Deep brain stimulation: Imaging on a group level

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ARTICLE INFO

Keywords:
Deep brain stimulation
Imaging
Group analysis
Subthalamic nucleus

ABSTRACT

Deep Brain Stimulation (DBS) is an established treatment option for movement disorders and is under investigation for treatment in a growing number of other brain diseases. It has been shown that exact electrode placement crucially affects the efficacy of DBS and this should be considered when investigating novel indications or DBS targets. To measure clinical improvement as a function of electrode placement, neuroscientific methodology and specialized software tools are needed. Such tools should have the goal to make electrode placement comparable across patients and DBS centers, and include statistical analysis options to validate and define optimal targets. Moreover, to allow for comparability across different centers, these need to be performed within an algorithmically and anatomically standardized and openly available group space. With the publication of Lead-DBS software in 2014, an open-source tool was introduced that allowed for precise electrode reconstructions based on pre- and postoperative neuroimaging data. Here, we introduce Lead Group, implemented within the Lead-DBS environment and specifically designed to meet aforementioned demands. In the present article, we showcase the various processing streams of Lead Group in a retrospective cohort of 51 patients suffering from Parkinson’s disease, who were implanted with DBS electrodes to the subthalamic nucleus (STN). Specifically, we demonstrate various ways to visualize placement of all electrodes in the group and map clinical improvement values to subcortical space. We do so by using active coordinates and volumes of tissue activated, showing converging evidence of an optimal DBS target in the dorsolateral STN. Second, we relate DBS outcome to the impact of each electrode on local structures by measuring overlap of stimulation volumes with the STN. Finally, we explore the software functions for connectomic mapping, which may be used to relate DBS outcomes to connectivity estimates with remote brain areas. The manuscript is accompanied by a walkthrough tutorial which allows users to reproduce all main results presented here. All data and code needed to reproduce results are openly available.

1. Introduction

The modulation of neural networks by Deep Brain Stimulation (DBS) is an efficacious and established treatment option for specific neurological and psychiatric disorders, and is currently investigated for other brain diseases. DBS treatment is best explored in movement disorders (Benabid et al., 1991; Kupsch et al., 2006a), with the subthalamic nucleus (STN) and internal pallidum (GPi) as most established targets (Schuepbach et al., 2013). The application is continuously extended to other indications and targets (for a review see Lozano and Lipsman, 2013). Aside from its clinical value, DBS opens an invaluable window into the human brain and it is increasingly adopted to probe causal relationships between stimulated targets and behavioral effects, such as risk control (Irmen et al., 2019; Nachev et al., 2015), movement speed (Neumann et al., 2018b), memory learning (de Almeida Marcelino et al., 2019) or verbal fluency (Ehlen et al., 2017; Mikos et al., 2011).

In early clinical studies which led to FDA- and CE-approval for indications like Parkinson’s Disease, Dystonia or Essential Tremor, the
exact electrode placements were not investigated (Deuschl et al., 2006; Kupsch et al., 2006b; Schuepbach et al., 2013). However, in these, DBS targets had already been well informed and established by decades of ablative surgery, which – on average – leads to similar clinical effects (Aliné et al., 2019; Starr et al., 1998). Still, a multitude of studies have shown that DBS electrodes need to be accurately placed to maximize clinical improvements (e.g. Dembek et al., 2019a; Horn, 2019; Hor V. et al., 2019a). Thus, when probing novel targets, things could turn out differently. For instance, in depression and Alzheimer’s Disease, clinicians report that some patients have largely benefited from DBS while others did not (Laxton et al., 2010a; Riva-Pose et al., 2017). In the case of depression, however, two prospective, randomized, sham-controlled trials have failed (Dougherty et al., 2015; Holtzheimer et al., 2012). While some patients had responded well to treatment, their group effects may have been diminished by non-responders. Some (albeit not all) of this variability in outcomes might be explained by analyzing lead placement. By doing so, one could possibly find relationships between clinical outcome and the underlying modulated anatomical space, as was shown for other diseases (Al-Fatly et al., 2019; Baldermann et al., 2019; Dembek et al., 2019b; Horn, 2019b; Li et al., 2020; Reich et al., 2019).

Thus, large-scale group studies that include electrode placement could comprehensively help to investigate relationships between stimulation sites and clinical/behavioral outcomes. While this has been done in multiple retrospective analyses, we see potential for prospective trials, too.

With the publication of the software Lead-DBS in 2014 (Horn and Kühn, 2015) and its further methodological advancement over the years (Ewert et al., 2019, 2018; Horn et al., 2019a, 2014; Horn and Blankenburg, 2016), an openly available tool was created, which allows for precise electrode reconstructions based on pre- and post-operative imaging data.

One key goal of the software is to make electrode placement transferable and comparable across centers and patients by warping their coordinates into a common stereotactic space. While this idea is surely not novel (the concept has been around in the neuroimaging community for decades, for an overview see e.g. (Ashburner, 2012)), the process still has its limitations in an inherent loss of precision. Errors of placements in DBS electrode locations are prone to occur when studying them in a common stereotactic space. Over the years, our group and others have focused on minimizing these sources of errors across each step of the pipeline and hence improving the accuracy of Lead-DBS (Ewert et al., 2019b, 2018b; Hellerbach et al., 2018; Horn et al., 2019a; Husch et al., 2018; Schonecker et al., 2009; Dembek et al., 2019b). Strategies such as multispectral warps, subcortical refinements, brain shift correction, phantom-validated electrode localizations, the possibility of manual refinements of warp-fields and detection of electrode orientation have led to a freely available pipeline that aims at maximizing precision both in native and common space (for an overview see (Horn et al., 2019a)). The registration pipeline of Lead-DBS was recently evaluated in a large comparative study and results were comparable to manual expert segmentations of subcortical nuclei (Ewert et al., 2019). This was promptly replicated by a different center based on a different dataset (Vogel et al., 2020). While Lead-DBS is capable to register patient data to different stereotactical spaces, a worldwide standard of the neuroimaging community has been adopted as default: The Montreal Neurological Institute (MNI) space in its most current and best-resolved version (ICBM 2009b Nonlinear Asymmetric space, (Fonov et al., 2009)).

Once electrodes are in such a common space, this allows for analyses of DBS electrodes on a group level, and direct comparability of results between patients, research groups and software tools. Various publications could demonstrate that electrode reconstructions remain informative in common space and may be used to predict outcomes or behavioral measures across cohorts and DBS centers (Al-Fatly et al., 2019; Baldermann et al., 2019b; de Almeida Marcelino et al., 2019; Horn et al., 2019a; Li et al., 2020; Neumann et al., 2018b).

Here, we introduce a novel open source toolbox, Lead Group, which was implemented within the Lead-DBS environment and specifically designed with group level analyses in mind. While Lead Group has been available in prototypical form for a while, it has not been written up methodologically and development work was only now completed, including documentation, a test-dataset, step-by-step tutorial and a largely improved user-interface.

To showcase the functional repertoire of Lead Group (see Fig. 1), in this manuscript, we apply the tool to investigate a previously published retrospective cohort of 51 patients suffering from Parkinson’s disease (PD) that underwent STN-DBS surgery. Electrodes of the whole group are visualized in both two- and three-dimensional views. Different types of variable mappings are presented and novel types of connectome derived approaches investigated. We present concise results and release this dataset in form of a Lead group project. A step-by-step tutorial that allows for reproduction of core result figures presented here is included as supplementary material.

2. Methods and material

2.1. Patient cohort

To illustrate the multiple analysis pipelines and visualization options available within Lead Group, we included data from a retrospective cohort, which has been described in detail elsewhere (Horn et al., 2019a). Briefly, fifty-one patients implanted with two quadripolar DBS electrodes (Model 3389; Medtronic, Minneapolis, MN) to bilateral STN to treat Parkinson’s disease (PD) were included. Patients underwent DBS surgery at Charité – Universitätsmedizin Berlin. DBS response was defined as the percentage improvement along the Unified Parkinson’s Disease Rating Scale (UPDRS)-III motor score ON vs. OFF, which was assessed within an interval of 12–24 months after surgery. Clinical ratings took place after a washout period from dopaminergic medication of more than 12 h. Imaging data of all patients consisted of multispectral preoperative MRI (T1 and T2 weighted) sequences scanned at 1.5T, axial, coronal and sagittal postoperative T2 sequences for 45 patients or postoperative CT scans for the remaining 6 patients. This study was approved by the local ethics committee of the Charité, University Medicine Berlin (master vote EA2/186/18).

Fig. 1. Lead Group Pipeline. The main features and options of the toolbox are shown, including the setup of a group study and settings, which can be chosen for the following processing steps: Visualization of all electrodes in 2D and 3D as well as statistical analyses in relation to either local or connected structures. Stages highlighted in bold text are described in more detail in the paper.
2.2. Electrode localization

Before patient folders may be imported and further processed in Lead Group, it is necessary to localize electrodes for each patient using Lead-DBS (which is optimized for either single-patient use, bulk-processing with parallel computing, or job submission systems on compute clusters). Localization methods were carried out using default parameters of the Lead-DBS v.2 pipeline (Horn et al., 2019a). Briefly, linear coregistration of postoperative images to preoperative MRI scans were performed using a linear transform solved using Advanced Normalization Tools (ANTs; http://stnava.github.io/ANTs/; Avants et al., 2008)). Preoperative scans were multispectrally normalized into MNI (ICBM 2009b NLIN Asym; Fonov et al., 2009) space using ANTs and the “Effective: low variance” protocol with subcortical refinement implemented in Lead-DBS. This normalization scheme was top performer in two recent evaluations for registrations of subcortical structures such as the STN and GPI (Ewert et al., 2019; Vogel et al., 2020). Electrode localizations were flipped to one hemisphere to increase statistical power. Since symmetric stimulation relationships are assumed in the motor domain, this has been a usual practice to analyze effect-placement relationships since at least 2004 (Reich et al., 2019; Wodarg et al., 2012). Although direct ways of landmarking are mostly available parcellation of the sensorimotor cortex, the Human Motor Area Template (HMAT; Mayka et al., 2006), which contains regions defined S1, M1, supplementary and presupplementary motor area (SMA/preSMA), dorsal and ventral premotor cortex (PMd/PMr; section S1.12 in the walkthrough tutorial).

To set up the group analysis in Lead group, all 51 patients were selected and their percentage improvement on the UPDRS-III motor score entered as a variable into the Lead Group GUI (section S1.1 in the walkthrough tutorial appended within supplementary material). Some analyses offered by Lead Group are parametric in nature, i.e. could directly take advantage of the continuous variable %-UPDRS-III improvement. However, others are meant to compare groups (e.g. to analyze differences between hospitals or compare top vs. poor responders). To demonstrate these analysis streams, as well, a median split was applied to assign a variable separating good (25) from poor (23) responders, with 3 patients lying exactly on the median score of 44% (not assigned by the variable). This step arbitrarily split the group in two subgroups of similar size. Stimulation parameters, i.e. active contacts and amplitudes, were specified for each individual patient. Volumes of tissue activated (VTA, representing a rough approximation of the surrounding tissue modulated by DBS) were calculated using a finite element method (FEM) approach (Horn et al., 2019a, 2017c). As alternatives, four other heuristic models are implemented in Lead-DBS (Dembek et al., 2017; Kuncel et al., 2008; Madler and Coenen, 2012; Baniasadi et al., 2020) which are not used in the present manuscript.

To graphically illustrate the electrode placement in relation to respective clinical outcomes following DBS, active contacts of all patients entered as a variable into the Lead group (see S1.13 in the walkthrough tutorial). For each tract of a group connectome, improvements associated with VTAs that are connected to the tract are compared to the improvement values of VTAs not connected to the tract in two-sample T-tests. The method is referred to as “discriminative fibertract analysis” in the software and was introduced in Balderrmann et al. (2019b). An alternative method employing E-fields instead of binarized VTA and Spearman’s rank correlations instead of T-tests is available, commonly leads to very similar results and was introduced in Irmen et al. (2020). This latter method is not used here. By running the aforementioned T-test for every tract, each receives a predictive value in form of a T-score that can be positive or negative. Tracts are then color-coded by their T-score for visualization. Fibers mapped in red are predominantly connected to VTAs that were associated with better treatment response. The opposite would account for “negative fibers”. These are not shown given the large overall improvement of the cohort. Also, based on clinical and pathophysiological knowledge, it is unreasonable to hypothesize that DBS with poor placement would contribute to worsening of motor symptoms above and beyond side-effects which are not covered by the UPDRS-III and not largely present in long-term stimulation-settings as the ones studied here. Of note, T- and p-values in this analysis are not directly transferrable to asserting “significance” of results given the mass-univariate nature of the approach (hence, p-values are not even displayed by the software and T-values should be seen as “weights”). However, results can be used to cross-predict outcomes in out-of-sample data (leave-one-out design, k-fold cross-validation or training the tract-model on one cohort to predict outcome in the second). We perform leave-one-out cross-validation on the tract shown here and refer to the walkthrough-tutorial and a recent study (Li et al., 2020) for further details/examples.

2.5. Statistical analysis

While the aforementioned processing steps mainly serve to visually describe DBS effects with regard to their anatomical sites, Lead group further provides limited statistical tests and ways to export metrics to run more elaborate statistical analyses in different software. For instance, it is straightforward to export intersection volumes between VTAs and a specific anatomical atlas structure (such as the STN) or correlate these with clinical improvement values directly within Lead group (see
umes were correlated with the clinical outcome variable by conducting a Spearman’s rank-correlation. Random permutations (× 5000) were conducted to obtain p-values. Similarly, the values of the top and bottom responding half of the cohort were compared using a two-sample T-test. The same two types of analyses can be applied to connectivity estimates (e.g. of tract counts connecting VTAs with a cortical region such as the SMA). Similarly, those metrics can instead be exported for further analysis elsewhere.

3. Results

3.1. Clinical improvement

The 51 patients (age 60 ± 7.9; 17 female) improved by 45.4 ± 23.0% on the UPDRS III motor score, from a postoperative baseline of 38.6 ± 12.9 to 21.1 ± 8.8 points. For further demographic details on the cohort, please see (Horn et al., 2019a, 2017c).

3.2. Electrode placement

Active contacts were mapped to anatomical template space and visualized in 2D slice views (Fig. 2). Contacts of the top responding half are shown in light red (and the best-responding patient in dark red) while the bottom half is shown in light blue (with the poorest responder in dark blue). A similar export is shown in 3D in the left panels of Fig. 3 which separately shows the two medium-split halves of active contacts. The right panel shows 3D electrodes with realistic dimensions instead of point-clouds.

3.3. Electrode position weighted by clinical improvement

After the clinical regressor was mapped to coordinates of active electrode contacts and VTAs, these were visualized in various forms using Lead group in 3D (Fig. 5) and exported to visualize them in a NIfTI-viewer such as 3D Slicer (www.slicer.org) in 2D (Fig. 4).

Fig. 5A shows the active contacts of both sides that were nonlinearly flipped to the left hemisphere. Contacts were color-coded by clinical improvement values, showing a predominantly better improvement within the STN as outside of it. This point cloud was then used to fit a scattered interpolant from which an equidistant volumetric grid could be generated. In Fig. 5B, the raw points of this interpolation grid are visualized, leading to a potentially clearer impression of the spatial extent of the optimal target region. Fig. 5C uses a different approach to visualize the same interpolated data grid by showing a 3D isosurface that is further color-coded by improvement values of surrounding points. By doing so, a point cloud (of active coordinates) is transformed to a volume which is shown as 2D slices in the upper panel of Fig. 4.

Mentioned methods use active coordinates, while it is also possible to map improvement values to the spatial extent of each VTA. Fig. 5D and bottom panel of Fig. 4 show results of voxelwise T-maps across weighted VTAs.

Independent of method or visualization strategy, these results favor an optimal target within the STN and at anterior level of the red nucleus at its largest extent. This confirms general clinical heuristics and priorly published articles that came to the same conclusion (Akram et al., 2017; Bot et al., 2018; Horn et al., 2019a; Nguyen et al., 2019).

3.4. Distance to target

Above approaches aimed at defining optimal targets in a data-driven fashion, i.e. by weighting electrode coordinates or VTAs with clinical improvement scores and aggregating those values on a group level. Alternative research questions could aim at validating known targets or coordinates. For instance, if an optimal target coordinate was reported in the literature, an aim could be to validate the target using a novel cohort (Horn et al., 2019a). Alternatively, distances to anatomical structures could be used. Here, we explore this latter option by calculating distances between each active contact coordinate and an atlas definition of the STN. To do so, a “target report” was generated within Lead group (see section S1.10 in the walkthrough tutorial), which calculated the distance in mm of each electrode contact to the closest voxel center of the chosen atlas structure. In addition, a threshold can be selected so that a binary table will be provided, indicating whether or not a contact resides inside or outside of the anatomical structure. Of note, this “structure” of choice (here the STN) can be defined by any map available in NIfTI format in template space. This NIfTI file does not necessarily need to represent a brain nucleus like the STN in our example. In Fig. 6, these distances are reported for the best (82% improvement) and the poorest (−11% improvement) responders in synopsis with their electrode reconstructions. Not surprisingly, their proximity to the target differs largely and the active contact of the best responder resided within the STN on both sides.

3.5. Intersection with local structures

Instead of calculating absolute electrode distances, a similar approach is to calculate the intersections between each VTA and an anatomical atlas structure (see section S1.11 in walkthrough tutorial). These intersecting volumes may be either used in statistical tests in Lead group, or exported for further analysis. In our example, we hypothesized, that clinical improvement would correlate positively with the volume of STN intersection and accordingly, that the group of top half responders, as initially assigned by a median split, would intersect with the STN to a significantly higher degree than the group of bottom half responders (Fig. 7). As in the previous analysis, this concept can be carried out using NIfTI files that represent various sorts of information. Here, an anatomical structure (STN) is used, but the analysis could be carried out using files that represent any type of data such as functional activation maps, electrophysiological results, connectivity heatmaps or structure tract-density maps.

3.6. Fiber counts to connected structures

Based on the PPMI 8S connectome, fibers traversing through each VTA were isolated and the ones terminating in each cortical region defined by the HMAT parcellation were counted using Lead group. These numbers were correlated with clinical improvements across the group. As can be seen in Fig. 8, the number of fibers reaching preSMA (R = 0.29) and PMv (R = 0.3) could explain part of the variance in clinical improvements. In turn, less fiber counts connecting VTAs to M1 or S1 were associated with better %UPDRS-III improvement (R = −0.4 and R = −0.46). Of these results, only the latter two would remain significant after applying Bonferroni correction to p-values.
3.7. Discriminative fibers

The above analysis aimed at identifying cortical regions to which connections were positively or negatively associated with clinical improvements. An additional analysis stream available within Lead group could complement this concept by identifying specific tracts that were associated with clinical improvement. To do so, mass-univariate T-tests were conducted for each tract of the normative PD connectome between improvement values of connected vs. unconnected VTAs. Fibers were then color-coded by their T-value. This analysis revealed that the most positively associated tracts of the connectome traversed within the internal capsule and seemed to branch off to the STN in a similar fashion and at a similar location as axon-collaterals of cortico-spinal/-bulbar fibers that represent the hyperdirect pathway when revealed by single-axon tracing in the macaque (e.g. compare to Figs. 2–4 in Coudé et al., 2018a or Fig. 4 panel B subpanel v in Petersen et al., 2019). Crucially, tracts that continued downstream and bypassed the STN (i.e. fibers of the cortico-spinal tract) received lower T-values and are not shown due to thresholding. This is remarkable, since the hyper-direct pathway (i.e. corticospinal tract axons that branch off collaterals to the STN) is considered hard if not impossible to differentiate from the corticospinal tract based on diffusion-based tractography (Petersen et al., 2019). Still, strictly anatomically speaking, the result in Fig. 9 B is false in that it only shows the collaterals, not the axons continuing downstream (drawn in as white dashed lines). To address this and similar shortcomings of diffusion tractography, Petersen et al. have recently genuinely applied holographic manual reconstructions to define an atlas that properly defines hyper-direct pathways (among other structures) to the STN (Petersen et al., 2019). Repeating the same analysis using this pathway atlas revealed the same connections (but included the anatomically correct downstream passages of axons; Fig. 9 C). Of note, this holographic tract atlas is not based on diffusion MRI but on prior anatomical knowledge and is thus
Fig. 5. Different ways of mapping the same variable in Lead group. Panel A: All active contacts, shown as point clouds colored by clinical improvement (right contacts flipped to left hemisphere). Panel B: A scattered interpolant is fit to point cloud shown in (A), the result is projected to an equidistant grid. Panel C: data from B shown as an isosurface that is further color-coded by values in surrounding data points. Panel D: While A-C use spatial location of active coordinates, only, D is based on VTAs of all electrodes weighted by clinical improvement over which a voxel-wise T-test was performed. An isosurface at an arbitrary T-value of 10.56 (chosen visually) is shown; Color bar relates to Panels A–C and clinical improvement is guided by percentage UPDRS-III motor score improvement. Left hemisphere is displayed, with STN in orange.

Fig. 6. “Target report” feature showing distance from contact centers to their closest STN voxel centers. For each active contact (highlighted in red or bold text), the distance from the contact center to the STN is shown for patients with best (light red) and worst (light blue) clinical outcomes.

Fig. 7. VTA intersections with the STN explain clinical improvement. Left side: Spearman’s rank-correlation between clinical improvement and intersections (summed across both hemispheres) between VTA and the STN. Patients with best vs. poorest responses (Fig. 6) are highlighted by large circles. Right side: Patients were median-split into two groups, based on their percentage improvement on the UPDRS-III score. The group of better responders (red) showed significantly higher VTA overlap with the STN.
not prone to include false positive connections. It has the further advantage that smaller bundles (such as Edinger’s comb system, ansa lenticularis, lenticular fascicle, etc.) are included (which are generally not well represented in dMRI datasets but are likely functionally important).

It is crucial to reiterate that the discriminative fibers method does not test for significance of isolated tracts. It performs mass-univariate T-tests and hence leads to alpha error accumulation. We recommend to disregard p-values in this context altogether and Lead group will not display those anywhere. T-values should be seen as weights of how discriminative each bundle may be (relative to other bundles). To statistically validate the isolated tracts, we propose to use the results to predict out-of-sample data. This could be data from a second cohort or applied in context of a cross-validation (k-fold or leave-one-out validation) strategy. A graphical user-interface that facilitates these analyses is soon to be released and we currently supply example scripts within the Lead-DBS package (see walkthrough tutorial). An example of how results of this analysis could be informed on one cohort to predict clinical improvement in a second one may be found in Li et al. (2020). In the present case, leave-one-out cross-validation was performed to test for significance of the overall result ($R = 0.27$ at $p = 0.02$ between empirical improvement values and fiber-score overlap with the tract).

4. Discussion

Neuroimaging methods are, without any doubt, inevitable to advance Deep Brain Stimulation. Not only can they assist surgical targeting, but also post-operative analyses of DBS effects and to gain added knowledge about functional neuroanatomy. Here, we present a freely-available open-source toolbox that was designed to carry out neuroimaging-based DBS research on a group level. Although our own development focused on patients undergoing DBS with chronically-implanted electrodes, Lead group was used to localize stereotactic intracranial EEG (iEEG) electrodes in first studies, as well (Chaitanya et al., 2020; Toth et al., 2019; Wang et al., 2020; Ren et al., 2020).

To demonstrate the functional repertoire of Lead group, we analyze a retrospective cohort of 51 PD patients that underwent DBS surgery to the STN. This example application of Lead group led to results that were mostly confirmatory in nature but give a comprehensive picture of optimal DBS placement in the STN to treat PD. Specifically, our analyses confirm that an optimal DBS target resided within the dorsolateral STN.

4.1. Neuroimaging and DBS

The use of neuroimaging in the field of DBS has a long-standing history with x-ray and myelography applications as early examples. With the rise of MRI and CT modalities, it became standard to include neuroimaging data into the clinical procedure. For instance, Hariz and colleagues published a paper that reported use of T2-weighted MRI for pre- and postoperative imaging in a time at which most centers still used indirect targeting on T1-volumes or ventriculography (Hariz et al., 2003).

The rise of MRI and CT made it possible in numerous work to report on electrode placement in individual patients (e.g. Krause et al., 2015; Laxton et al., 2010b for examples). However, while screenshots of post-operative imaging serve the purpose of confirming electrode placements, they do not make them comparable to other patients and centers, in a standardized way.

Instead, when using normalized and model-based electrode reconstructions in a stereotactic space, electrode placement may be
Fig. 9. Discriminative fibers. In panels A&B, tracts that are most positively associated with clinical improvement, are isolated from all whole-brain fibers of a normative connectome and colored by their T-value. Fibers with strongest discriminative value pass from the motor and premotor cortices via the internal capsule to the STN. SMA (dark blue) and preSMA (light blue) defined by the HMAT atlas (A). Within the STN (B), most discriminative fibers (shown from posterolateral) traverse within the internal capsule and seem to branch off to the STN in a similar fashion as the hyperdirect pathway (e.g. compare to Figs. 2-4 in Coude et al., 2018 and panel C). Please note that the hyperdirect pathway is implemented by collaterals of axons that pass by the STN. The connectome analysis seems to reveal collaterals only. The main branches of the axons that pass by the STN, which we know exist, are manually drawn in with dashed white lines. In panel C, the same analysis was repeated. Instead of a normative connectome, the holographic tract atlas by Petersen et al., 2019 was used. By doing so, the hyperdirect pathway emerges as the most discriminative tract (over all structures represented in the atlas), as well (beyond hyperdirect pathway fibers, a few connecting STN and the pallidum are also displayed).

characterized in a more transferable and objective fashion. This concept has been used for a while now and is not exactly novel (e.g. Buxton et al., 2011; Eisenstein et al., 2014; Frankemolle et al., 2010; Maks et al., 2009; Nowinski et al., 2005). While the neuroimaging field (mostly driven by the fMRI literature) largely converged on reporting results in a space defined by the Montreal Neurological Institute (MNI space), most of the functional neurosurgery literature expressed results in functional coordinates that are relative to the anterior and posterior commissure (AC/PC; see (Horn et al., 2017a) for an overview). This approach has strong limitations because it does not take patient-specific anatomical variability into account (Horn et al., 2017a; Nestor et al., 2014). The Mayberg group may have been among the first to clinically adopt use of the MNI space for DBS localizations, potentially because surgical targets for depression resided more distant to the AC/PC (leading to larger errors) and because modern imaging modalities like fMRI, diffusion MRI and PET formed elementary components of their pioneering research (Choi et al., 2015; Riva-Posse et al., 2017, 2014).

4.2. A tool to shift DBS imaging research to a group level

Despite aforementioned examples that showed the promise of group localizations, an open-source software capable of performing these analyses has not been developed (while a commercial solution is available in form of the CranialCloud software; D’Haese et al., 2015). Lead-DBS and Lead group were specifically designed to perform group analyses in the field of DBS imaging and have empowered a growing number of peer-reviewed articles (see https://www.lead-dbs.org/about/publications/). Examples that used group statistics span across different diseases like PD (Bouthour et al., 2019; Horn et al., 2019c), essential tremor (Al-Fatly et al., 2019; Kroneberg et al., 2019), Dystonia (Neumann et al., 2017), Meige syndrome (Yao et al., 2019), OCD (Baldermann et al., 2019b; Huys et al., 2019; Li et al., 2020), epilepsy (Middlebrooks et al., 2018; Wang et al., 2019), Tourette’s Syndrome (Neumann et al., 2018a) or refractory thalamic pain syndrome (Levi et al., 2019). Using Lead-DBS, a sweet spot for STN-DBS in PD was defined and used to predict improvement of motor symptoms in out-of-sample data (Dembek et al., 2019a). Different subregions of the STN were associated with different non-motor outcomes by exploring local DBS effects (Petry-Schmelzer et al., 2019). Side-effects, such as depression (Irmen et al., 2020), hyperhidrosis (Yang et al., 2019) or ataxia and dystarthisia (Al-Fatly et al., 2019) have been mapped to anatomy using Lead group. In a sample of epilepsy patients implanted for DBS to the anterior nucleus of the thalamus (ANT), functional connectivity seeding from the VTAs was analyzed with respect to clinical response, using a normative connectome (Middlebrooks et al., 2018). A different study applied Lead group to investigate a novel parietal surgical approach for ANT-DBS in epilepsy (Wang et al., 2019). In another recent study, resting-state functional MRI was acquired in PD patients while DBS was switched on and off (Horn et al., 2019c). Here, DBS was able to shift functional connectivity profiles towards the ones observed in healthy controls. Focusing on a different analysis path, electrophysiological measures recorded from the LFP-signal of STN-DBS electrodes were mapped to subcortical anatomy of the human brain (Horn et al., 2017b). This confirmed that elevated beta-power was predominantly expressed within the sensorimotor functional zone of the STN, a finding that was reproduced and extended by two different teams again using Lead group (Geng et al., 2018; van Wijk et al., 2017). The concept is now referred to as subcortical electro-physiology mapping (see https://lead-dbs.org/helpsupport/knowledge-base/lead-dbs-methods/subcortical-electrophysiology-mapping-semt-for-a-primer) and was applied in further studies (Lofredi et al., 2018; Neumann et al., 2017; Tinkhauser et al., 2019).

The ability to nonlinearly map electrodes of patient cohorts into a comparable and well-defined space also led to the possibility of exploring subtle differences in their brain connectivity profiles. After pioneering work that applied commonly available pipelines from the neuroimaging field or commercial tools (Akrain et al., 2018; Vanegas-Arroyave et al., 2016), Lead group was further improved to perform such analyses, as well (Horn et al., 2017a). Since then, the tool has empowered research that explored optimal connectivity profiles in PD (Horn et al., 2017c; Irmen et al., 2020), OCD (Baldermann et al., 2019b, 2019c; Li et al., 2020) and Essential Tremor (Al-Fatly et al., 2019).

Extending this line of research, it was used to relate connectivity profiles seeding from DBS electrodes to behavioral instead of clinical changes induced by DBS. For instance, Neumann et al. showed that
specific connections of the electrodes would lead to changes in movement velocity vs. reaction times in a motor task (Neumann et al., 2018b).

De Almeida showed that functional connectivity between STN-DBS electrodes and a specific site in the ipsilateral cerebellum was associated with partly restoring motor learning in PD patients (de Almeida Marcelino et al., 2019). Finally, focusing on localized instead of connectivity-mediated effects, Irmen et al. showed that modulating specific subregions of the STN could restore risk-taking behavior to a level observed in healthy controls (Irmen et al., 2019).

From a methodological standpoint, one consideration is often problematic when investigating DBS effects using neuroimaging. Namely, often, a single score (e.g. improvement in quality of life) is of interest but two stimulation sites (left and right electrodes) were active. In other words, if hemiscores (such as left and right tremor improvement) are not available, there is no clear optimal way of how to relate stimulation location to clinical effects. One option is to mirror VTAs and treat the joint (e.g. left and mirrored right) volume as a single “modulated volume”. This is sensible in case of assumed symmetry of effects. Alternatively, each VTA can be considered separately and could be tagged by the same score. This leads to more complex statistics and, less optimally, repeated entries of the same score. In the present manuscript, we chose to mirror results to one hemisphere but must emphasize that there is no single optimal way to solve this issue (since it will remain unknown which of the two electrodes or whether both of them led to observed effects). If asymmetry of stimulation effects is assumed, behavioral paradigms could be optimized to capture these relationships (e.g. by turning on single electrodes and observing effects separately).

4.3. Optimal placement in STN-DBS for treatment of PD

While above results demonstrate general benefits of a DBS imaging group level tool, results obtained from the example cohort in the present manuscript should be set into scientific context, as well.

In summary, our results confirm previous findings, that the stimulation of the STN, and more precisely its dorsolateral part is linked to UPDRS-III improvement (e.g. Caire et al., 2013). As mentioned above, this finding is not novel. In fact, recent studies that were carried out by four centers, each using three different methodologies, converged on almost the exact same optimal target coordinate (Akram et al., 2017; Bot et al., 2018; Horn et al., 2019a; Nguyen et al., 2019; for a review see Horn, 2019).

One of those studies used commercial software (Akram et al., 2017), one a method that directly builds upon the imaging data in native patient space (Bot et al., 2018) and the third and fourth used Lead group (Horn et al., 2019a; Nguyen et al., 2019). Moreover, the three latter studies were able to significantly explain variance in clinical improvement by measuring distance from each DBS electrode to the optimal coordinate. This illustrates that the precision of DBS imaging research has evolved to become useful, after a list of earlier studies had partly shown conflicting results (Horn, 2019). Despite strong evidence for an association between optimal electrode placement and DBS efficacy, it is out of question, that variance in electrode placement cannot entirely explain variance in clinical outcome.

Our results further showed that treatment success was positively associated with structural connectivity to preSMA and PMv. These results did not survive corrections for multiple comparisons but are in line with previous results (Akram et al., 2017; Horn et al., 2017c; Vanegas-Arroyave et al., 2016). Here, we elaborate on this finding by isolating a specific fiber bundle that seems to be associated with clinical improvement.

4.4. Limitations

Mapping DBS electrodes to a group template inherently comes with a loss of precision and a multitude of related problems and limitations. Already beginning within the patient’s own space, brain shift introduces non-linear displacements between postoperative and preoperative scans, favoring the use of postoperative MRI, which makes it possible to directly visualize both the electrode and target structure in the same space (Hariz et al., 2003). This problem can partly be overcome by applying brain shift correction (Horn et al., 2019a) as applied here, but a residual error should be assumed to remain, especially in patients with large pneumocephalus volumes (Lee et al., 2010).

Errors in localizing DBS electrodes themselves may potentially introduce a greater source of bias than could be assumed. To this end, Lead-DBS has incorporated a phantom-validated algorithm for automatic localizations based on post-operative CT volumes (Husch et al., 2018) as well as a multitude of manual refinement and control views. Still, empirical data on observer-dependencies or inter-rater errors of electrode localizations with Lead-DBS are lacking (such a study is currently underway). Non-linearly warping electrodes into template space introduces an additional bias that cannot be completely overcome. Based on experience when visualizing the same patient in native and MNI space and comparisons with results from other tools, we are confident that localizations in MNI space are meaningful, since they have been used to explain (Horn et al., 2019a; Joutsa et al., 2018; Yao et al., 2019) or even predict (Al-Fatly et al., 2019; Baldermann et al., 2019; Horn et al., 2017a) significant amounts of variance in clinical improvements in a number of studies.

However, the amount of error introduced by nonlinear registrations remains unclear. When analyzing cohorts in Lead group, it is important that the co-registration, normalization, brain shift correction and electrode reconstruction steps of each single patient are meticulously controlled for processing inaccuracies or errors. Lead-DBS (which is used for these steps) includes multiple control views to make sure that the steps led to accurate results (the three options marked in green in the GUI).

Furthermore, we continue work on additional ways to improve accuracy in almost all parts of this pipeline. Some validation studies of electrode localizations in standard space were carried out using electrophysiology by various groups (Horn et al., 2017b; Neumann et al., 2017; Nowacki et al., 2018; Rappel et al., 2019; Tinkhauser et al., 2019; van Wijk et al., 2017). For instance, agreement between electrophysiology-defined and atlas-defined boundaries in standard space showed high agreement across 933 microelectrode recording trajectories when localizing recording-sites using Lead-DBS (Rappel et al., 2019). Still, even if reconstructions in MNI space are meaningful, we must assume a slight bias since by definition, nonlinear registrations will always introduce inaccuracies. Of note, the exact same bias applies when instead warping atlas structures from template to native space (since most modern registration strategies are diffeomorphic;Avants et al., 2008). Over the last decade, we aimed at minimizing this nonlinear error by introducing various concepts ranging from multi-step linear transforms (Schönecker et al., 2009) over the introduction of multiple algorithms (Ewert et al., 2018; Horn et al., 2019a, 2017a, 2017b; Horn and Kühn, 2015) to the current multispectral default method that was empirically validated in two studies by different groups (Ewert et al., 2019; Vogel et al., 2020). Further methodological work such as the possibility to manually refine warp-fields has been published and implemented in Lead-DBS/Lead group (Eddow et al., 2019) but was not yet applied in the present work. Despite these efforts that may minimize bias introduced by warping electrodes to template space, these can likely never be overcome completely. Thus, the gold-standard for localizing DBS electrodes will always remain in native patient space, when the research questions we ask allow us to do so. A further limitation of Lead-DBS and Lead group is the accuracy of the implemented VTA models. While our pipeline includes the only finite element model based VTA model that is available in an industry pipeline, more secure models have been described in the literature (Chaturvedi et al., 2013; Gunalan et al., 2017). Lead-DBS uses a VTA model that thresholds the E-Field magnitude as this practice was suggested to yield good approximations by others (Astroim et al., 2015).

However, recent results by leading groups in this field suggested significant limitations of the approach (Duffy et al., 2019; Gunalan et al., 2017). Moreover, limitations apply to the concept of the VTA itself. Namely, it is impossible to represent the bioelectrical effects of DBS within...
a binary volume of any form. Such a representation cannot include information about which axons of which orientation, diameter or neurotransmitter types are modulated. While GABAergic neurons deplete by DBS almost immediately, Glutamatergic neurons do not (Steiner et al., 2019; Milesevic et al., 2018b) – leading to differential modulation effects (while recent evidence suggests that the DBS effect in the STN for PD is predominantly mediated by GABAergic neurons (Milesevic et al., 2018a)). Furthermore, models do not incorporate microscale anisotropy (while the use of macroscale anisotropy has been explored; Buxton et al., 2006) or heterogeneity of tissue (fluid-filled regions surrounding neurons and axons may lead to strong spreads of current; Sriperumbudur et al., 2018). This inherent limitation of representing DBS effects as a sphere has led to more advanced concepts such as pathway activation models (Gunalan et al., 2017) which have yet to enter the open-source software field to become broadly applicable (such developments are currently underway; Butenko et al., 2020).

Instead of analyzing DBS effects on an axonal/neuronal level, Lead group works on a voxel-level, to analyze connectomic DBS effects. Thus, it approaches modeling problems from a neuroimaging perspective – while others have approached it from a cellular modelling perspective. While this strategy has been useful to predict clinical and behavioral effects and it does not require a multitude of biophysical assumptions, it is limited in the potential predictions that it can theoretically make (Petersen et al., 2019).

A related limitation lies in the use of normative connectomes. While their utility could be shown to predict various clinical symptoms in out-of-sample data (Al-Fatly et al., 2019; Balderrmann et al., 2019b; Horn et al., 2017a, 2017c; Joutsa et al., 2018; Weigand et al., 2018), these datasets lack patient-specificity and should be seen as brain atlases of the wiring diagram of the human brain. And while atlases have been used in the field of DBS since the introduction of the Clarke-Horsley apparatus in 1906 (Clarke and Horsley, 1906), insights derived from atlases should be transferred to individual patients cautiously, if at all (Coenen et al., 2019). Moreover, diffusion-weighted imaging based tractography and resting-state functional MRI, the modalities usually applied for non-invasive connectivity mapping, are both highly derived and show a multitude of inherent problems that lead to a high number of false-positive and false-negative (Maier-Hein et al., 2017; Petersen et al., 2019) results.

Furthermore, it has to be pointed out, that the statistical methods within Lead group are currently limited to univariate tests. This was a deliberate choice since Lead group is not meant to replace statistical software needed for more complex analyses. To do so, results can be easily exported and carried out externally (see info box page 6 in the walkthrough tutorial).

In sum, limitations in precision – from registrations and localizations in native space, warping bias in template space and limitations of applied biophysical models and connectomes – add up and make DBS imaging research challenging, especially so on a group level. Strategies to reduce bias include i) acquiring high-quality multimodal preoperative MRI data, ii) accurate postoperative imaging, iii) care- and skillful analysis and meticulous data control in every step of the pipeline and iv) cautious interpretation of results. Over the years, we have identified typical pitfalls and included control views, correction tools and mediation strategies to reduce bias wherever possible throughout the Lead-DBS software package.

5. Conclusions

We present a novel open-source toolbox that is designed to shift deep brain stimulation imaging to a group-level. We show utility of the toolbox by presenting largely confirmatory results in a cohort of Parkinson’s Disease patients that underwent deep brain stimulation surgery to the subthalamic nucleus. Specifically, we validate an optimal target within this nucleus that has conclusively been described by four independent groups within the past two years. Furthermore, we show connectivity profiles and a specific tractogram that were associated with good clinical outcome in our analyses. Finally, we discuss findings and applications of group-level deep brain stimulation imaging while making aware of a multitude of limitations that apply to this strand of research.

Data availability statement

The aggregated dataset in form of a Lead-Group project used to create figures and analyses is openly available (https://osf.io/kj456/). Raw data (patient MRI and postoperative CTs) cannot be openly shared because it contains patient information. All code used to analyze data presented in the present manuscript is openly available within the Lead-DBS software suite (https://github.com/netstim/leaddbs; https://www.lead-dbs.org/). A step-by-step instruction manual to reproduce findings is available in the supplementary data of the present manuscript.

Declaration of competing interest

A.A.K. has received honoraria as speaker for Boston Scientific, Abbott and Medtronic, not related to the current work. A.H. has received speaker honoraria for Boston Scientific and Medtronic, not related to the current work.

CRediT authorship contribution statement

Svenja Treu: Writing - original draft, Visualization, Formal analysis, Investigation. Bryan Strange: Writing - review & editing, Funding acquisition. Simon Oxenford: Methodology, Visualization. Wolf-Julian Neumann: Supervision, Writing - review & editing. Andrea Kühn: Resources, Funding acquisition, Writing - review & editing. Ningfei Li: Software, Methodology, Visualization. Andreas Horn: Conceptualization, Software, Methodology, Visualization, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Acknowledgement

This study was supported by the German Research Foundation (DFG grant SPP2041, “Clinical connectomics: a network approach to deep brain stimulation” to AKK as well as Emmy Noether Grant 410169619 to AH) and an FPI Predoctoral Fellowship (BES-2016-079470) to ST.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.117018.

References

Akram, H., Dayal, V., Mahlknecht, P., Georgiev, D., Hyam, J., Folytine, T., Limouzin, P., De Vita, E., Jahanshahi, M., Ashburner, J., Behrens, T., Hartig, M., Zrinzo, L., 2018. Connectivity derived thalamic segmentation in deep brain stimulation for tremor. NeuroImage Clin. https://doi.org/10.1016/j.nicl.2018.01.008.
Akram, H., Georgiev, D., Mahlknecht, P., Hyam, J., Folytine, T., Limouzin, P., Jahanshahi, M., Hartig, M., Zrinzo, L., Ashburner, J., Behrens, T., Sotropoulos, S.N., Jbabdi, S., De Vita, E., 2017. Subthalamic deep brain stimulation sweet spots and hyperdirect cortical connectivity in Parkinson’s disease. Neuroimage. https://doi.org/10.1016/j.neuroimage.2017.07.012.
Al-Fatly, B., Ewert, S., Kühler, D., Kroneberg, D., Horn, A., Kühn, A.A., 2019. Connectivity profile of thalamic deep brain stimulation to effectively treat essential tremor. Brain 142, 3086–3098. https://doi.org/10.1093/brain/awz236.
Ahniet, Y., Alkhalfan, F., Qiao, N., Velimirovic, M., 2019. Outcomes in lesion surgery versus deep brain stimulation in patients with tremor: a systematic review and meta-analysis. World Neurosurg. https://doi.org/10.1016/j.wneu.2018.11.175.
Ashburner, J., 2012. SPM: a history. NeuroImage 62, 791–800. https://doi.org/10.1016/j.neuroimage.2011.10.025.
Åstrand, M., Diczfoly, E., Martens, H., Wårdell, K., 2015. Relationship between neural activation and electric field distribution during deep brain stimulation. IEEE Trans. Biomed. Eng. https://doi.org/10.1109/TBME.2014.2363494.
Avants, B.B., Epstein, C.I., Grossman, M., Gee, J.C., 2008. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly
and neuroendogenative brain. Med. Image Anal. https://doi.org/10.1016/j.medimag.2021.07.004.

Baldner, M., Z., Hablu, M., Dembek, T.A., Kohl, S., Kuhn, J., Visser-Vandewalle, V., Horn, A., Hu, Y., 2019a. Weight change after striatal/capsule deep brain stimulation relates to connectivity of the bed nucleus of the stria terminalis and hypothalamus. Brain Sci. https://doi.org/10.3390/brainsci9010026.

Baldner, M., Z., Melzer, D., Hablu, M., Kohl, S., L., Tintermeyer, M., Hu, Y., Visser-Vandewalle, V., Kühn, A.A., Horn, J., Kuhn, J., 2019b. Connectivity profile predictive of effective deep brain stimulation in obsessive compulsive disorder. Biol. Psychiatry. https://doi.org/10.1016/j.biopsych.2018.12.019.

Banisadr, M., Proverbio, D., Goncalves, J., Hertel, F., Husch, A., 2020. FastField: an open-source toolbox for efficient approximation of deep brain stimulation electric fields. bioRxiv 15 (2). https://doi.org/10.1101/2020.03.07.976462.aa14b-13.

Bertoli, A.L., Pollak, P., Schramm, D., Citterio, M., Horvat, M., Perret, J.E., de Roopveld, J.G., D.M., 1991. Long-term survival of tremor by modification of the vestibular intermedium thalamic nucleus. Lancet 337, 403–406. https://doi.org/10.1016/0140-6736(91)91717-T.

Bo, M., Schwenkreis, P., Onderkoenig, V.J.L., Veron, R., Contarino, F.M., De Bie, R., A.M.A., van den Munchop, F., 2018. Deep brain stimulation for Parkinson's disease: defining the optimal location within the subthalamic nucleus. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp-2017-316007.

Bourjou, W., Beréa, M., Kibler, A., Zacharia, A., Tomkova, Chauoi, E., Fleury, V., Benis, D., Momjian, S., Bally, J., Lüsecher, C., Krack, P., Burkhard, P.K.R., 2019. Dyskinesia-inducing lead contacts optimize outcome of subthalamic stimulation in Parkinson's disease. Mov. Disord. https://doi.org/10.1002/mds.27853.md27853.

Butenko, E., Bahl, C., Schröder, M., Kolding, R., van Rienen, U., 2020. OSS-DBS: Open-Source Simulation Platform for Deep Brain Stimulation with a comprehensive automated modeling. PloS Comput. Biol. (in press).

Butson, C.R., Cooper, S.E., Henderson, J.M., McIntyre, C.C., 2006. Predicting the effects of deep brain stimulation on neural diffusion tensor imaging. Neuroimage Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics). https://doi.org/10.1007/11867635.

Butson, C.R., Cooper, S.E., Henderson, J.M., Wolgumuth, A., McIntyre, C.C., 2011. Probabilistic analysis of activation volumes generated during deep brain stimulation. Neuroimage 54, 2096–2104. https://doi.org/10.1016/j.neuroimage.2010.10.059.

Caire, F., Ranoux, D., Guérard, D., Burbaud, P., Cuny, E., 2013. A systematic review of Bot, M., Schuurman, P.R., Odekerken, V.J.J., Verhagen, R., Contarino, F.M., De Bie, R., A.M.A., van den Munchop, F., 2018. Deep brain stimulation for Parkinson's disease: defining the optimal location within the subthalamic nucleus. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp-2017-316007.

Bouchard, J., Genest, M., Benra, A., Kühn, A.A., Welcome, F., Trottier, I., Wolski, V., Wolf, E., Hoevels, M., Visser-Vandewalle, V., Fink, G.R., Horn, A., Blankenburg, F., 2016. Toward a standardized structural-functional group classification of DBS target nuclei. Neuroimage 184, 586–598. https://doi.org/10.1016/j.neuroimage.2018.09.061.

Bo, M., Schwenkreis, P., Onderkoenig, V.J.L., Veron, R., Contarino, F.M., De Bie, R., A.M.A., van den Munchop, F., 2018. Deep brain stimulation for Parkinson's disease: defining the optimal location within the subthalamic nucleus. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp-2017-316007.

Bourjou, W., Beréa, M., Kibler, A., Zacharia, A., Tomkova, Chauoi, E., Fleury, V., Benis, D., Momjian, S., Bally, J., Lüsecher, C., Krack, P., Burkhard, P.K.R., 2019. Dyskinesia-inducing lead contacts optimize outcome of subthalamic stimulation in Parkinson's disease. Mov. Disord. https://doi.org/10.1002/mds.27853.md27853.

Butenko, E., Bahl, C., Schröder, M., Kolding, R., van Rienen, U., 2020. OSS-DBS: Open-Source Simulation Platform for Deep Brain Stimulation with a comprehensive automated modeling. PloS Comput. Biol. (in press).

Butson, C.R., Cooper, S.E., Henderson, J.M., McIntyre, C.C., 2006. Predicting the effects of deep brain stimulation on neural diffusion tensor imaging. Neuroimage Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics). https://doi.org/10.1007/11867635.

Butson, C.R., Cooper, S.E., Henderson, J.M., Wolgumuth, A., McIntyre, C.C., 2011. Probabilistic analysis of activation volumes generated during deep brain stimulation. Neuroimage 54, 2096–2104. https://doi.org/10.1016/j.neuroimage.2010.10.059.

Caire, F., Ranoux, D., Guérard, D., Burbaud, P., Cuny, E., 2013. A systematic review of Bot, M., Schuurman, P.R., Odekerken, V.J.J., Verhagen, R., Contarino, F.M., De Bie, R., A.M.A., van den Munchop, F., 2018. Deep brain stimulation for Parkinson's disease: defining the optimal location within the subthalamic nucleus. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp-2017-316007.

Bouchard, J., Genest, M., Benra, A., Kühn, A.A., Welcome, F., Trottier, I., Wolski, V., Wolf, E., Hoevels, M., Visser-Vandewalle, V., Fink, G.R., Horn, A., Blankenburg, F., 2016. Toward a standardized structural-functional group classification of DBS target nuclei. Neuroimage 184, 586–598. https://doi.org/10.1016/j.neuroimage.2018.09.061.

Bo, M., Schwenkreis, P., Onderkoenig, V.J.L., Veron, R., Contarino, F.M., De Bie, R., A.M.A., van den Munchop, F., 2018. Deep brain stimulation for Parkinson's disease: defining the optimal location within the subthalamic nucleus. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp-2017-316007.

Bourjou, W., Beréa, M., Kibler, A., Zacharia, A., Tomkova, Chauoi, E., Fleury, V., Benis, D., Momjian, S., Bally, J., Lüsecher, C., Krack, P., Burkhard, P.K.R., 2019. Dyskinesia-inducing lead contacts optimize outcome of subthalamic stimulation in Parkinson's disease. Mov. Disord. https://doi.org/10.1002/mds.27853.md27853.

Butenko, E., Bahl, C., Schröder, M., Kolding, R., van Rienen, U., 2020. OSS-DBS: Open-Source Simulation Platform for Deep Brain Stimulation with a comprehensive automated modeling. PloS Comput. Biol. (in press).

Butson, C.R., Cooper, S.E., Henderson, J.M., McIntyre, C.C., 2006. Predicting the effects of deep brain stimulation on neural diffusion tensor imaging. Neuroimage Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics). https://doi.org/10.1007/11867635.

Bo, M., Schwenkreis, P., Onderkoenig, V.J.L., Veron, R., Contarino, F.M., De Bie, R., A.M.A., van den Munchop, F., 2018. Deep brain stimulation for Parkinson's disease: defining the optimal location within the subthalamic nucleus. J. Neurol. Neurosurg. Psychiatry. https://doi.org/10.1136/jnnp-2017-316007.
