIM are about four
times larger than 1 cm above it, and low frequency components
always reverse polarity over this distance. For these low
frequency responses, the voltage gradients along the four
contact electrode shaft were calculated between electrode
contacts 1–4 (used for normalisation), contacts 1–3, and 1–2.

The gradients were found to differ significantly (p<0.01)
between VIM (1: 0.29 : 0.03) and STN (1 : 0.78 : 0.37). Latencies
for both components did not differ significantly between the
targets.

An interindividually consistent location difference of
electrodes was found only for the y coordinate (4.5 mm;
p=1.03 \times 10^{-11}).

Casual observations
Early in the series in two subjects, exhibiting no or minor
clinical gains, SEP did not meet the target criteria described
above. Instead, sequences of a negative-positive-negative
complex with intermediate amplitudes were recorded (see fig
2); this could be correlated to electrode positions between the
mean VIM and STN y coordinates in these patients.

In two further patients with planned STN implantations a
second surgical intervention was performed for unilateral
electrode revisions because of missing clinical stimulation
effects. Their SEP configuration resembled a VIM pattern with
a monophasic negative component. In both patients the elec-
trodes were shifted to a more anterior position by 3 mm.
Correspondingly, after this correction an STN-like SEP con-
figuuration was obtained; clinically, both patients improved.

In one subject an additional recording was performed only
3 mm above the target position in VIM: this SEP contained a

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**Figure 2** Characteristic SEP recordings of three subjects with
sketch of the recording technique and of assumed recording positions based
on characteristic SEP features. The parasagittal scheme of the
sensorimotor thalamus (nuclei from anterior to posterior: VOA, VOP,
VIM, VC) and the subthalamic nucleus delineate the anatomical
relation of the target nuclei to each other and the vicinity of VIM to the
somatosensory relay nucleus (VC, dashed line). A highly significant
change in the SEP pattern was regularly observed when comparing
VIM to STN recordings. A transitional response type was obtained in three
cases with recordings from intermediate positions.

**Figure 3** SEP recorded along the trajectory just 3 mm above VIM
(A) and after driving the electrode down into VIM (B). Note the
immediate change in amplitude and polarity for the low frequency
component and the amplitude increase for the burst response.
low frequency positivity with the typical waveshape of trajec-
torial SEP described above. Driving down the electrode 3 mm
into the presumed VIM area, a monophasic negative low fre-
quency response and a high amplitude burst component (15.5
µV; burst: 0.51 µV) were obtained (fig 3).

DISCUSSION
SEP recorded from the definite electrode implant for DBS are
reliably indicative for the region targeted for in tremor condi-
tions—that is, VIM/Zona incerta. Parameters of low fre-
quency components and the analysis of recently described
local high frequency SEP activity provide useful information
for the functional identification of target zones. This SEP
approach is robust against surrounding electromagnetical
noise and provides data independent from the patient’s
vigilance level and cooperation.

The distinct VIM pattern in SEP recordings can be related to
the anatomical difference along the γ axis. SEP can thus
enrich stereotactic surgery by functional data (fig 2).

Low frequency SEP (<100 Hz)
In routine SEP diagnostics, latency and amplitude of low fre-
quency components (for example, N20 in median nerve SEP)
are evaluated in a large variety of neurological disorders to
assess the integrity of the somatosensory system. They are
assumed to reflect mainly postsynaptic potentials.

When recording from VIM electrodes, a large monophasic
negativity peaking around 17 ms was obtained, rapidly
decreasing just millimetres above VIM as well as more
rostrally towards STN. Given the macroscopic nature of the
used electrode, we propose this sharply rising component to
originate as mixed near-field contributions from the main
somatosensory thalamic relay nucleus (VC), dorsally border-
ing to VIM (see fig 2), and the caudal VIM itself, which also
receives short latency somatosensory input. This assump-
tion is based on the following arguments: (1) the rising SEP
amplitude gradient, the closer one records to the neighbouring
VC/VIM areas, (2) the phase reversal, occurring on the caudal
level of VC/VIM, congruent with earlier semi-microelectrode
recordings, proving short latency somatosensory input as to
VIM as to VC, and (3) the steep voltage gradients along the
four contact electrode. These findings congruently suggest a
near-field origin of the negative wave. Notably, we observed no
correlation between SEP recorded in VIM and parkaesthesias
c elicited by DBS.

An intermediate SEP configuration was observed casually
along a presumed transition zone between VIM and STN.
These SEPs are characterised by a diphasic, primarily negative
component.

A monophasic positive SEP component of comparatively
small amplitude is typically recorded in STN. This configura-
tion was found at all studied recording sites with the
exception of recordings near or in VIM. Thus, the low
amplitude profile of SEP recorded along STN trajectories
makes the search for SEP peak amplitudes for STN targets a
useless enterprise.

High frequency SEP (around 1000 Hz)
This burst response of 5–10 oscillatory potentials features fast
dynamic characteristics suggesting a generation via synchro-
nised action potentials, eventually from local bursting relay or
intersynaptic and/or the most cranial parts of medial lemnis-
cal fibres.

The analysis of this high frequency response has proved a
further useful parameter to identify VIM, but only in cases with
comparatively low amplitude low frequency SEP. The
burst power was severalfold higher in VIM than in surround-
ing basal ganglia motor structures, including STN, without
any overlap. The steep burst increase, moving from any
extrathalamic recording site into VIM, hints at a near field
generated potential, probably originating from the neighbour-
thalamic relay nucleus.

Comparison with previous SEP studies
In contrast with earlier studies on human subcortical SEP,
using cephalic or extracephalic skin reference electrodes,
intracranial bipolar recordings were analysed in this study.
This technical difference could explain the earlier
findings of similar SEP patterns in STN and VIM, distinguish-
able only from SEP recorded in the somatosensory relay
nucleus, whereas with the present bipolar montage a polarity
change of primary SEP components could be revealed
between VIM and more rostral as well as cranial sites.

Only few data have been published on subcortical high fre-
quency SEP bursts, interpreting them as sequential action
potentials, arising in the brain stem, medial lemniscus, and
thalamus. A recent study, using the present bipolar depth
recording technique provided support for the hypothesis that
the 1000 Hz burst reflects local rather than propagated
activity as the narrow bipolar montage (see fig 2) could
emphasise near field, high frequency potentials.

Conclusions
SEP from the final electrode for DBS are a useful tool to pro-
vide the therapeutic team with functionally based information
on the electrode position. The method is capable of supporting
VIM target identification for DBS tremor suppression.
Occasionally, it provides a clue for corrections in STN surgery
in cases of posterior electrode mislocalisations. SEP are
recorded at the last instance when corrections can be achieved
without a second surgical approach. The method is appealing
for its low demands on equipment and its robustness against
electromagnetically noisy surroundings. All SEP evaluation
criteria are independent from the patient’s vigilance state
and cooperation. SEP from the definite deep brain electrode do
not reach the spatial significance of single cell microrecord-
ings, yet they provide a quick and robust information on the
momentary electrode placement. Thus, their position in the
diagnostic procedure during DBS implantation, in particular
the relation between macroscopic SEP and cellular microelec-
tronic recordings, may be worth further study.

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REFERENCES
1 Obeso JA, Rodriguez MC, Gorospe A, et al. Surgical treatment of
2 Benabid AL, Benazzouz A, Limousin P, et al. Dyskinesias and
3 Gross RE, Lozano AM. Advances in neurostimulation for
5 Ondo W, Almaguer M, Jankovic J, et al. Thalamic deep brain
stimulation: comparison between unilateral and bilateral placement.
6 Factor SA. Parkinson’s disease: motor fluctuations. Current
7 Knack P, Poepping M, Weinert D, et al. Thalamic, pallidal, or
subthalamic surgery for Parkinson’s disease? J Neurol 2000;247 (suppl
2):122–34.
8 Pillon B, Ardouin C, Damien P, et al. Neuropsychological changes
between “off” and “on” STN or Gpi stimulation in Parkinson’s disease.
9 Vesper J, Klostermann F, Stockhammer F, et al. Results of chronic
subthalamic nucleus (STN) stimulation for Parkinson’s disease - a one-year
10 Starr PA, Vitek JL, Bakay RA. Deep brain stimulation for movement
MS society websites: www.mssociety.org.uk and www.nationalmssociety.org

Patients turning up with folders full of printouts from the internet are increasingly common sights in outpatient departments. The response from clinicians often tends towards annoyance and even suspicion. Furthermore, a disease such as multiple sclerosis is linked to much mystery (concerning causes) and controversy (concerning treatments), and as such, the internet abounds with sites making all manner of claims. Physicians therefore need to be able to recommend informative and reliable sites to patients.

The MS Society (UK) provides an easy-to-use and comprehensive web site (www.mssociety.org.uk). Particularly noteworthy are downloadable booklets and information sheets. “Newly-diagnosed” patients are sure to find many of these highly useful. Other sections in the web site include links to local support groups, information on working with MS, insurance issues, and pages for carers. The site also gives an overview of research activity in an accessible and balanced way.

Equally impressive is the US equivalent (www.nationalmssociety.org). Again, information is laid out in a user-friendly way with a multitude of links to other web sites pertaining to the disease. Of particular note to the neurologist, however, is the section on clinical study measures, which sets out in detail, with downloadable forms and user guides, the wide variety of rating scales that have been used in clinical studies of MS, providing a useful resource for all those involved in the management of the disease.

The internet has revolutionised so much of the way we all live our lives, and patients with neurological diseases are increasingly turning to it for information. Control and regulation of information on the internet is a problem, but perhaps if neurologists were to become more involved in writing patient group websites, we could enhance the service we give to patients and prevent some of the more ludicrous medical claims coming to the attention of our patients.

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References