Right on track: Towards improving DBS patient selection and care

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CHAPTER 9

Summary

Deep Brain Stimulation (DBS) is an effective treatment to ameliorate motor complications in Parkinson's Disease (PD) patients and improve Quality of Life (QoL). Careful screening for DBS eligibility is crucial to select optimal candidates for surgery. To further optimize the screening process of PD patient eligibility there are still some unmet needs. First, there is a need of information on rejection policies after referral for DBS. Second, there is a need for information on factors that influence patients' postoperative satisfaction and QoL. Finally, there is a need for novel biomarkers to complement the current DBS screening battery. This thesis addresses these aspects and identifies directions for future research.

In **Chapter 2**, the reasons for rejection after an out-patient based pre-screening visit after referral for DBS were assessed by performing a chart review of 289 patients referred to the Leiden University Medical Center (LUMC) or the Maastricht University Medical Center (MUMC). The most frequent reason for rejection was suboptimal oral treatment or satisfying control of symptoms with oral treatment, which constituted 50% of the rejections. Twenty-three percent of referred patients had unrealistic expectations of DBS surgery, i.e. a desire to have relief of a symptom that is typically DBS-unresponsive. Moreover, the chart review showed that in 38% of rejections, unrealistic expectations contributed to the reason to reject (2nd most encountered reason to reject), although only in 4% constituted 'unrealistic expectations' the only reason to reject for DBS surgery. Impaired balance or medication-resistant freezing contributed in 36% of rejected patients to the reason to reject, whereas cognitive impairment was considered a reason to reject in 30% of rejections. These results suggest that the yield of appropriate referrals to DBS centers can be improved by educating referring neurologists on the contraindications for DBS surgery. Further, needless referrals can be avoided by determining whether patients have persistent unrealistic expectations of DBS surgery. In **Chapter 3**, studies on preoperative factors influencing postoperative QoL were systematically reviewed. From the 18 included studies, it was derived that only high baseline levodopa-responsiveness of motor symptoms appears to contribute to higher postoperative QoL (although not confirmed by all studies), whereas the majority of studied factors did not appear to influence QoL on group-level. Strikingly, various relative contra-indications for DBS surgery such as cognitive impairment and psychiatric dysfunction appear to be unrelated to postoperative QoL. However, it should be noted that these factors were only present to a limited degree (i.e. no severe cognitive impairment or severe psychiatric dysfunction was present in the studied cohorts) and results cannot be simply extrapolated to more severe symptom loads. These results suggest that QoL after DBS might be highly individually determined and results depend heavily on study design, used scale, and cultural background. In **Chapter 4**, a comparison between intraoperative test stimulation and postoperative stimulation settings was drawn in 119 PD patients after DBS of the Subthalamic Nucleus (STN). In the majority of cases, the postoperatively selected contact corresponded with the

intraoperatively defined 'best depth', or was immediately dorsal to it. More importantly, higher stimulation intensities were required postoperatively than intraoperatively to relieve rigidity or to induce capsular side-effects. We speculate that these findings stem from differences in current directionality (i.e. current vector), differences in current propagation due to increased encapsulation of the electrode used for chronic stimulation, and differences in sizes of the 'volume of tissue activated'. These results may ultimately be used to increase the efficiency of identification of the postoperative stimulation settings. In **Chapter 5**, we aimed to study whether postoperative ON-OFF testing (i.e. a stimulator-challenge-test (SCT)) alters patients' perceived impression of DBS effects and improves satisfaction after surgery in 54 patients. Both patient-reported satisfaction of surgery and impression of change due to DBS increased after SCT. The severity of motor impairment, as well as responsiveness of motor symptoms due to DBS, were not associated with subjective outcomes. A higher level of non-dopaminergic disease severity, relatively unchanged after DBS, influenced both satisfaction and impression of change. SCT may accurately quantify postsurgical motor improvement and appears indicated in case of suboptimal satisfaction following DBS STN.

In the second part of this thesis, biomarkers derived from Electroencephalography (EEG) were evaluated for usage during the DBS screening. In **Chapter 6**, studies on the correlation between quantitative EEG (qEEG) measures and clinical symptoms were reviewed. From the 36 included studies it can be concluded that metrics reflecting EEG slowing (derived from spectral analyses) correlate with cognitive impairment and may predict future cognitive deterioration. qEEG biomarkers appear particularly suited to reflect cognitive (dys)function, but there is little evidence to support their use in reflecting motor function or other clinical domains in PD. Metrics reflecting connectivity or network synchronization were scarcely evaluated and never applied in a longitudinal design. In **Chapter 7**, a correlation between qEEG metrics and non-dopaminergic severity was demonstrated in 63 PD candidates for DBS. Both global EEG slowing and reduced functional connectivity in the $\alpha 2$ band (i.e. a lower Phase-Lag-Index (PLI)) were associated with higher non-dopaminergic disease severity. These correlations appear driven by the non-dopaminergic subdomains 'cognition' and 'psychotic symptoms', whereas there was no association of qEEG metrics with motor functioning. It appears that cortical biomarkers (i.e. qEEG metrics) correlate best to 'cortically-mediated' symptoms, such as cognition or psychiatric functioning. These results suggests that qEEG may have complementary value during the DBS screening process in determining neuropsychological functioning, apart from formal assessment of cognition or psychiatric functioning. In **Chapter 8,** an automated Machine Learning pipeline for classification of cognitive function in DBS candidates is evaluated. An EEG-based evaluation of the raw time series, without arbitrary choice of feature-selection, provides an accuracy of 92% in differentiating between PD patients with either clinically-determined 'good cognitive

function' or 'poor cognitive function' based on the cognitive 'extremes' in the entire cohort. The calibration of predicted class probability versus cognitive performance scores demonstrated a good correlation of the underlying model to actual functioning. Patients that had 'intermediate' cognitive performance scores did not classify as either previously defined class and had indeterminate predicted class probabilities. Although external validation was not possible due to the uniqueness of the studied cohort, the Machine Learning algorithm demonstrated good internal validity and provides a proof-of-concept for automated classification of cognitive profiles based on EEG-data of DBS candidates.