


**Directional Local Field Potentials: A Tool to Optimize Deep Brain Stimulation**

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P.B. and M.S. are joint senior authors.

**Funding agencies:** G.T. is funded by the Rosetrees Trust, the National Institute of Health Research Oxford Biomedical Research Center, and the European Academy of Neurology (EAN). P.B., A.P., and H.T. are funded by the Medical Research Council (MC_UU_12024/1), and S.A.S. by the Medical Research Council (MR/N003446/1), and S.A.S. by the Rosetrees Trust.

**Relevant conflicts of interest/financial disclosures:** G.T. received financial support for congress participation from Boston Scientific. I.D. received financial support from Boston Scientific.

Full financial disclosures and author roles may be found in the online version of this article.

**Received:** 28 June 2017; **Revised:** 21 August 2017; **Accepted:** 3 October 2017

Published online 18 November 2017 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27215
A major advance in DBS technology was the introduction of directional DBS leads with segmented contacts and multiple source current steering.\(^1,2\) The middle two levels of conventional ring-contact DBS electrodes are replaced with three segmented (noncircular) contacts (Fig. 1A), which allow steering of the stimulation field. Two intraoperative studies,\(^1,3\) a postoperative clinical trial and a case report,\(^4,5\) have reported an increased therapeutic window and efficacy of directional compared to spherical stimulation.

These advantages are offset by the complexity of programming directional DBS. The monopolar contact review is the crucial initial step and gold standard for the management of DBS patients\(^6,7\) and requires a highly trained person.\(^8\) The use of directional DBS leads implies testing of a total of 16 stimulation contacts (8/hemisphere), with 12 (6/hemisphere) of them being segmented (Fig. 1A) and requires much more time. Thus, tools that can expedite programming and optimize the use of directional electrodes are strongly needed.\(^9\)

Local field potential (LFP) activity in the beta band (13-35 Hz) has previously been shown to be related to motor symptoms in Parkinson’s disease (PD) and to predominantly arise in the motor portion of the STN.\(^10,12\) Importantly, it has also been demonstrated that the ring contact closest to the beta source is clinically more efficient compared to other contacts.\(^11,13-15\)

Here, we test the hypothesis that delivery of stimulation in the direction of the highest beta-band activity in the STN provides the best stimulation effect and that the LFP may therefore serve as a tool to assist DBS programming.

**Patients and Methods**

Twelve PD patients undergoing STN-DBS surgery were implanted with directional leads (Boston Scientific, Marlborough, MA; Supplementary Table 1). LFPs were recorded during surgery from the directional contacts after each lead was placed in its final position (Fig. 1B). Normalized beta activity was derived from each directional contact by normalization of the individual beta peak activity by the whole beta band (13-35 Hz). In cases where no beta peak was present, the low beta band (13-20 Hz) was normalized. Monopolar contact review took place 4 to 7 months postsurgery. Clinical efficacy (% rigidity improvement/stimulation current) and therapeutic window (TW) were calculated for each directional contact and compared with the corresponding normalized beta activity. Detailed methods are included in the Supplementary Material.

**Results**

**Relationship Between Beta Activity and Response to stimulation**

In 15 of 19 hemispheres tested, we found a positive relationship (\(t_{18} = 4.65; P < 0.001\), one-sample \(t\) test) between normalized beta activity and clinical efficacy (ranked values: Fig. 1C; absolute nonranked values: Supplementary Fig. 3). Thus, the higher the relative beta activity recorded from a specific directional contact, the better its clinical efficacy. In all cases, the contact with highest beta was consistently one of those with higher clinical efficacy, and in 12 of 19 cases (63%), it corresponded to the contact with the highest clinical efficacy. In 7 of 19 cases (36%; hemispheres 13-19), we did not find a clear beta peak, but despite this, the relationship was similar to those with a clear peak in the beta band. There was also no difference in the predictive value of the level and orientation of the beta peak between those hemispheres with a beta peak up to 20 Hz (=2, 3, 5, 6, 7, 10, and 11) and those hemispheres with a beta peak above 20 Hz (hemispheres 1, 4, 8, 9, and 12). The ring level
FIG. 1.

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containing the contact with the highest beta activity
was localized in the dorsal STN (ventral STN = 0;
middle STN = 4; dorsal STN = 15).

Predictive Value of Beta Activity for the Most Efficient Stimulation Contact

In Figure 2A, we tested the predictive value of contacts ranked by relative beta power for clinical efficacy. This shows that the stimulation contact with the highest beta activity was able to predict the stimulation contact with the highest clinical efficacy in 63% of cases. More strikingly, when including the contact with the second-highest beta activity, the prediction rose to 84%, and up to 92% if only hemispheres with a clear beta peak (n = 12) were considered. In contrast, conventional clinical testing had only a 17% likelihood of identifying the most efficient contact if only one contact was assessed, and a 34% likelihood if two contacts were assessed. Figure 2B shows that the mean clinical efficacy of the two contacts with the highest beta activity was significantly higher (31.3 ± 3.2%/mA [milliamperes]) compared to the mean clinical efficacy (26.1 ± 2.7%/mA) of the remaining contacts of the same electrode (t18 = 3.75; P = 0.0015, paired t test).

Relationship Between Clinical Efficacy and Therapeutic Window

Another important clinical parameter is the therapeutic window, which also includes the side-effect threshold. Figure 2C shows that the LFP-based strategy identified the contact with the widest therapeutic window in 42% of cases if only the contact with the highest beta activity was considered, and in 74% if the two highest beta contacts were considered. No relevant difference in the predictive value was found when hemispheres with a clear beta peak were exclusively considered. Additionally, Figure 2D shows that the mean therapeutic window of the two contacts with the highest beta activity was significantly higher (1.45 ± 0.27 mA) compared to the mean TW (0.96 ± 0.17 mA) of the remaining contacts of the same electrode (t18 = 3.11; P = 0.006, paired t test).

Discussion

In this study, we demonstrate, in a sizeable patient cohort, that the two segmented contacts of the directional DBS electrode with maximal STN beta activity are highly likely to include the contact that turns out to have the best efficacy with a wide therapeutic window. Clinical testing was performed at least 4 months after lead implantation, when the majority of any stun effect has lapsed and the clinical relevance of contact screening therefore heightened. Thus, the LFP can serve as a predictive and supportive tool for multicontact lead programming. This is in line with previous studies showing similar results for the ring contact electrode, as well as with an intraoperative trial and a single, early postoperative case report with directional stimulation.

Why should beta power in the LFP predict the clinical efficacy of stimulation fields of different orientation? It has been shown that the dorsal part of STN is the most effective site for STN stimulation in PD, and that this is also the focus of beta activity. Yet, the LFP cannot afford direct information about the contact specific therapeutic window, because side effect threshold depends on the vicinity of the stimulation field to neighboring structures. On the other hand, as current directed to the dorsal STN is less likely to spread to these neighboring areas, the prediction of the contact with the lowest threshold for clinical effect may also explain the predictive value for the contact with the widest therapeutic window.

LFP-Based Programming

If we assume that it takes around 20 minutes to assess stimulation at each contact, then monopolar contact review of segmented leads will take around 4 hours (12 segmented contacts). This would be fatiguing for both clinician and patient, leading to variability in assessments. If only those two segmented contacts that have the highest beta activity are screened on each side, then there is approximately a 90% probability of selecting the contacts that have the lowest effect threshold. This would only take 80 minutes, reducing assessment time by approximately two thirds. Moreover, as discussed...
above, the two segmented contacts with the highest beta activity are also more likely to have a wider therapeutic window. Hence, this method potentially offers a physiologically based, time-saving approach to the programming of directional electrodes.

Limitations

In this investigation, we only studied those sides with at least two points of upper-limb rigidity and more than a minimum range of responses to stimulation across contacts. We also limited the electrophysiological-clinical comparison to the clinical data acquired during the monopolar review session, where rigidity was the only systematically assessed item. However, rigidity is also the most sensitive clinical sign to DBS.\textsuperscript{6} These inclusion criteria were chosen to optimize the clinical comparison across contacts, and to avoid ceiling and floor effects. The value of beta activity and of other LFP features in predicting the best contact for tremor suppression needs further evaluation.

In addition, we assumed that the monopolar review in and of itself is predictive of chronic stimulation settings.\textsuperscript{6,19} Moreover, manual clinical contact testing,
although the current “gold standard” for determining the best stimulation contacts, is a subjective method with some degree of inter-rater variability. Any noise in the gold-standard estimation will only have served to degrade the apparent predictive value of the LFP.

Intraoperative time constraints meant that LFPs could only be recorded for around 2 minutes (with interindividual variability), and longer recordings might have been more representative. Importantly, we also assumed that lead position and orientation did not change after LFP recording. Furthermore, our data may have been contaminated by stun effects, which can be detected as the STN is traversed and lead to diminished beta power.10

Future Directions and Conclusion

Tools that can assist DBS programming by the clinician or even run fully automatically are desirable in this era of directional, multicontact leads. This could streamline the postoperative management of patients, and free up clinical resources to contend with the increasing numbers of such patients dictated by growing experience with this therapy and by the move to offer DBS earlier during the disease course.21 Nevertheless, the clinical advantage, or lack thereof, of chronic directional DBS still needs to be definitively demonstrated.

The method presented is of potential predictive value with respect to subsequent programming, regardless of whether microelectrode recordings are used or not in targeting the STN. In time, optimal contact prediction might be based on a variety of features. The electrophysiological approach taken here might be supplemented by radiological-anatomical strategies that could provide more-accurate information about surrounding structures. However, presently, these are challenging to implement, given that target structures are small and image resolution is limited, so that the error rate in lead localization is not negligible.22

In conclusion, the present study suggests that the amplitude of subthalamic beta LFP activity is predictive of the most efficient stimulation contact and can form the basis for a rapid programming tool useful for multicontact directional DBS leads.

References

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.