March 25

Neuroimaging Technological Advancements for the Targeting in Functional Neurosurgery

Alexandre Boutet, MD, MSc[1,2]
Robert Gramer, BSc[2]
Christopher J. Steele, PhD[3]
Gavin J. B. Elias, BA[2]
Jürgen Germann, MSc[2]
Ricardo Maciel, MD, MSc[2,4]
Walter Kucharczyk, MD[1,2]
Ludvic Zrinzo, MD, PhD[5]
Andres M. Lozano, MD, PhD[2]
Alfonso Fasano, MD, PhD[2,4,6]

[1]Department of Medical Imaging, University of Toronto, ON, Canada
[2]University Health Network, Toronto, ON, Canada
[3]Montreal
[4]Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Division of Neurology, University of Toronto, Toronto, Ontario, Canada
[5]Functional Neurosurgery Unit, Department of Clinical and Movement Neurosciences, University College London, Queen Square Institute of Neurology, London, United Kingdom; The National Hospital for Neurology and Neurosurgery, London, United Kingdom.
[6]Krembil Brain Institute, Toronto, Ontario, Canada.

Corresponding author contact information:
Dr. Alfonso Fasano, MD. PhD
Movement Disorders Centre - Toronto Western Hospital
399 Bathurst St, 7McL412
Toronto, ON Canada M5T 2S8
Phone (office): +1(416)603-5800
Fax +1 (416) 603-5004
e-mail: alfonso.fasano@uhn.ca
e-mail: alfonso.fasano@gmail.com

Keywords: Deep brain stimulation; functional neurosurgery; MRI; neuroimaging.

Abstract

Purpose of review
Ablations and particularly deep brain stimulation (DBS) of a variety of CNS targets are established therapeutic tool for movement disorders. Accurate targeting of the intended structure is crucial for optimal clinical outcomes. However, most targets used in functional neurosurgery are poorly visualized on routine MRI and indirect targeting methods are commonly used. This article reviews recent neuroimaging advancements for targeting in movement disorders.

Recent findings
Dedicated MRI sequences can often visualise anatomical structures commonly targeted during DBS surgery, including at 1.5T field strengths. Due to recent technological advancements, MR images using ultra-high magnetic field strengths and new acquisition parameters allow for markedly improved visualization of common movement disorder targets. In addition, novel neuroimaging techniques have enabled group-level analysis of DBS patients and delineation of areas associated with clinical benefits. These areas might diverge from the conventionally targeted nuclei and may instead correspond to white matter tracts or hubs of functional networks.

Summary
Neuroimaging advancements have enabled direct visualization-based targeting as well as optimization and adjustment of conventionally targeted structures.

Introduction

A wide range of brain disorders are thought to arise from abnormal neural activity in brain circuits. Deep brain stimulation (DBS) is a surgical treatment directed toward modulating dysfunctional circuits [1]. During DBS surgery, electrodes are inserted into precise brain structures, usually part of the underlying aberrant circuit. For example, in Parkinson's disease (PD), the most commonly targeted brain structure is the subthalamic nucleus (STN), an essential hub in the brain's motor circuitry [2]. Globus pallidus interna (GPi) is also a target in PD, however less often used [3]. The thalamic ventral intermediate (VIM) nucleus and GPi are commonly used for essential tremor and dystonia, respectively [4]. The same brain areas are targets for ablative treatments with radiofrequency, radiation (gamma-knife radiosurgery) and ultrasound (MRI-guided focused ultrasound).

Although clinical benefits produced via DBS are best known in movement disorders such as PD, dystonia and tremor, there is mounting evidence that DBS neuromodulation has its place in treating psychiatric and cognitive disorders [1, 4]. The therapeutic effects achieved with DBS hinge upon selective stimulation of the intended structure through accurate and precise placement of the electrodes – maximizing therapeutic benefits while minimizing spillover onto neighboring structures that may produce adverse effects [5, 6]. Despite significant advances in neuroimaging technology over the past decades, routinely acquired preoperative brain magnetic resonance imaging (MRI) sequences remain deficient at directly visualizing DBS targets for stereotactic planning purposes [7, 8]. Some groups have developed dedicated MRI sequences that visualise some of the anatomical structures commonly targeted during DBS surgery on MRI at 1.5T field strengths such as the STN and posteroventral GPi. Nevertheless, some commonly used targets, such as the VIM cannot be visualised on 1.5T structural MRI, and many groups have continued to use indirect targeting methods when performing DBS – relying on identifiable surrogate anatomical landmarks and coupled with other techniques such as intraoperative micro-electrode recordings (MER) and/or clinical evaluation in awake patients [9].

While neuroimaging plays a central role in today's DBS surgery, it was not until 1940s that it was used to guide stereotaxic surgeries targeting a precise brain structure via a coordinate system. Spiegel et al. (1947) [10] and Tasker (1965) [11] pioneered stereoencephalography to triangulate brain structures through radiographic skull landmarks. As computerized tomography (CT) and MRI became widely available, their ability to non-invasively discern internal brain structures made them gold standards for DBS preoperative planning. Drawing from atlases with a defined coordinate system, relationships between targets and anatomical landmarks such as the anterior and posterior commissures are commonly used to plan DBS surgeries [9]. The known inter-surgeon variability when identifying these landmarks is problematic, however [12]. Current neurosurgical technique entails combining indirect, coordinate-based targeting and MRI-guided direct target visualization. In many cases this standard planning is further supplemented with intraoperative techniques such as MERs and clinical stimulation to produce motor, sensory, physiologic, or cognitive phenomena [9, 13, 14].

In this review we will summarize the recent neuroimaging technological advancements and their utility as new methods for optimizing targeting in functional neurosurgey. First, technological developments including ultra-high field (UHF) MRI and novel MRI pulse sequences allowing

improved targets visualization will be discussed. Then, refinement of current DBS targets for movement disorders based on structural and functional connectomes will be reviewed.

Direct target visualization with ultra-high field MR imaging

While acquisition of 3 Tesla (3T) MRI for clinical neuroimaging has become routine in most neurological and neurosurgical centers, thanks to technological advances, UHF (i.e., 7T) MRI are becoming increasingly available [15, 16]. Compared to the widely used 1.5T MRI in the 1990s, when planning DBS surgery for movement disorders, 3T MRI offer superior visualization of the targets [17, 18]. Lower field strengths MRI may be used for intra-operative validation of targeting accuracy [19, 20]. The net benefit of using UHF MRI in comparison to 3T is still being investigated (Table 1).

From a physics standpoint, higher magnetic field strength offers clear advantages while also introducing disadvantages that must be acknowledged. The main benefit of using UHF is the desirable increase in signal-to-noise ratio (SNR) [16, 21-23], which theoretically grows linearly in relation to magnetic field strength [17, 18]. Higher SNR in turn allows increased spatial resolution, permitting the visualization and delineation of smaller neuroanatomical structures. Such precision is warranted as structures of interest targeted with DBS in movement disorders are generally subcentimetre in scale [24]. Naturally, as the spatial resolution inherent to lower magnetic field strengths approaches or is inferior to the dimensions of the desired structure, MRI volume averaging leads to blurring of the anatomy. Also, optimal SNR is particularly relevant in DBS planning since it scales inversely with distance from cortex [22, 25]. Moreover, due to the non-uniform distribution of SNR throughout the head at UHF MRI, SNR of deep structures has been shown to particularly improve with increasing magnetic field strengths [26]. Importantly, there is little trade-off in terms of acquisition times at UHF MRI; incorporating similar protocols to those used in current clinical imaging, UHF MRI can acquire smoother, less grainy images than those obtained at lower field strengths in a comparable timeframe [8, 15, 17]. For example, diagnostic quality T1-weigthed (T1W) and T2-weighted (T2W) 7T images can both be obtained in approximately 10 minutes [8]. In addition to improved SNR, UHF MRI is reported to confer a better contrast-to-noise ratio (CNR), improving the ability to differentiate two small abutting structures [16, 22]. Given that the STN is bordered by several small structures such as the ansa lenticularis, zona incerta, and substantia nigra, this capacity becomes crucial [27]. By reducing the gap between MRI and histology, this increased spatial resolution opens the door to highly accurate and detailed MRI atlases [24, 28, 29], thus further refining the surgeon's ability to target specific territory within a given circuit (e.g. the dorso-lateral STN involved in motor functions).

Recent studies have investigated the validity of UHF MRI in the context of DBS surgery for movement disorders. UHF allows visualization of otherwise obscure (or indiscernible) brain structures on the clinical 1.5T or 3T MRI [16, 21, 27, 30-34]. At these commonly used field strengths, 3T has been reported to provide improved STN visualization for PD DBS [18]. With its far superior SNR and spatial resolution, UHF MRI permits accurate delineation of STN borders and has been shown to correlate well with MER recordings. This has also been demonstrated for UHF-imaging [21], although a slight discrepancy between the two sources of information was described in another study [34], highlighting the possible image distortions at UHF MRI. However, these small discrepancies could also be explained by distortion of brain issue by the advancing surgical probes. On the other hand, the fact that clinical outcomes have been shown to correlate

with the proportion of stimulation overlapping the STN at 7T partly validates the accurate anatomical representation of UHF MRI [21]. At higher magnetic field strengths, STN can also be segmented and parcellated based upon white matter projections, raising the prospect of precise, substructure level targeting of previously indiscernible areas (i.e., the motor division of STN) [32]. This direct visualization of DBS targets may improve surgical techniques and clinical outcome given inter-individual variability in STN location has been reported [21].

UHF MRI may also hold promise for essential tremor DBS, which most commonly targets the motor thalamus [1]. Indeed, the potential benefits here may even be more pronounced than for PD; while the STN may be adequately visualised on routinely acquired MRI [7], the thalamic intranuclei, including the VIM, are not appreciated at all on current MRI protocols. These nuclei can be visualized with appropriate MRI sequences at 7T MRI [31, 33], however, which is a notable advantage when planning DBS surgery for tremor.

Although UHF MRI can theoretically provide substantial advantages, there are only about 60 centers worldwide at present; as such, the poor availability of this technology remains a barrier to mainstream clinical practice [16]. Additionally, higher magnetic field strengths are more prone to susceptibility artefacts and image distortions [17, 30], leading in theory to greater risk of mistargeting. Moreover, UHF MRI has not been reported in conjunction with a commercially available stereotactic frame; UHF MR images must therefore be co-registered with stereotactic images using another modality, a step that can introduce registration errors. While this limitation would be particularly problematic for DBS surgery given the small scale of structures involved, most of the subcortical structures targeted in movement disorders are located deep in the brain and have been shown to have little distortion when compared to the routine 1.5T MRI [35]. Due to their proximity to the paranasal sinuses, areas such as the inferior frontal and temporal lobes are most at risk of distortion; given these are not targets for movement disorder DBS at present, the problem of UHF MRI-related distortion is of less concern here than it might be for psychiatric indications. Lastly, from a practical standpoint, the risk of metallic implants in UHF MRI has not been thoroughly evaluated and may thus limit the clinical generalizability of this technology [23, 36, 37]. Patients with metallic implants such as aneurysm clips and cardiac metallic devices are increasingly prevalent, and safety studies, such as those recently performed with 3T MRI and DBS [38, 39], will be needed before they can safely undergo UHF MRI.

In conclusion, UHF MRI still remains an experimental technique requiring a more specialized knowledge base and clinical expertise than is typical in the field of clinical radiology. As even higher field strengths [27] and image distortion correction methods are being developed, continued testing is required to bring the potential benefits, obstacles, and trade-offs presented by UHF MRI relative to lower field strength MRI more clearly into focus.

Direct target visualization with new MRI pulse sequences

In addition to increasing the magnetic field strength, changing the MRI acquisition parameters is also a promising technique. MRI pulse sequences are designed to provide varying kinds of contrasts through their sensitivity to different tissue properties. For example, routinely acquired structural MRI pulse sequences such as T1W and T2W sequences are mostly sensitive to the time taken for the water molecules (i.e., protons) to realign with the MRI magnetic field and the time for the excited water molecules (i.e., protons) to go out of phase from those molecules aligned with

the magnetic field, respectively. These sequences can usually differentiate between grey matter, white matter, and other basic components such as fat and cerebrospinal fluid. However, at lower field strengths (1.5T or 3T), they generally fail to delineate smaller nuclei and sub-nuclei. On routinely used T2W sequence, for instance, the STN appears hypointense and may be difficult to differentiate from surrounding structures [7], necessitating the use of adjunct indirect targeting methods.

In recent years, developments in MRI pulse sequences and advances in imaging processing have led to the development of sequences sensitive to other aspects of tissue composition. The STN is an iron-rich structure which is likely responsible for its relative hypointensity on T2W imaging [40, 41]. SWI, a type of gradient echo (GRE) sequences, is highly sensitive to iron content by taking advantage of the T2* artefact associated with its paramagnetic properties [42]. Not surprisingly, the STN exhibits striking hypointensity when imaged with SWI pulse sequences [40, 41, 43]. However, the iron present in nearby structures also influences the signal in the STN, degrading the contrast and limiting the ability to differentiate the STN from its surroundings [42]. Fortunately, a novel variation of SWI – quantitative susceptibility imaging (QSM) – quantifies the susceptibility in each structure and represents them on a scale that enhances the contrast between neighboring structures (Table 1) [40-42]. The STN [40, 41, 44], and (to a lesser degree) the GPi [45], have been shown to be better appreciated via SWI sequences such as QSM. With this marked increase in contrast between structures, delineation of subcortical structures such as the thalamus, GPi, and STN can be performed using an automated computer algorithm [46, 47]. Furthermore, by providing a quantifiable tissue composition signal that mainly reflects iron quantity, QSM sequences can provide data on the expected age-related changes in small subcortical nuclei such as STN [48, 49]. Of note, QSM images visualization require niche expertise for the necessary image preprocessing. This pulse sequence-dependent enhancement of target area visualization may help improve current targeting approaches and decrease the number of surgical passes, enhancing practice and improving outcomes. As such, it is extremely promising, and may be particularly powerful when combined with UHF MRI.

Finally, proton-density weighted MR images reflect the actual density of protons in tissues and is another sequence of interest since it provides excellent contrast between white and grey matter structures, making it useful in defining the GPi within the components of the lentiform nucleus as well as the pedunculopontine nucleus.

Targeting circuits of interest

Recent research suggests that optimal structures to be targeted may not be appreciable via routine structural imaging. For example, it has been suggested that the clinical benefits of DBS may be better understood as emerging from white matter pathways [50-55] or focal hubs of functional networks [56] rather than discrete structures such as deep grey matter nucleus. Interestingly, when these functional and structural networks are targeted more directly, the resultant target may spatially diverge from conventional coordinates (Table 1).

Conventionally, DBS for movement disorders has targeted discrete grey matter nuclei. Although these targets are known to be associated with clinical benefits, recent evidence suggest that entities such as white matter tracts [51, 57, 58] or functional networks [56] may also be responsible for the

therapeutic effects of DBS. White matter tracts and functional networks cannot be visualized on routinely acquired structural MRI and require different MRI acquisition parameters to be appreciated: diffusion-weighted imaging (DWI) for tractography and resting-state functional magnetic resonance imaging (rsfMRI) for functional networks. In some cases, newly visualized white matter pathways may be employed as independent targets for neurosurgical intervention. One example of this approach pertains to the dentato-rubro-thalamic tract, part of the cerebello-thalamo-cortical tremor network, which is being investigated as a direct DBS target for tremor using tractography methods [51, 57, 58]. A similar tactic has been adopted in the realm of neuropsychiatric DBS, with tractography-dependent targeting of the medial forebrain bundle pathway for treatment of depression [59]. Another variation is the use of white matter tracts to refine and delineate a more conventional target. This includes triangulating VIM based on the relative positions of pyramidal and medial lemniscus tracts for tremor surgery [60], and also the tract-based parcellation of the STN and thalamic nuclei into sub-regions with preferential motor connections [32, 61]. Thus far, few DBS studies for movement disorders [51, 58] have explored the prospective application of these new techniques, although prospective targeting of white matter tracts is increasingly described in the context of other neurosurgical techniques for movement disorders [62] as well as DBS for psychiatric disorders [63]. Given the substantial inter-patient variability in white matter pathways, this type of targeting is likely to be more sensitive to individual neuroanatomical differences, leading to more personalized DBS delivery [64]. However, it will be critical for investigators to remain cognizant of the bewildering variety of tractography methods, the need for rigorous methods, and the importance of visual inspection in order to stave off spurious results [65]. Constantly evolving MRI hardware and pulse sequence designs should limit spurious results and allow visualization of structures, as of now, only seen on histology.

Data-driven connectome targeting

The conventional DBS targets for movement disorders have been most commonly empirically derived from lesioning studies [66]. Although these targets provide clinical benefits in movement disorders, it is plausible that they may not be optimal. Indeed, pinpointing the effective component across the volume of lesions may have been difficult partly due to the lack of group-level analysis methods. Recent neuroimaging advances allowing (1) precise transformation of patients' brain into an average brain (i.e. normalization to Montreal Neurological Institute – MNI – brain template) [67], (2) DBS electrode localization [68], and (3) estimation of the volume of tissue activated (VTA) [68-70] have enabled this group-level analyses to be conducted for DBS (Figure 1). This approach, in which probabilistic maps based on clinical outcomes are computed from regions of interest have also been performed with ablative therapies [71]. Easy-to-use analysis pipelines performing electrode localization and VTA estimation are now available in commercially available (e.g. Medtronic SureTune, Medtronic Inc.; Elements, Brainlab Inc.) and research software (e.g. Lead-DBS). Once normalized in an average brain, electrode locations and VTAs from patients can be weighted with clinical outcomes to derive a cohort probabilistic maps of efficacy [72-77]. This agnostic approach is driven by clinical data provided by DBS programming, an empirical clinical process that is usually blinded to precise electrode location. Challenging the routinely targeted structures, less conventional efficacious targets such as the posterior subthalamic areas in DBS for tremor might be suggested with such methods [73]. Moreover, areas associated with specific clinical benefits such as tremor, rigidity, or bradykinesia in PD may now be defined, opening the door to individualized DBS targeting based on dominant disease

phenotypes [72, 75]. A similar approach has also been used to delineate areas responsible for DBS adverse effects such as paresthesia and diplopia [72-74].

Computation of these maps of clinical benefits and adverse effects become highly important with the increasing use of directional leads, introducing more programming possibilities and complexity [78]. Directional leads stimulation can be preferentially directed towards the optimal target, minimizing stimulation of unwanted areas. Neuroimaging techniques using CT scan or x-rays have been developed to determine the lead orientation [79-82] and most recent VTA modelling software can compute this steered stimulation [68, 83]. Following electrode localization and VTA modelling, clinicians can then use these tools to inform programming. Given time constraints and patient fatigue, it is impracticable to thoroughly assess a large number of stimulation parameters via clinical means; this restriction could be mitigated by using probabilistic maps of clinical outcomes, providing patient-specific targeting and guiding subsequent programming.

Limits of the current methods include (1) suboptimal patients' brain normalization – and thus electrode localization – of *abnormal* (e.g., markedly atrophic) brains; (2) limited VTA modelling, which does not take stimulation frequency or pulse width into account and typically makes assumptions about electrode-tissue impedance; and (3) large number of patients required for robust results.

In addition to defining probabilistic areas of clinical benefits and adverse effects, probabilistic group-level approaches can also leverage normative connectomes to explore the network connectivity associated with desired and undesired outcomes. Since the vast majority of DBS patients do not undergo DWI and rsfMRI imaging, probabilistic areas of clinical benefits could – until recently – only be described and computed using routinely acquired structural scans. Now, however, neuroimaging techniques have permitted the aggregation of large DWI and rsfMRI datasets derived from healthy subjects into publicly available, standard space such as the MNI brain template. While native patient imaging may better reflect the underlying patient-specific connectivity, state of the art normative data gathered through initiatives such as the Human Connectome Project and Brain Genomics Superstruct Project offer unparalleled spatial resolution and signal-to-noise ratio [56, 84, 85]. Once electrode localizations and VTA modelling have been performed and the resulting constructs have been normalized to an average brain (e.g. MNI brain), each VTA can be employed as a seed in the normative templates to investigate associated white matter pathways and functional networks (Figure 1). In other words, by tapping into high-quality, publicly available, normative datasets, it is now possible to explore white matter pathways and functional networks associated with best clinical outcomes using only routinely acquired neuroimaging data – native patient DWI and rsfMRI sequences are not required. While this approach is only a recent development, it is already providing encouraging results and as recently been described by A. Horn (2019) [86]. Normative connectomic mapping has been shown to predict clinical outcomes in both PD DBS patients with STN electrodes [56] and in psychiatric DBS patients [87], for instance. Ultimately, the probabilistic zones and networks identified by these analyses in an average brain could then be transformed to the native patients' brain in order to guide preoperative planning in a manner that is both personalized and driven by large retrospective clinical outcome datasets.

Conclusions

Although neuroimaging techniques used for preoperative DBS planning have evolved – from stereoencephalogram to MRI – over the years, indirect anatomical landmarks remain indispensable to some conventional targeting paradigms. Historical and empirical DBS targets have yet to be refined. The expansive and growing cohort of movement disorder patients treated with DBS coupled with newly available neuroimaging techniques offer the opportunity to perform group analyses and better resolve which structures impart the greatest clinical benefits (or adverse effects) to patients. While traditionally targeted grey matter nuclei might play a role in the therapeutic effects of DBS, there is mounting evidence that white matter pathways and functional networks, entities typically occult on routinely acquired structural imaging, are notably involved in disease pathophysiology, and thus must be more earnestly considered in targeting. Using this new data, it is possible to consider personalized medicine in the context of DBS surgery for movement disorders. Given the inter-individual variability in brain structures, it is logical that not every patient should be targeted with a generic method. Furthermore, depending on the disease phenotype, it is also sensible that slight variations of the same target may confer more optimal benefits. These new technologies should allow progress toward patient individualized targeting, better definition of established surgical targets and possibly discovery of new ones.

Acknowledgements
None.

Conflicts of interest
Dr. Fasano is a consultant for Abbvie, Medtronic, Boston Scientific, Sunovion, Chiesi farmaceutici, UCB, Ipsen. Dr. Lozano is the owner of Functional Neuromodulation and a consultant for Boston Scientific, Medtronic and Abbott.

Funding
None.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
31
These authors report that image distortions at 7T is comparable to 1.5T for DBS targets.
37
This study demonstrates that the STN can be parcellated at 7T into sub-regions with preferential white matter connectivity.
38
These authors report that 7T can be used to visualize intra-thalamic nuclei, confirmed to be anatomically accurate.
43

This study shows that QSM is optimal to visualize the STN compared to the more commonly used T2W*-weighted sequences.

•• Of major importance

49

This study shows that normative data can be used to predict clinical improvement in Parkinson's disease patients based on connectivity associated with volume of tissue activated.

68

The authors report a streamline easy-to-use MATLAB-based platform to perform deep brain stimulation analysis.

72

This study demonstrates how to compute a probabilistic map of clinical outcomes using statistically validated techniques.

1. Lozano AM, Lipsman N. Probing and regulating dysfunctional circuits using deep brain stimulation. Neuron. 2013;77(3):406-24.
2. Okun MS. Deep-brain stimulation for Parkinson's disease. N Engl J Med. 2012;367(16):1529-38.
3. Follett KA, Weaver FM, Stern M, Hur K, Harris CL, Luo P, et al. Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease. N Engl J Med. 2010;362(22):2077-91.
4. Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, et al. Deep brain stimulation: current challenges and future directions. Nat Rev Neurol. 2019.
5. Li Z, Zhang JG, Ye Y, Li X. Review on Factors Affecting Targeting Accuracy of Deep Brain Stimulation Electrode Implantation between 2001 and 2015. Stereotact Funct Neurosurg. 2016;94(6):351-62.
6. Bot M, Schuurman PR, Odekerken VJJ, Verhagen R, Contarino FM, De Bie RMA, et al. Deep brain stimulation for Parkinson's disease: defining the optimal location within the subthalamic nucleus. J Neurol Neurosurg Psychiatry. 2018;89(5):493-8.
7. Ranjan M, Boutet A, Xu DS, Lozano CS, Kumar R, Fasano A, et al. Subthalamic Nucleus Visualization on Routine Clinical Preoperative MRI Scans: A Retrospective Study of Clinical and Image Characteristics Predicting Its Visualization. Stereotact Funct Neurosurg. 2018;96(2):120-6.
8. Abosch A, Yacoub E, Ugurbil K, Harel N. An assessment of current brain targets for deep brain stimulation surgery with susceptibility-weighted imaging at 7 tesla. Neurosurgery. 2010;67(6):1745-56; discussion 56.
9. Lozano CS, Ranjan M, Boutet A, Xu DS, Kucharczyk W, Fasano A, et al. Imaging alone versus microelectrode recording-guided targeting of the STN in patients with Parkinson's disease. J Neurosurg. 2018:1-6.
10. Spiegel EA, Wycis HT, Marks M, Lee AJ. Stereotaxic Apparatus for Operations on the Human Brain. Science. 1947;106(2754):349-50.
11. Tasker RR. Simple localization for stereoencephalotomy using the "portable" central beam of the image intensifier. Confin Neurol. 1965;26(3):209-12.

12. Pallavaram S, Yu H, Spooner J, D'Haese PF, Bodenheimer B, Konrad PE, et al. Intersurgeon variability in the selection of anterior and posterior commissures and its potential effects on target localization. Stereotact Funct Neurosurg. 2008;86(2):113-9.
13. Aviles-Olmos I, Kefalopoulou Z, Tripoliti E, Candelario J, Akram H, Martinez-Torres I, et al. Long-term outcome of subthalamic nucleus deep brain stimulation for Parkinson's disease using an MRI-guided and MRI-verified approach. J Neurol Neurosurg Psychiatry. 2014;85(12):1419-25.
14. Zrinzo L, Hariz M, Hyam JA, Foltynie T, Limousin P. Letter to the Editor: A paradigm shift toward MRI-guided and MRI-verified DBS surgery. J Neurosurg. 2016;124(4):1135-7.
15. Forstmann BU, Isaacs BR, Temel Y. Ultra High Field MRI-Guided Deep Brain Stimulation. Trends Biotechnol. 2017;35(10):904-7.
16. Springer E, Dymerska B, Cardoso PL, Robinson SD, Weisstanner C, Wiest R, et al. Comparison of Routine Brain Imaging at 3 T and 7 T. Invest Radiol. 2016;51(8):469-82.
17. Chandran AS, Bynevelt M, Lind CR. Magnetic resonance imaging of the subthalamic nucleus for deep brain stimulation. J Neurosurg. 2016;124(1):96-105.
18. Cheng CH, Huang HM, Lin HL, Chiou SM. 1.5T versus 3T MRI for targeting subthalamic nucleus for deep brain stimulation. Br J Neurosurg. 2014;28(4):467-70.
19. Cui Z, Pan L, Song H, Xu X, Xu B, Yu X, et al. Intraoperative MRI for optimizing electrode placement for deep brain stimulation of the subthalamic nucleus in Parkinson disease. J Neurosurg. 2016;124(1):62-9.
20. Warnke P. Deep brain stimulation: awake or asleep: it comes with a price either way. J Neurol Neurosurg Psychiatry. 2018;89(7):672.
21. Duchin Y, Shamir RR, Patriat R, Kim J, Vitek JL, Sapiro G, et al. Patient-specific anatomical model for deep brain stimulation based on 7 Tesla MRI. PLoS One. 2018;13(8):e0201469.
22. Forstmann BU, de Hollander G, van Maanen L, Alkemade A, Keuken MC. Towards a mechanistic understanding of the human subcortex. Nat Rev Neurosci. 2016;18(1):57-65.
23. Kraff O, Quick HH. 7T: Physics, safety, and potential clinical applications. J Magn Reson Imaging. 2017;46(6):1573-89.
24. Ewert S, Plettig P, Li N, Chakravarty MM, Collins DL, Herrington TM, et al. Toward defining deep brain stimulation targets in MNI space: A subcortical atlas based on multimodal MRI, histology and structural connectivity. Neuroimage. 2018;170:271-82.
25. Wiggins GC, Polimeni JR, Potthast A, Schmitt M, Alagappan V, Wald LL. 96-Channel receive-only head coil for 3 Tesla: design optimization and evaluation. Magn Reson Med. 2009;62(3):754-62.
26. Ugurbil K. Magnetic resonance imaging at ultrahigh fields. IEEE Trans Biomed Eng. 2014;61(5):1364-79.
27. Massey LA, Miranda MA, Zrinzo L, Al-Helli O, Parkes HG, Thornton JS, et al. High resolution MR anatomy of the subthalamic nucleus: imaging at 9.4 T with histological validation. Neuroimage. 2012;59(3):2035-44.
28. Tullo S, Devenyi GA, Patel R, Park MTM, Collins DL, Chakravarty MM. Warping an atlas derived from serial histology to 5 high-resolution MRIs. Sci Data. 2018;5:180107.
29. Keuken MC, Bazin PL, Crown L, Hootsmans J, Laufer A, Muller-Axt C, et al. Quantifying inter-individual anatomical variability in the subcortex using 7 T structural MRI. Neuroimage. 2014;94:40-6.

30. Dammann P, Kraff O, Wrede KH, Ozkan N, Orzada S, Mueller OM, et al. Evaluation of hardware-related geometrical distortion in structural MRI at 7 Tesla for image-guided applications in neurosurgery. Acad Radiol. 2011;18(7):910-6.
31. Kanowski M, Voges J, Buentjen L, Stadler J, Heinze HJ, Tempelmann C. Direct visualization of anatomic subfields within the superior aspect of the human lateral thalamus by MRI at 7T. AJNR Am J Neuroradiol. 2014;35(9):1721-7.
32. Plantinga BR, Temel Y, Duchin Y, Uludag K, Patriat R, Roebroeck A, et al. Individualized parcellation of the subthalamic nucleus in patients with Parkinson's disease with 7T MRI. Neuroimage. 2018;168:403-11.
33. Tourdias T, Saranathan M, Levesque IR, Su J, Rutt BK. Visualization of intra-thalamic nuclei with optimized white-matter-nulled MPRAGE at 7T. Neuroimage. 2014;84:534-45.
34. Verhagen R, Schuurman PR, van den Munckhof P, Contarino MF, de Bie RM, Bour LJ. Comparative study of microelectrode recording-based STN location and MRI-based STN location in low to ultra-high field (7.0 T) T2-weighted MRI images. J Neural Eng. 2016;13(6):066009.
35. Duchin Y, Abosch A, Yacoub E, Sapiro G, Harel N. Feasibility of using ultra-high field (7 T) MRI for clinical surgical targeting. PLoS One. 2012;7(5):e37328.
36. Dula AN, Virostko J, Shellock FG. Assessment of MRI issues at 7 T for 28 implants and other objects. AJR Am J Roentgenol. 2014;202(2):401-5.
37. Feng DX, McCauley JP, Morgan-Curtis FK, Salam RA, Pennell DR, Loveless ME, et al. Evaluation of 39 medical implants at 7.0 T. Br J Radiol. 2015;88(1056):20150633.
38. Boutet A, Hancu I, Saha U, Crawley A, Xu DS, Ranjan M, et al. 3-Tesla MRI of deep brain stimulation patients: safety assessment of coils and pulse sequences. J Neurosurg. 2019:1-9.
39. Hancu I, Boutet A, Fiveland E, Ranjan M, Prusik J, Dimarzio M, et al. On the (Non-) equivalency of monopolar and bipolar settings for deep brain stimulation fMRI studies of Parkinson's disease patients. J Magn Reson Imaging. 2018.
40. Dimov AV, Gupta A, Kopell BH, Wang Y. High-resolution QSM for functional and structural depiction of subthalamic nuclei in DBS presurgical mapping. J Neurosurg. 2018:1-8.
41. Liu T, Eskreis-Winkler S, Schweitzer AD, Chen W, Kaplitt MG, Tsiouris AJ, et al. Improved subthalamic nucleus depiction with quantitative susceptibility mapping. Radiology. 2013;269(1):216-23.
42. Liu C, Li W, Tong KA, Yeom KW, Kuzminski S. Susceptibility-weighted imaging and quantitative susceptibility mapping in the brain. J Magn Reson Imaging. 2015;42(1):23-41.
43. Lefranc M, Derrey S, Merle P, Tir M, Constans JM, Montpellier D, et al. High-resolution 3-dimensional T2*-weighted angiography (HR 3-D SWAN): an optimized 3-T magnetic resonance imaging sequence for targeting the subthalamic nucleus. Neurosurgery. 2014;74(6):615-26; discussion 27.
44. Alkemade A, de Hollander G, Keuken MC, Schafer A, Ott DVM, Schwarz J, et al. Comparison of T2*-weighted and QSM contrasts in Parkinson's disease to visualize the STN with MRI. PLoS One. 2017;12(4):e0176130.
45. Nolte IS, Gerigk L, Al-Zghloul M, Groden C, Kerl HU. Visualization of the internal globus pallidus: sequence and orientation for deep brain stimulation using a standard installation protocol at 3.0 Tesla. Acta Neurochir (Wien). 2012;154(3):481-94.
46. Cobzas D, Sun H, Walsh AJ, Lebel RM, Blevins G, Wilman AH. Subcortical gray matter segmentation and voxel-based analysis using transverse relaxation and quantitative

susceptibility mapping with application to multiple sclerosis. J Magn Reson Imaging. 2015;42(6):1601-10.
47. Visser E, Keuken MC, Forstmann BU, Jenkinson M. Automated segmentation of the substantia nigra, subthalamic nucleus and red nucleus in 7T data at young and old age. Neuroimage. 2016;139:324-36.
48. Keuken MC, Bazin PL, Backhouse K, Beekhuizen S, Himmer L, Kandola A, et al. Effects of aging on T(1), T(2)*, and QSM MRI values in the subcortex. Brain Struct Funct. 2017;222(6):2487-505.
49. Keuken MC, Bazin PL, Schafer A, Neumann J, Turner R, Forstmann BU. Ultra-high 7T MRI of structural age-related changes of the subthalamic nucleus. Journal of Neuroscience. 2013;33(11):4896-900.
50. Akram H, Dayal V, Mahlknecht P, Georgiev D, Hyam J, Foltynie T, et al. Connectivity derived thalamic segmentation in deep brain stimulation for tremor. Neuroimage Clin. 2018;18:130-42.
51. Coenen VA, Allert N, Madler B. A role of diffusion tensor imaging fiber tracking in deep brain stimulation surgery: DBS of the dentato-rubro-thalamic tract (drt) for the treatment of therapy-refractory tremor. Acta Neurochir (Wien). 2011;153(8):1579-85; discussion 85.
52. Kincses ZT, Szabo N, Valalik I, Kopniczky Z, Dezsi L, Klivenyi P, et al. Target identification for stereotactic thalamotomy using diffusion tractography. PLoS One. 2012;7(1):e29969.
53. Pouratian N, Zheng Z, Bari AA, Behnke E, Elias WJ, Desalles AA. Multi-institutional evaluation of deep brain stimulation targeting using probabilistic connectivity-based thalamic segmentation. J Neurosurg. 2011;115(5):995-1004.
54. See AAQ, King NKK. Improving Surgical Outcome Using Diffusion Tensor Imaging Techniques in Deep Brain Stimulation. Front Surg. 2017;4:54.
55. Vanegas-Arroyave N, Lauro PM, Huang L, Hallett M, Horovitz SG, Zaghloul KA, et al. Tractography patterns of subthalamic nucleus deep brain stimulation. Brain. 2016;139(Pt 4):1200-10.
56. Horn A, Reich M, Vorwerk J, Li N, Wenzel G, Fang Q, et al. Connectivity Predicts deep brain stimulation outcome in Parkinson disease. Ann Neurol. 2017;82(1):67-78.
57. Coenen VA, Allert N, Paus S, Kronenburger M, Urbach H, Madler B. Modulation of the cerebello-thalamo-cortical network in thalamic deep brain stimulation for tremor: a diffusion tensor imaging study. Neurosurgery. 2014;75(6):657-69; discussion 69-70.
58. Coenen VA, Varkuti B, Parpaley Y, Skodda S, Prokop T, Urbach H, et al. Postoperative neuroimaging analysis of DRT deep brain stimulation revision surgery for complicated essential tremor. Acta Neurochir (Wien). 2017;159(5):779-87.
59. Schlaepfer TE, Bewernick BH, Kayser S, Madler B, Coenen VA. Rapid effects of deep brain stimulation for treatment-resistant major depression. Biol Psychiatry. 2013;73(12):1204-12.
60. Sammartino F, Krishna V, King NK, Lozano AM, Schwartz ML, Huang Y, et al. Tractography-Based Ventral Intermediate Nucleus Targeting: Novel Methodology and Intraoperative Validation. Mov Disord. 2016;31(8):1217-25.
61. Johansen-Berg H, Behrens TE, Sillery E, Ciccarelli O, Thompson AJ, Smith SM, et al. Functional-anatomical validation and individual variation of diffusion tractography-based segmentation of the human thalamus. Cereb Cortex. 2005;15(1):31-9.

62. Krishna V, Sammartino F, Agrawal P, Changizi BK, Bourekas E, Knopp MV, et al. Prospective Tractography-Based Targeting for Improved Safety of Focused Ultrasound Thalamotomy. Neurosurgery. 2019;84(1):160-8.
63. Riva-Posse P, Choi KS, Holtzheimer PE, Crowell AL, Garlow SJ, Rajendra JK, et al. A connectomic approach for subcallosal cingulate deep brain stimulation surgery: prospective targeting in treatment-resistant depression. Mol Psychiatry. 2018;23(4):843-9.
64. Anthofer J, Steib K, Fellner C, Lange M, Brawanski A, Schlaier J. The variability of atlas-based targets in relation to surrounding major fibre tracts in thalamic deep brain stimulation. Acta Neurochir (Wien). 2014;156(8):1497-504; discussion 504.
65. Nowacki A, Schlaier J, Debove I, Pollo C. Validation of diffusion tensor imaging tractography to visualize the dentatorubrothalamic tract for surgical planning. J Neurosurg. 2018:1-10.
66. Miocinovic S, Somayajula S, Chitnis S, Vitek JL. History, applications, and mechanisms of deep brain stimulation. JAMA Neurol. 2013;70(2):163-71.
67. Ewert S, Horn A, Finkel F, Li N, Kuhn AA, Herrington TM. Optimization and comparative evaluation of nonlinear deformation algorithms for atlas-based segmentation of DBS target nuclei. Neuroimage. 2019;184:586-98.
68. Horn A, Li N, Dembek TA, Kappel A, Boulay C, Ewert S, et al. Lead-DBS v2: Towards a comprehensive pipeline for deep brain stimulation imaging. Neuroimage. 2019;184:293-316.
69. Chaturvedi A, Lujan JL, McIntyre CC. Artificial neural network based characterization of the volume of tissue activated during deep brain stimulation. J Neural Eng. 2013;10(5):056023.
70. Schmidt C, Grant P, Lowery M, van Rienen U. Influence of uncertainties in the material properties of brain tissue on the probabilistic volume of tissue activated. IEEE Trans Biomed Eng. 2013;60(5):1378-87.
71. Boutet A, Ranjan M, Zhong J, Germann J, Xu D, Schwartz ML, et al. Focused ultrasound thalamotomy location determines clinical benefits in patients with essential tremor. Brain. 2018;141(12):3405-14.
72. Akram H, Sotiropoulos SN, Jbabdi S, Georgiev D, Mahlknecht P, Hyam J, et al. Subthalamic deep brain stimulation sweet spots and hyperdirect cortical connectivity in Parkinson's disease. Neuroimage. 2017;158:332-45.
73. Dembek TA, Barbe MT, Astrom M, Hoevels M, Visser-Vandewalle V, Fink GR, et al. Probabilistic mapping of deep brain stimulation effects in essential tremor. Neuroimage Clin. 2017;13:164-73.
74. Eisenstein SA, Koller JM, Black KD, Campbell MC, Lugar HM, Ushe M, et al. Functional anatomy of subthalamic nucleus stimulation in Parkinson disease. Ann Neurol. 2014;76(2):279-95.
75. Butson CR, Cooper SE, Henderson JM, Wolgamuth B, McIntyre CC. Probabilistic analysis of activation volumes generated during deep brain stimulation. Neuroimage. 2011;54(3):2096-104.
76. King NKK, Krishna V, Sammartino F, Bari A, Reddy GD, Hodaie M, et al. Anatomic Targeting of the Optimal Location for Thalamic Deep Brain Stimulation in Patients with Essential Tremor. World Neurosurg. 2017;107:168-74.

77. Nowinski WL, Belov D, Pollak P, Benabid AL. Statistical analysis of 168 bilateral subthalamic nucleus implantations by means of the probabilistic functional atlas. Neurosurgery. 2005;57(4 Suppl):319-30; discussion -30.
78. Schupbach WMM, Chabardes S, Matthies C, Pollo C, Steigerwald F, Timmermann L, et al. Directional leads for deep brain stimulation: Opportunities and challenges. Mov Disord. 2017;32(10):1371-5.
79. Hellerbach A, Dembek TA, Hoevels M, Holz JA, Gierich A, Luyken K, et al. DiODe: Directional Orientation Detection of Segmented Deep Brain Stimulation Leads: A Sequential Algorithm Based on CT Imaging. Stereotact Funct Neurosurg. 2018;96(5):335-41.
80. Hunsche S, Neudorfer C, Majdoub FE, Maarouf M, Sauner D. Determining the Rotational Orientation of Directional Deep Brain Stimulation Leads Employing Flat-Panel Computed Tomography. Oper Neurosurg (Hagerstown). 2019;16(4):465-70.
81. Reinacher PC, Kruger MT, Coenen VA, Shah M, Roelz R, Jenkner C, et al. Determining the Orientation of Directional Deep Brain Stimulation Electrodes Using 3D Rotational Fluoroscopy. AJNR Am J Neuroradiol. 2017;38(6):1111-6.
82. Sitz A, Hoevels M, Hellerbach A, Gierich A, Luyken K, Dembek TA, et al. Determining the orientation angle of directional leads for deep brain stimulation using computed tomography and digital x-ray imaging: A phantom study. Med Phys. 2017;44(9):4463-73.
83. Anderson DN, Osting B, Vorwerk J, Dorval AD, Butson CR. Optimized programming algorithm for cylindrical and directional deep brain stimulation electrodes. J Neural Eng. 2018;15(2):026005.
84. Glasser MF, Sotiropoulos SN, Wilson JA, Coalson TS, Fischl B, Andersson JL, et al. The minimal preprocessing pipelines for the Human Connectome Project. Neuroimage. 2013;80:105-24.
85. Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M, et al. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. J Neurophysiol. 2011;106(3):1125-65.
86. Horn A. The impact of modern-day neuroimaging on the field of deep brain stimulation. Curr Opin Neurol. 2019.
87. Baldermann JC, Melzer C, Zapf A, Kohl S, Timmermann L, Tittgemeyer M, et al. Connectivity Profile Predictive of Effective Deep Brain Stimulation in Obsessive-Compulsive Disorder. Biol Psychiatry. 2019.

Tables

Table 1. Advantages, disadvantages and future developments of the reviewed neuroimaging advancements.

	Advantages	Disadvantages	Future Developments
UHF MRI	1. Higher SNR 2. Higher spatial resolution	1. Lack of availability 2. Image distortion 3. Safety concerns with metallic implants 4. Specialized knowledgebase and clinical expertise 5. Requirement for image co-registration with another stereotactic imaging modality	1. Higher magnetic field strengths (e.g. 9 Tesla) 2. Correction of image distortion 3. Development of coils and equipment that allow acquisition of stereotactic images
New MRI Pulse Sequences (e.g. QSM)	1. Better contrast between small structures 2. No need for purchase of expensive new equipment 3. More easily incorporated into existing surgical workflows	1. Imaging preprocessing 2. Specialized knowledgebase and clinical expertise 3. Not always possible to perform with commercially available stereotactic frames	1. Integrated into commercial software 2. Development of coils and equipment that allow acquisition of stereotactic images
Targeting Connectomes	1. Refine current targets 2. Direct visualization of target (e.g. tracts)	1. Functional neuroimaging acquisition 2. Specialized knowledgebase and clinical expertise	1. Prospective validation 2. Improved MRI pulse sequences

		3. Requirement for image co-registration with another stereotactic imaging modality	
Probabilistic maps for targeting	1. Refined current targets 2. Data-driven approach 3. Direct visualization of target (e.g. maps)	1. Large patient cohorts required 2. Specialized knowledgebase and clinical expertise 3. Requirement for image co-registration with another stereotactic imaging modality	1. Prospective validation 2. Refined VTA modelling

UHF MRI: Ultra-high field MRI; MRI: Magnetic resonance imaging; SNR: signal to noise ratio; QSM: Quantitative susceptibility imaging.

Figures

Figure 1. Neuroimaging pipeline methods for single (A) and group (B) level analysis in DBS patients. (A) Using preoperative and postoperative MRI (or postoperative CT) native head scans, DBS electrodes are localized and transformed into an average brain (e.g. MNI brain). Using the computed VTA, the stimulated structures in a single patient can then be investigated. (B) Following normalization and electrode localization of a cohort of DBS patients, each patient VTA can be weighted by clinical scores and a probabilistic map of clinical benefits can be computed on a structural MRI (B1: axial T1W MNI brain MRI). Using the weighted VTA, publicly available normative dataset of white matter tracts (B2) and functional networks (B3) can be used to investigate connections associated with clinical benefits (or adverse effects) (B4, B5). MRI: Magnetic resonance imaging; CT: computerized tomography. MNI: Montreal Neurological Institute, STN: Subthalamic nucleus, VTA: volume of tissue activated; T1-weigthed: T1W.