The impact of modern-day neuroimaging on the field of deep brain stimulation

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List of abbreviations

ASI	Anisotropic Scattering Imaging
DBS	Deep Brain Stimulation
DRTT	Dentatorubrothalamic tract
ET	Essential Tremor
GPi/GPe	internal/external pallidum
M1	Primary motor cortex
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
OCD	Obsessive Compulsive Disorder
PET	Positron Emmision Tomography
PD	Parkinson's Disease
PFC	Prefrontal córtex
PLI	Polarized Light Imaging
SN	Substantia Nigra
STN	Subthalamic Nucleus
SMA	Supplementary Motor Area
VTA	Volume of Tissue Activated

Abstract

Purpose of review: Deep brain stimulation is an established but growing treatment option for multiple brain disorders. Over the last decade, electrode placement and their effects were increasingly analysed with modern-day neuroimaging methods like spatial normalization, fibertracking or resting-state functional magnetic resonance imaging. Similarly, specialized basal ganglia MRI sequences were introduced and imaging at high field strengths becomes increasingly popular.

Recent findings: To facilitate the process of precise electrode localizations, specialized software pipelines were introduced. By those means, deep brain stimulation targets could recently be refined and significant relationships between electrode placement and clinical improvement could be shown. Furthermore, by combining electrode reconstructions with network imaging methods, relationships between electrode connectivity and clinical improvement were investigated. This led to a broad series of imaging-based insights about deep brain stimulation that are reviewed in the present work.

Summary: The reviewed literature makes a strong case that brain imaging plays an increasingly important role in deep brain stimulation targeting and programming. Furthermore, brain imaging will likely help to better understand the mechanism of action of deep brain stimulation.

Keywords: Deep brain stimulation, Parkinson's disease, movement disorders, dystonia, essential tremor, diffusion-weighted imaging, tractography, functional magnetic resonance imaging, basal ganglia.

Introduction

Deep brain stimulation (DBS) is an established treatment option that leads to significant improvement of motor symptoms in movement disorders like Parkinson's Disease (PD), dystonia and Essential Tremor (ET) [1,2]. DBS was further investigated in context of obsessive compulsive disorder (OCD), depression, Tourette's syndrome, Huntington's disease, addiction, Alzheimer's disease, pain and other brain disorders.

DBS electrodes are surgically implanted into deep structures of the brain which are usually small in size and often surrounded by a complex anatomical architecture ([3]). However, for effective symptom reduction, electrodes need to be placed precisely – not only within the target nucleus but often even within its correct functional *subzone*. Misplacement of electrodes by merely two millimeters may result in poor clinical improvement [3,4]. This combination of i) small targets with ii) complex anatomy and iii) the need for absolute precision poses novel challenges to neuroimaging field.

However, addressing these challenges is promising on various levels (fig. 1). First, as mentioned, therapeutic results are dependent on electrode placement [3-7]. Finding optimal "sweet spot" targets has been an ongoing endeavor for over a decade [4,6-15]. Second, DBS bears the unique opportunity to record signals from deep brain structures in the living human brain [16]. Mapping such signatures and responses to anatomy completes the picture of when, how and *where* they are expressed [17-23]. Third, electrode localizations may uncover the impact of DBS on distributed brain networks. Electrodes with a more lateral position have different connectivity profiles than the ones placed more medially. Researchers have begun to ask the question of how a DBS electrode *should* be connected to distant regions to yield maximal benefit [13,24-28].

The present review aims at discussing the current state of the art, primarily focusing on the last 12-18 months. First, *local* relationships between the actual electrode position and brain signatures, clinical outcomes or behavioral effects are discussed. Second, studies about *network* properties of DBS electrodes are discussed.

DBS Imaging: General methodological considerations

Software solutions for DBS imaging

To meet the high demand in precision for meaningful DBS electrode reconstructions, specialized software suites were developed. The cicerone platform [29] was a first freely available research tool later commercialized in form of the Boston Scientific Guide software. A similar system was developed at Vanderbilt University and commercialized by the Medtronic company under the name Optivize. These early products are discontinued while a spinoff of the latter remains commercially available as the Neurotargeting LLC CranialCloud software. The first open-source application, Lead-DBS, was introduced in 2014 ([30], www.lead-dbs.org) and is still under active development [3]. A second open-source application was published under the name DBSproc [31]. In addition, several commercial applications were developed by Brainlab, Medtronic, Boston Scientific and Neurotargeting LLC. These are targeted for clinical use and may lack the flexibility, transparency and reproducibility required for academic research. However, their solutions are certified for clinical use and generally more user-friendly – i.e. ideal solutions for clinical work.

Specialized MRI sequences for basal ganglia imaging & ultra-highfield imaging

To achieve a proper definition of *DBS electrode* placement, high resolution *post*operative imaging is needed. However, given excellent signal-to-noise (electrodes vs. brain) and resolution of commonly available CT scans, this part of the imaging pipeline is generally well covered. Instead, a good definition of surrounding *anatomy* is based on *pre*operative MRI. Since target structures are small and complex, enhancing contrast and resolution is key. For instance, the internal part of the pallidum (GPi) is divided from the external pallidum (GPe) by the internal medullary lamina. Visualizing this lamina is already challenging, but the GPi is even further subdivided into medial and lateral parts by the *accessory* medullary lamina. Whether this structure plays a functional role in mediating DBS outcome is unknown – but could be investigated with increasing precision of DBS imaging. A similar structure of potential relevance is Edinger's comb – a fanned out body of fibers and cells that connects the striatopallidofugal system with both STN and substantia nigra. These exemplary structures are invisible on common MRI but *can* be visualized using specialized MRI hardware and sequences [32,33]. Thus, a focus on *pre*operative imaging could lead to enhanced precision of DBS localizations. For this purpose, specialized basal ganglia sequences were introduced. Quantitative susceptibility mapping (QSM) is a technique that measures a mix of absolute iron and other concentrations on gradient echo sequences [34]. The method is helpful to visualize STN, pallidum, red nucleus and substantia nigra given their iron content [33,35-37]. QSM maps are usually calculated post-hoc on phase and magnitude acquisitions (see https://github.com/mathieuboudreau/qsm-tools for software packages). In contrast, Fast Gray

Matter Acquisition T1 Inversion Recovery (FGATIR) is a normal MRI sequence producing readily usable acquisitions with excellent contrast of the pallidum and its laminae [38]. Software like Lead-DBS is able to define subcortical anatomy using multiple preoperative MRI sequences simultaneously. It was shown that including T1, T2- and proton density weighted acquisitions to the process is better than using either alone [39]. Including specialized sequences may further improve results [3].

Finally, the use of ultra-highfield MRI (7T and above) was promoted for use in preoperative imaging [40-42]. This would make it possible to investigate obscure structures like the aforementioned ones [32]. Downsides are cost, poorer availability larger field distortions that could introduce a different type of bias.

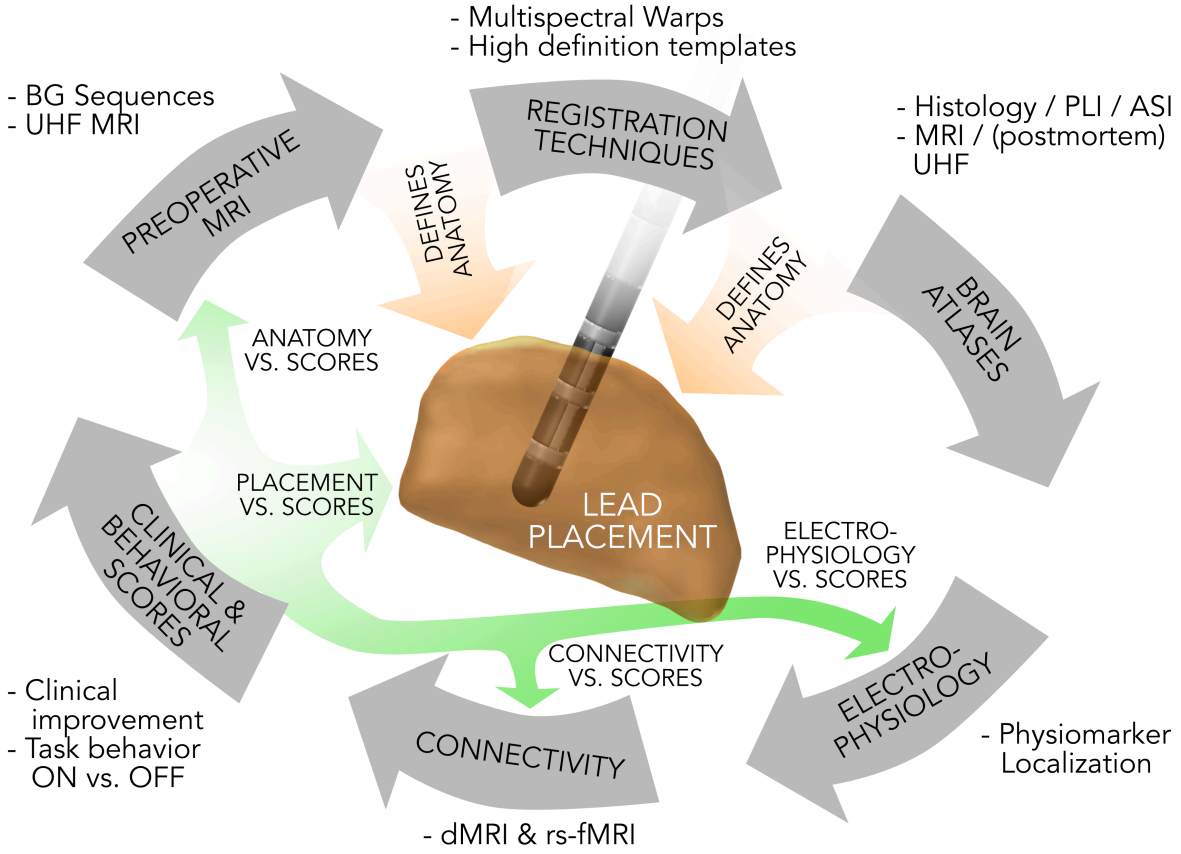

Fig. 2: Overview of the components of DBS imaging and the central role of reconstructing DBS electrode placements. Top components (preoperative MRI, registration techniques and brain atlases) define the exact location of anatomical structures. Postoperative CT or MRI define lead placement (not shown). Clinical and behavioral scores serve another crucial role that may be related to lead placement, brain connectivity, electrophysiology or preoperative MRI (green arrow). The latter (e.g. relating cortical atrophy patterns to DBS outcome) is not covered in this review but shown in the figure for completeness. Abbreviations: BG: basal ganglia, UHF MRI: ultra-highfield MRI, PLI: Polarized Light Imaging, ASI: Anisotropic Scattering Imaging.

DBS Imaging on the local level

In this chapter, the relationship between DBS electrode placement and clinical, electrophysiological and behavioral effects are reviewed.

Electrode placement vs. clinical outcomes

The most obvious use-case of DBS imaging is to relate electrode placement to clinical improvement. In PD, a multitude of such retrospective studies were published over the last decade (e.g. [3,4,6,8-11,43-50]).

Of those, some concluded that the optimal stimulation site should be dorsal to [6,8] or posterior to the STN, i.e. within the caudal zona incerta [46,47]. The remaining majority favored a sweet spot *within* dorsolateral STN [3,4,9-11,43-45,48,49]. Most of the early work yielded nonsignificant results and was often based on a low N of around ten patients. Two studies that did report significant relationships were not conclusive if even contradictory: In one, UPDRS-III improvement correlated with right hemispheric *anterioposterior* (Y-axis) contact location [48], in the other with *mediolateral* contact location (X-axis) [11]. Two recent studies applied a different concept and measured distance between a predefined "sweet spot" and centers of active DBS contacts (fig. 1). The first defined the sweet spot based on the cohort's own top-responders [4]. The closer the active contacts (N = 65 electrodes) resided to this point, the better the clinical improvement ($R = 0.52$, $p < 0.01$). The second study [3] used an N of 102 electrodes to validate a meta-analytically defined sweet spot [49]. Again, proximity of active DBS contacts to this spot correlated with clinical improvement ($R = 0.47$, $p = 0.001$) [3]. Crucially, the spots in these studies were virtually identical and may represent the best target definition available to date (fig. 2). This target resided in the center of the STN, potentially within the sensorimotor functional zone of the nucleus [51-53] (MNI coordinates: x = ±12.58, y = -13.41, z = -5.87 mm [14]; functional coordinates: ±12.02 mm lateral, 1.53 mm posterior and 1.91 mm below the midcommissural point [49]). The study by Horn and colleagues (2019) further showed that overlaps between VTA and STN volumes were equally predictive of clinical improvement ($R = 0.54$ at $p < 10^{-4}$; [3]). By including additional clinical co-variates, half the variance in clinical outcome could be explained ($R^2 = 0.51$ at $p < 0.001$; RMSE 15 %-UPDRS-III improvement).

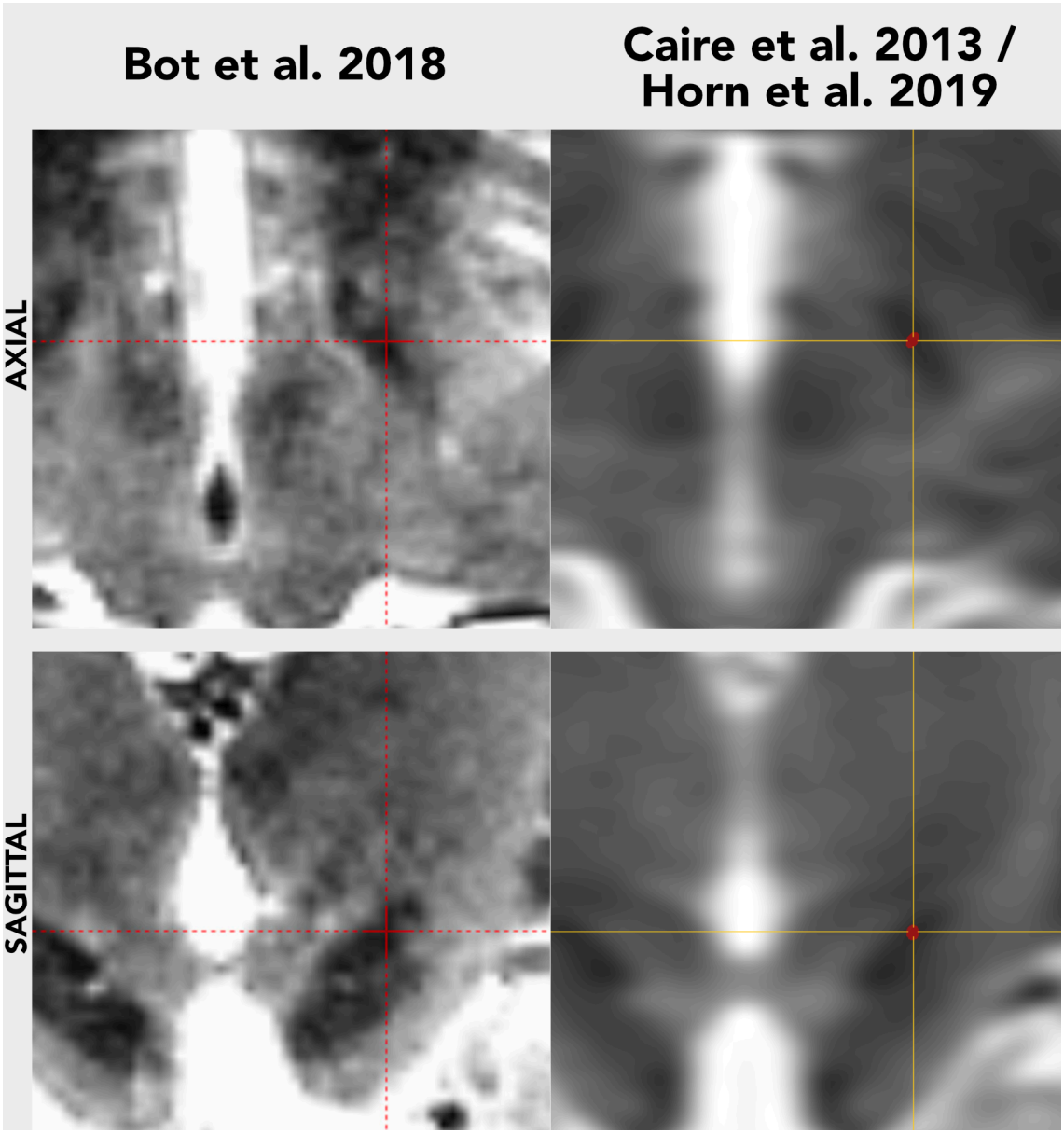

Fig. 2: Optimal stimulation sites for PD STN-DBS that were able to explain clinical improvement in two independent studies. The right-handed sweet spot was originally defined in the meta-analysis by Caire et al. 2013 and converted into MNI space in Horn et al. 2017. Proximity to this point correlated with %-UPDRS-III improvements (N = 102 electrodes, R = 0.47, p = 0.001). A virtually identical sweet spot was defined by Bot et al. 2018 that showed the same property (N = 65 electrodes, R = 0.52, p < 0.01). Views on the left side modified from Bot et al. 2018.

In other diseases, relationships between electrode placement and improvement were less studied so far (see [14] for an overview). For dystonia, one study defined an optimal target at 20.0 mm lateral, 5.8 mm anterior and 0.5 mm below the midcommissural point [54]. This coordinate was converted to an MNI coordinate at x = ±22.37, y = -5.57 and z = -4.97 mm in [14]. A very similar optimal target was defined at MNI coordinates of x = ±20.58, y = -6.56 and z = -4.84 mm for the right and x = -20.13, y = -

6.79 and z = -5.38 mm for the left hemisphere based on % improvement on the Toronto Western Spasmodic Torticollis Rating (TWSTR) score in 20 cervical dystonia patients [5]. The largest multicenter trial so far used a novel method to predict clinical outcome based on VTA overlaps with a probabilistic sweetspot volume [55]. Authors were able to explain 53% of the variance in motor score improvement. Here, the optimal stimulation site did not differ for cervical and generalized dystonia and resided within the ventroposterior GPi and adjacent subpallidal white matter.

For essential tremor, a study defined an optimal target 12.8 mm lateral to, 5.7 mm posterior to and 0.8 mm above the midcommissural point [56]. Dembek and colleagues used probabilistic mapping of VTAs to define an optimal point of tremor suppression along the inferior border of the VIM and within the adjacent white matter (i.e. the rostral zona incerta) [7].

Electrode placement vs. electrophysiological signatures

Increased beta synchrony in the STN has been linked to PD symptom severity (e.g. [16,57]). Similarly, increased theta synchrony was associated with dystonic symptom severity [20]. Using electrode localizations, it became feasible to determine *where* such physiomarkers are predominantly expressed. A first study located elevated beta power in PD to the sensorimotor functional zone of the subthalamic nucleus [17]. This was promptly reproduced and extended by different groups [18,19]. The approach was then applied to localize elevated theta synchrony recorded in the pallidum of dystonia patients [20] and gamma oscillations recorded during movement in PD [21]. Such studies combine electrophysiological findings with DBS imaging and may describe and refine target regions by means of electrophysiology. Their results largely converged with clinically defined sweet spot studies mentioned in the last paragraph (e.g. [3,4,17] for PD and [5,20,54] for dystonia).

Electrode placement vs. behavioral changes

Finally, a few studies investigated the relationship between DBS electrode placement and *behavioral* changes. Behavioral tasks were performed in DBS ON and OFF conditions and set into relationship with electrode placement. In a first study, PD patients took part in a task in which gambling longer brought more reward but also the risk to lose it all [58]. Irmen et al. showed that overall, PD patients were more risk-averse but normalized toward the level of healthy controls under DBS. Crucially, behavior in patients with *optimal* DBS placement normalized more toward the healthy level than in patients with *suboptimal* leads ($R = 0.53$ at $p = 0.007$). Thus, DBS placement could parametrically explain the degree of normalization of a cognitive non-motor feature.

In a different experiment, electrode connectivity estimates were related to different behavioral changes observed in DBS ON and OFF conditions. Strong connectivity to SMA explained changes in *reaction* time of a visuomotor tracking task. Based on a computational model that was built on top of

DBS electrode reconstructions, *movement* time was further explained by involvement of the indirect pathway. Thus, in conclusion, the involvement of hyperdirect and indirect pathways resulted in changes of reaction and movement times, respectively. These studies show that slight variations in electrode placement may not only explain differences in clinical outcome or recorded electrophysiological features but also in behavioral changes mediated by DBS.

DBS Imaging on a network level

The optimal connectivity of an effective DBS electrode

It was long thought that DBS exerted its function via local modulation of the target itself. However, accumulating evidence suggests that modulating effects on distributed brain networks are at least equally important for optimal outcome [25,59]. To address this shift in paradigm, first studies applied imaging-based connectivity methods to DBS [13,14,24-28,60-66].

For PD and the STN, one study used preoperative diffusion MRI (dMRI) data to investigate relationships between electrode connectivity and improvement of cardinal symptoms [62]. Connectivity of DBS electrodes to primary motor cortex (M1) explained improvement in tremor, to SMA in bradykinesia and to both SMA and PFC in rigidity. An overall beneficial effect of connectivity to the SMA was shown again in [13]. Connectivity-based sweet-spots in GPi-DBS for PD were successfully defined in [63] albeit the study assumed direct structural connections between GPi and cortex that are unlikely to exist [67].

In VIM-DBS for treatment of tremor, several studies found connectivity to the dentatorubrothalamic tract (DRTT) crucial to explain clinical improvement [61,68] (fig. 3). In the Calabrese study, authors combined DBS electrodes with an ultra-high-resolution postmortem brainstem connectome. Here, proximity to the DRTT correlated with clinical improvement ($R = 0.336$, $p = 0.005$) while proximity to the VIM did not ($R = 0.043$, $p = 0.726$). Others already translated these results into clinical practice by using tractography for surgical planning [66,69,70]. The functional involvement of the DRTT may represent the most accepted concept in connectomic deep brain stimulation. Still, two studies found that instead, involvement of the thalamic SMA/M1 segments were key for improving tremor [26,71]. Of note, these are not histological but imaging derived segments that all reside within the human motor thalamus [72] and are not mutually exclusive [61]. Still, findings were considered inconsistent and the mismatch was explained by poor angular resolution in the Pouratian study [61] but as a counter-argument in a low N of 9 patients included in the Akram study [26]. Whatever the final answer may be, it is certainly correct that highly powered studies are needed to yield robust results in this field. Unfortunately, scanning a high N of DBS patients constitutes a major practical challenge.

A novel development to overcome this limitation is to instead use normative connectomes – i.e. average brain connectomes that were calculated on large cohorts of subjects [73,74]. Advantages of normative connectomes are a high N, the acquisition on specialized MRI hardware and as a result a better definition of the wiring diagram of the brain [75]. This concept has been successfully applied to other areas of clinical neuroimaging, for instance to map stroke symptoms to brain regions [76-78] or to explain varying results in TMS treatment [79].

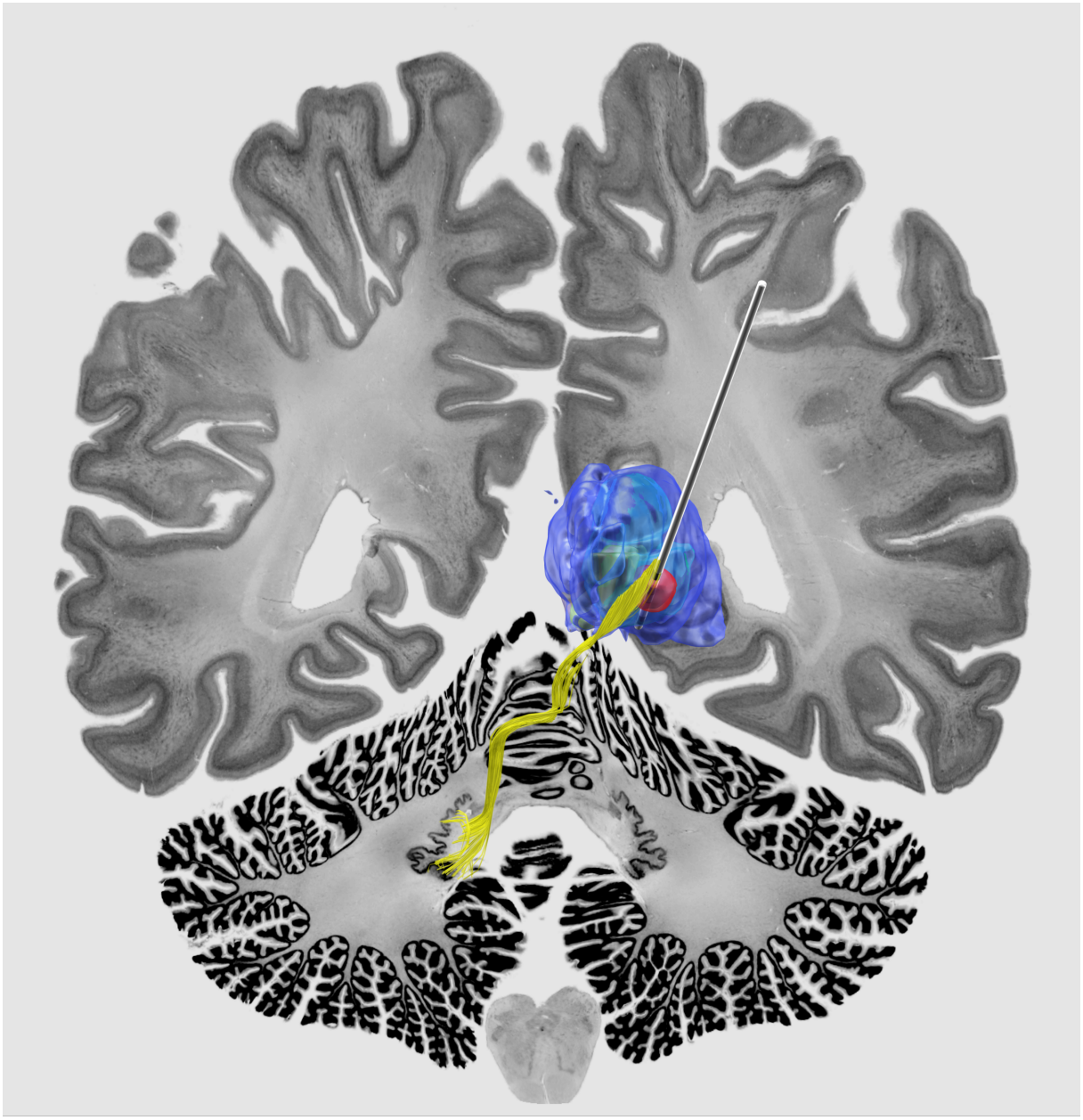

Fig. 3: Reconstruction of a DBS electrode implanted to treat Essential tremor. The dentatorubrothalamic tract (yellow) projects from the dentate nucleus to the thalamus (blue) and crosses sides at the Wernekinck decussatio. A volume of tissue activated is modeled in red. In the back, a coronal plate of the BigBrain dataset [80] *is shown. DRRT based on the Meola Brainstem connectome* [81]*, other structures defined by the DISTAL atlas* [82]*. The figure constitutes an example of using resources available in standard space (histology, normative tractograms, subcortical atlases) to characterize electrode placement.*

A first article demonstrated the feasibility in the field of DBS [14]. Here, the connectivity profile of effective VIM-DBS was estimated. A second article demonstrated that clinical DBS improvement could be predicted based on the connectivity profiles of electrodes alone [13] (fig. 4A). Specifically, the 'connectivity fingerprints' of electrodes in 95 PD patients were predictive of their clinical motor

improvement. In fact, the optimal connectivity profile of effective STN-DBS could be informed on data from a first DBS center and then used to predict outcome in patients of the second center. The concept was recently transferred to OCD where connectivity to a specific tract within the ALIC was highly predictive of clinical improvement [83] (fig. 4B). Of note, here, optimal connectivity profiles learned on normative connectome data were able to predict improvements in patients with individualized connectivity (dMRI) data and vice versa. This further supports the utility of normative connectomes in cases where individualized data is lacking.

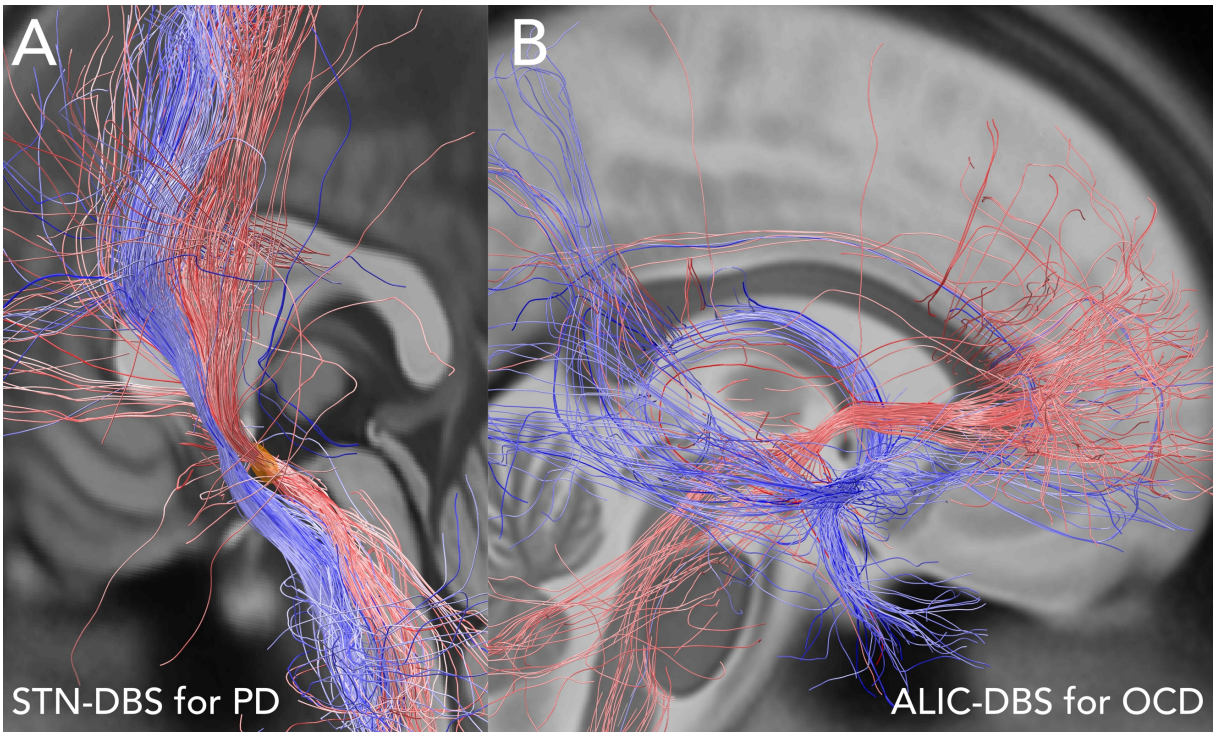

Fig. 4: Fibertracts positively (red) and negatively (blue) associated with clinical improvement. A) STN-DBS for treatment of PD, reanalysis of data presented in Horn et al. 2017. STN in orange. B) ALIC-DBS for treatment of OCD as presented in Baldermann et al. 2019. For each fibertract of a normative connectome, improvement scores in patients with connected vs. unconnected VTAs were compared in mass-univariate two-sample t-tests. Positive T-values result in red fibertracts, negative in blue. This method creates tract-based DBS targets that can be further validated in out-of-sample data. For details of the method see Baldermann et al. 2019.

Conclusion

Recent publications within the ~18-month scope of this review demonstrate the tremendous potential of modern-day deep brain stimulation imaging. With the central task to precisely reconstruct the DBS electrodes in relationship to an advanced model of surrounding anatomy and connectivity, a multitude of analyses in clinical, connectomic, electrophysiological and behavioral domains is possible (fig. 1). Given the high demand in precision and the potential complexity of such analyses, the use and development of specialized research pipelines appears worthwhile. Optimally, such software should be developed by the research society within multi-institutional open-source projects. This could foster a fast advance of the field and quick pipeline adaptations to incorporate specialized basal ganglia sequences, ultra-highfield imaging, postmortem and histological data or high definition normative connectomes. Hand in hand with refined methods and better imaging data, the questions that may be answered will evolve. From the most basic ones (e.g. defining a sweet-spot for UPDRS-III improvement), ever refined questions will emerge (e.g. specific tracts that mediate bradykinesia improvement in patients with atrophy in the SMA). In order to addressing concepts like the latter, in the future, we should now begin to further advance preoperative imaging sequences, refine methodological concepts and pool data to allow for highly powered studies.

Acknowledgements

The author would like to thank Dr. Maarten Bot for approving the use of data published in Bot et al. 2018 in figure 2 and proof-reading of the corresponding section. The author would further like to thank Dr. Juan Carlos Baldermann for approving use of data published in Baldermann et al. 2019 in figure 4.

Financial support and sponsorship

This work did not receive specific funding.

Conflicts of interest

AH received a one-time lecture honorarium from Medtronic not related to the present work.

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