A literature review of magnetic resonance imaging sequence advancements in visualizing functional neurosurgery targets

Alexandre Boutet, MD, MSc[1,2]*, Aaron Loh, MB BCh BAO[1]*, Clement T. Chow, BKin[1], Alaa Taha[1], Gavin J. B. Elias, BA[1], Clemens Neudorfer, MD[1], Jurgen Germann, MSc[1], Michelle Paff, MD[1], Ludvic Zrinzo, MD, PhD[3], Alfonso Fasano, MD[4,5], Suneil K. Kalia, MD, PhD[1], Christopher J. Steele, PhD[6,7], David Mikulis, MD[1,2], Walter Kucharczyk, MD[1,2], Andres M. Lozano, MD, PhD[1]

**Authors contributed equally to this work*

Affiliations:
[1]University Health Network, Toronto, Ontario, Canada.
[2]Joint Department of Medical Imaging, University of Toronto, Toronto, Ontario, Canada.
[3]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.
[4]Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, University Health Network, Division of Neurology, University of Toronto, Toronto, Ontario, Canada
[5]Krembil Brain Institute. Toronto, Ontario, Canada.
[6] Department of Psychology, Concordia University, Montreal, Quebec, Canada
[7] Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany

Correspondence: Andres M. Lozano, Division of Neurosurgery, Toronto Western Hospital, Toronto, ON. Email: lozano@uhnresearch.ca

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Abstract

Objective
Historically, pre-operative planning for functional neurosurgery has depended on the indirect localisation of target brain structures using visible anatomical landmarks. However, recent technological advances in neuroimaging have permitted marked improvements in MRI-based direct target visualization, allowing for refinement of “first pass” targeting. We review studies relating to direct MRI visualization of the most common functional neurosurgery targets (subthalamic nucleus, globus pallidus, thalamus) and summarize sequence specifications for the various approaches described in this literature.

Methods
The peer-reviewed literature on MRI visualization of the subthalamic nucleus, globus pallidus, and thalamus was obtained by searching MEDLINE. Publications examining direct MRI visualization of these DBS targets were included for review.

Results
A variety of specialized sequences and post-processing methods for enhanced MRI visualization are in current use. These include susceptibility-based techniques such as quantitative susceptibility mapping (QSM), that exploit the amount of tissue iron in target structures, and white matter attenuated inversion recovery (WAIR), that suppresses the signal from white matter to improve the distinction between grey matter nuclei. However, evidence confirming the superiority of these sequences over indirect targeting with respect to clinical outcome is sparse. Future targeting may utilize information about functional and structural networks, necessitating the use of resting state functional MRI and diffusion-weighted imaging.

Conclusions
Specialized MRI sequences have enabled considerable improvement in the visualization of common DBS targets. With further validation of their ability to improve clinical outcomes and advances in imaging techniques, direct visualization of targets may play an increasingly important role in pre-operative planning.

Abbreviations
ANT: anterior thalamic nuclei
CNR: contrast-to-noise ratio
DBS: deep brain stimulation
DYT: dystonia
ET: essential tremor
GPi: globus pallidus
GPi: globus pallidus internus
GRE: gradient echo
IR: inversion recovery
MRI: magnetic resonance imaging
PD: Parkinson's disease
QSM: quantitative susceptibility mapping
rsfMRI: resting-state functional magnetic resonance imaging
T2W: T2-weighted
T2*W: T2-star-weighted
SE: spine echo
SN: substantia nigra
SNR: signal-to-noise ratio
STN: subthalamic nucleus
SWI: susceptibility-weighted imaging
T: tesla
VC: ventrocaudalis

Introduction

Functional neurosurgery is dedicated to modulating aberrant circuits associated with a wide range of neurological conditions.[1] Broadly speaking, this can be achieved by lesioning (e.g., radiosurgery, radiofrequency ablation, and MR-guided focused ultrasound) or electrical stimulation of key brain structures (i.e., deep brain stimulation, DBS). While principally employed for the treatment of movement disorders such as Parkinson's disease (PD), essential tremor (ET), and dystonia (DYT), the field, mainly driven by DBS, has seen its spectrum of potential indications expand to psychiatric (e.g., obsessive-compulsive disorder, Tourette syndrome, depression, and anorexia nervosa) and cognitive disorders (e.g., Alzheimer's disease).[2] While direct magnetic resonance imaging (MRI)-visualization of the targeted brain structures has been used early on[3], generally it has been insufficient for pre-operative planning.[4]

Indirect targeting methods, which estimate the location of targets in relation to fixed and identifiable anatomical landmarks on MRI, have traditionally been used because DBS targets could not be visualized on ventriculography and CT.[4] However, indirect targeting fails to account for inter-individual variability in the location of target structures.[5] To improve DBS targeting accuracy, indirect targeting methods were coupled with a variety of other techniques such as intraoperative microelectrode recordings and intra-operative stimulation testing in awake patients.[6] However, these methods are associated with prolonged procedural times and require multiple penetrations of deep brain structures, increasing the risk of intra- and post-operative complications.[7]

Routine brain MRI sequences acquired with standard field strengths and acquisition parameters have shortcomings in visualizing DBS targets.[8-10] However, with advances in stereotactic frames, MRI hardware and pulse sequences, direct visualization of certain structures, such as the subthalamic nucleus (STN), is replacing indirect targeting methods for pre-operative planning at some institutions.[7,11] Nonetheless, other structures, including thalamic nuclei, still require indirect targeting as their direct radiological visualization remains challenging.[12,13] MRI techniques optimizing white/grey matter contrast[14,15] or leveraging differences in tissue composition such as iron content[16] have been developed to improve the delineation of DBS targets. The therapeutic effects achieved with DBS surgery hinge upon the precise and selective modulation of the intended target structure, maximizing treatment efficacy while minimizing any off-target spillover into neighboring structures that might produce adverse effects. Therefore, it seems plausible that direct MRI targeting will be increasingly incorporated into pre-operative planning at most institutions.

Here, the goal was to review the many different MRI techniques that have been developed to date to enhance visualization of the most common grey matter nuclei targeted with DBS, while also discussing the relevant anatomy and clinical indications of these structures. Finally, we discuss the potential implications of expected MRI advancements on DBS surgery.

Search methods

A comprehensive search was conducted on June 1, 2020 using the MEDLINE database. The goal was to perform a scoping study[17] reviewing the literature to examine the extent of research activity, to summarize research findings, and to identify research gaps. The search strategy employed terms related to "Magnetic Resonance Imaging" and "Deep Brain Stimulation" and the most common neurosurgical targets (see supplementary materials and Supplementary Figure 1 for

detailed search methods and syntaxes). To maintain the clinical relevance of this review, only studies using clinically used field strengths (i.e., 1.5T or 3T MRI) were included.

Most common DBS targets

Figure 1 provides a visual comparison between non-optimized routine (red outline) and optimized (green outline) MRI sequences from the literature to visualize DBS targets. Accompanying acquisition parameters are detailed in Table 1. These optimized MR images were selected based on general trends among studies comparing MRI sequences for visualizing common DBS targets (Table 2).

1. Subthalamic nucleus

Relevant anatomy

STN is a small (approximately 8 mm in maximal transverse histological dimension[18]), almond-shaped grey matter structure located inferior to the thalamus. It features complex neuroanatomical relationships, being bounded by the internal capsule anterolaterally, the substantia nigra (SN) ventrolaterally, cerebellothalamic fibres posteromedially, and fields of Forel and zona incerta superiorly (Figure 2a).[19,20] STN has three main functional subdivisions: a superior, posterior and lateral "sensorimotor" area, a central "associative" area, and an "emotive" medial, anterior and inferior tip.[20-22]

Clinical indications for DBS targeting

The sensorimotor STN is the main target for PD, whereas DBS of the "associative and emotive" STN has been investigated as a treatment for obsessive-compulsive disorder.[1,2]

Direct MRI visualization

T2-weighted (T2W) and inversion recovery (IR) imaging have classically been the most common approaches used to directly visualize STN.[23,24] More recently, susceptibility-weighted imaging (SWI) and T2-star-weighted magnitude imaging (T2*W) have been employed. Finally, novel image processing techniques, such as quantitative susceptibility mapping (QSM) applied to SWI-based acquisitions, have shown promise in enhancing MRI visualization of STN.[8] STN is most reliably demarcated from adjacent zona incerta and SN on coronal slices.[25]

Most commonly, T2W sequences have been used for direct targeting of STN.[24] In these sequences, the nucleus can be identified as a hypointense lentiform structure – presumably due to iron deposition[26] – measuring approximately 7 mm in maximal radiological dimension.[18] The interface between STN and SN is not always visible on T2W images, especially at 1.5T[27] (and also at 3T[28]). Moreover, visualising the STN on T2W sequences will only lead to improved targeting if stereotactic images are optimised for contrast and if they are processed to minimise geometrical distortion.[29]

IR sequences aim to enhance the visualization of a given structure by selectively suppressing certain tissues with a specific composition. When using a fluid-attenuated inversion recovery (FLAIR) sequence, which nulls the signal from fluid, STN remains hypointense with reduced geometric distortion compared to traditional T2W imaging. Although there is limited evidence comparing FLAIR sequences to other visualization techniques, Senova et al.[30] showed that pre-operative targeting in PD patients with a 3T FLAIR sequence (3D sampling perfection with

application-optimized contrasts by using different flip angle evolution (SPACE) FLAIR) was associated with both minimal geometric distortion and significantly higher contrast with surrounding structures, as well as better clinical outcomes at 12 months over routine T2W imaging (Figure 1c and Table 1). However, similar to T2W sequences, STN borders adjacent to the SN remain difficult to delineate even at 3T.[25]

Other less commonly used IR sequences have also been used to visualize STN for DBS surgical planning; these include short T1 inversion recovery (STIR), which nulls signal from fat, phase sensitive inversion recovery (PSIR), and more recently, fast grey matter T1 inversion recovery (FGATIR), intended to null white matter signal.[24] Notably, PSIR is the only sequence in which the geometrical distortion with a stereotactic head frame has been shown to be less than 1% at 1.5T[31], while STIR sequence has demonstrated increased contrast between STN and SN at 3T, offering improved delineation of the inferior STN border.[32] Finally, FGATIR has shown promise in visualizing all STN borders in PD and ET patients, owing to increased contrast-to-noise ratio (CNR) (Figure 1d and Table 1).[33] Despite encouraging results, the use of these IR sequences in clinical settings remains relatively low to date, perhaps due to the specialized knowledgebase required, single vendor implementation, and the need for replication of relevant findings in larger studies.

SWI uses GRE sequences, which enhance the effect created by magnetic susceptibility differences between tissues. This is particularly valuable for STN imaging due to the increased iron content of this structure in the context of neurodegenerative diseases, and with increasing age.[34] The paramagnetic property of STN can be leveraged to enhance its differentiation from neighboring structures. SWI images, as well as accompanying T2*W[25,35] and susceptibility-weighted phase imaging (SWPI)[36], have been successfully used to visualize all STN boundaries (Figure 1e and Table 1). However, these techniques are limited by geometrical distortion, which have been shown to be as much as 0.8, 0.5, and 0.7 mm in the x, y, z planes, respectively, in a fast low-angle shot sequence (FLASH).[37] These distortions arise because GRE sequences are prone to the non-local susceptibility effect, which causes geometrical distortion and consequently, blurring and enlargement of STN borders.[24] This occurs because the high iron content of STN creates a local magnetic field in the MRI, which induces the relaxation of protons in surrounding tissues, thereby producing a susceptibility effect outside STN even in the absence of a susceptibility source. Moreover, the non-uniform distribution of iron in the STN disproportionately exaggerates the distortion of certain borders.[24]

QSM is a post-processing technique that allows for quantification and correction of geometrical distortions when visualizing STN with GRE sequences (Figure 1f and Table 1).[8,28] This technique reduces the non-local susceptibility effect by providing a clearer picture of tissue susceptibility and magnetic properties, irrespective of patient position (and thus STN orientation).[24,38] In addition, it provides a more accurate measurement of brain iron concentration, allowing for improved discrimination of surrounding iron-rich gray matter structures in PD patients, including the SN. As with other SWI-based sequences, the geometrical accuracy of QSM post-processing has had limited validation in larger clinical studies, although Rasouli et al. showed a strong correlation of QSM with intraoperative microelectrode recording (MER) delineation of the STN in 25 PD patients.[28] Furthermore, the technique remains difficult to implement at most clinical centers as image generation is technically demanding and often requires a significant amount of

processing time.[39] However, online reconstruction techniques have shown promise in addressing these practical limitations, reducing the image construction time to < 30 seconds on standard computers.[40] That being said, QSM reconstruction algorithms remain a work in progress.[41]

Table 2 lists studies that have compared sequences for direct STN visualization. In general, susceptibility-based sequences[16,25,42-44] and optimized IR sequences such as FGATIR and STIR[30,32,33,45-47] demonstrated superior signal-to-noise ratio (SNR) and CNR compared to the more traditionally used T2W and IR (e.g., FLAIR) sequences. Indeed, routine T2W and IR sequences have repeatedly offered suboptimal visualization of all STN borders at 1.5T. Unsurprisingly, higher field strength MRI (i.e., 3T) can improve STN border visualization with these sequences.[30,48]

2. Globus pallidus

Relevant anatomy

Named after its pallid appearance on anatomical specimens, GP is a lens-shaped grey matter structure situated between the putamen and internal capsule (Figure 2b). The putamen and GP, which together form the lentiform nucleus, are demarcated by the external medullary lamina. GP itself is divided into two constituent parts by the medial medullary lamina: GPi and globus pallidus externus.[33] GPi borders the optic tract ventrally and the internal capsule medially. The motor component is functionally segregated in the posterior GPi.[49]

Clinical indications for DBS targeting

After STN, GPi is the most common target for DBS in the management of PD.[2] Although both sites arguably provide similar motor benefits, STN contributes to medication intake reduction whereas GPi may be better suited for PD patients with cognitive impairment and medication-associated dyskinesias.[50,51] GPi is also the main target for dystonia, and has shown promise in the treatment of Tourette syndrome.[2] While uncommonly used, stimulation of the globus pallidus externus has also been shown to improve PD symptoms[52].

Direct MRI visualization

In our center's experience, T2W and PD[15] (Figure 1j and Table 1) sequences are most commonly used for direct visualization of the GP. In contrast to STN, GPi is better appreciated on axial slices.[9] On T2W images, the GP can be seen as a hypointense structure[53], whereas it is mildly hyperintense on proton density images.[15] At lower field strengths (i.e., 1.5T), these sequences generally resolve the optic tract, external medullary lamina and adjacent putamen, and the internal capsule bordering the pallidum posteromedial side. Delineation of additional boundaries, such as the medial medullary lamina, may not always be reliably obtained.[15] Among other sequences, Nowacki et al.[54] investigated the use of a T1W sequence in dystonia patients, specifically the modified equilibrium Fourier transform (MDEFT) technique, which is employed at high field strengths due to its advantageous contrast characteristics. Using this MDEFT approach at 3T field strength, the caudate-putamen and pallidal subdivisions, the GPe and GPi, were well demarcated in most patients (Figure 1k and Table 1). Because the central trajectory was used in 88% of all cases, MDEFT-based planning was deemed accurate and reliable.

IR sequences, on which the pallidum appears as a hypointense structure, have also been used. While IR spin-echo sequences (e.g., IR-FSE) at 1.5T have been shown to visualize the optic tract and external medullary lamina.[53] FGATIR additionally allowed delineation of the internal medullary lamina.[33] FGATIR has further been modified to enhance the distinction between GPi and GPe by using parameters suppressing fluid and white matter sequence (FLAWS sequence)(Figure 1l and Table 1).[55] In this study, FLAWS was generated through the registration of two contrasts, the standard T1-weighted anatomical contrast of the brain (i.e., MPRAGE), and the suppression of the white matter signal (i.e., FGATIR), demonstrating enhanced visualization of subcortical structures in healthy participants.

As with STN, susceptibility-based sequences permit direct visualization of the pallidum. T2* and QSM sequences have been shown to discern GPi and GPe in PD patients.[56] However, with an SWI-like sequence at 3T, Ide et al.[57] showed that the medial medullary lamina was less readily identifiable with increasing age, which may be related to increased mineralization in the GP and/or a loss of myelin.

Few studies have compared sequences for direct visualization of the GP and its subdivisions in a head-to-head manner (Table 2). A handful of reports found that GPi was best visualized using susceptibility-based sequences when compared to T1W, T2W, or IR sequences at 1.5T and 3T.[9,16,44,57] Another found that, at 3T, the internal medullary lamina in PD and ET patients was better visualized on FGATIR sequence compared to the more commonly employed FLAIR and T1W imaging (i.e., MPRAGE).[33] While these findings are not necessarily conflicting, additional studies comparing sequences would be helpful in establishing a consensus for optimal visualization of the pallidum and its internal architecture.

3. Thalamus

Relevant anatomy

A large grey matter structure, the thalamus is located immediately above the hypothalamus and medial to the posterior limb of the internal capsule, forming the lateral wall of the third ventricle and floor of the lateral ventricles (Figure 2c). Within the thalamus, the internal medullary lamina divides the structure into anterior, medio-dorsal, ventral, and lateral groups, with each group comprising several distinct nuclei.[58] Functionally, the thalamus has a distinct topographical organisation. In simple terms, the posterior part contributes to sensory processing, whereas the motor thalamic relay is located in the ventrolateral part. Finally, the anterior and medio-dorsal nuclear groups are considered to be involved in limbic and associative functions, respectively.[58]

Clinical indications for DBS targeting

Stimulation of the thalamic ventral intermediate nucleus (VIM) is well established for the management of essential tremor and, to a lesser extent, tremor secondary to other pathological conditions such as multiple sclerosis or stroke.[2] Modulation of the ventrocaudal (VC) nucleus has been performed to treat chronic pain disorders, particularly central post-stroke pain.[59] Additionally, the centromedian nucleus (part of the intra-laminar nuclei) has been targeted for multiple neurological and psychiatric indications including Tourette Syndrome, PD and epilepsy, while stimulation of the anterior thalamic nuclei (ANT) has shown potential in suppressing global seizure activity in epilepsy patients.[1,2]

Direct MRI visualization

Thalamic nuclei, including VIM, are notoriously difficult to visualize on routine MRI sequences and often necessitate the use of atlas-derived coordinates for pre-operative planning.[60] On routinely acquired T1W and T2W sequences, the thalamus is mildly hyperintense and hypointense, respectively.[61] Despite its many nuclei, it appears fairly homogenous with little distinction between subdivisions. However, studies in healthy participants have shown that the inversion time (TI) of T1W sequences may be optimized, allowing suppression of gray matter.[14,62] The resulting gray and white matter differentiation enables identification of the main thalamic groups: anterior, dorsomedial, lateral, and ventral.[14] Optimizing the repetition time (TR) of T1W (i.e., MPRAGE) has also been shown to enable specific delineation of anterior thalamic nucleus (ATN), improving targeting prior to DBS epilepsy surgery (Figure 1p and Table 1).[62] To further optimize visualization of thalamic nuclei, MPRAGE has been combined with phase data from 3D GRE sequences, which enabled the distinction of additional thalamic substructures such as the VIM (Figure 1q and Table 1).[63] These techniques have yet to be demonstrated in diseased populations.

In one study using a 3T proton density sequence, it was possible to visualize VIM in healthy subjects as a mildly hypointense band crossing the anterior third of the thalamus, from lateral to medial.[64] However, it was inconsistently seen at 1.5T. Furthermore, the sensory thalamic nuclei (i.e., VC nucleus) was seen as another hypointense band located posteriorly.[64] Using a PD sequence at 3T, direct targeting of VIM has been successfully performed in a tremor patient.[65]

IR sequences have also enabled visualization of VIM. Specifically, studies have shown VIM to be slightly hyperintense relative to the posterior nuclei on STIR sequences.[66,67] IR sequences, including STIR and FGATIR, have also been used for targeting of the ANT based on delineation of the mammillothalamic tract, which terminates in ANT.[61,68,69] An IR sequence suppressing signal from white matter (i.e., White matter Attenuated Inversion Recovery (WAIR)) has demonstrated significant enhancement of contrast between different gray matter territories in PD and ET patients, with promise in visualizing the internal subdivisions of the thalamus (Figure 1r and Table 1).[13] On WAIR, VIM appears as a hypointense band crossing the ventrolateral region of the thalamus relative to the surrounding nuclei.

Across the very small number of studies comparing thalamic visualization sequences, IR sequences have been found to be superior to routine T1W imaging (Table 2).[61,68]

Limitations

As recently as 15 years ago, indirect targeting based on anatomical landmarks was the mainstay of pre-operative surgical planning for most functional neurosurgery services. However, advances in MRI hardware and techniques have allowed direct targeting to become more accessible and clinically feasible.[24] In spite of these improvements, there is limited consensus on the optimal MRI sequences for direct visualization of common DBS targets. While addressing this issue, this review contains significant limitations, highlighting gaps in the literature that future studies may seek to confront. First, a large proportion of the studies were performed in healthy volunteers, which may not accurately reflect the radiological findings in DBS patients (Supplementary Table 1). For example, patients with PD, the most common DBS indication, demonstrate more pronounced brain atrophy and decreased white matter volume than healthy subjects.[70,71] This phenomenon,

compounded by normal age-related atrophy, has been hypothesized to underlie the decreased STN visibility in older PD patients.[10] Second, demonstrable improvements in image quality and the use of novel sequences are limited by the persistent requirement of using specific head coils (usually lower SNR and potentially geometrical distortion) that may not physically accommodate stereotactic head frames. Alternatively, frameless techniques or MRI/computed tomography (CT) scans co-registration may be used. However, this may add errors of coregistration that reduce first pass accuracy.[72] Second, an important practical consideration of these novel sequences is that while the delineation of DBS targets is improved, it may be difficult to visualize frame or frameless fiducials, as well as other anatomical landmarks such as the anterior and posterior commissures, which are commonly used to provide the overall anatomical picture necessary for preoperative planning. Consequently, an MRI-MRI registration — between a sequence visualizing DBS targets and an anatomical sequence — may be required. The accuracy of co-registering these optimized sequences to anatomical MRI sequences has not been thoroughly assessed in the literature. For example, Rasouli et al.[28] described a registration method between QSM and T1W without providing accuracy measurement. Novel composite sequences simultaneously acquire a sequence providing both anatomical details and DBS target visualization, which may mitigate the problem.[35] Additionally, to leverage the advantages provided by these optimized sequences, generally 3T and coils incompatible with stereotactic head frames have to be used, which creates an additional step of co-registration with a CT, potentially introducing geometric error. While such co-registrations inherently introduce error, a systematic review of MRI/CT fusion for localisation of electrode placement concluded that fusion was an accurate, reliable, and safe modality for assessing electrode location.[73] Third, studies that quantitatively compare sequences with regard to visualization and clinical outcomes remain few and far between, with little evidence establishing the superiority of one sequence over another. Most importantly geometrical distortions associated with most of these optimized sequences remain to be tested. Finally, studies also investigating whether direct target visualization definitively improves clinical outcomes when compared to indirect targeting should be done.

Summary framework to optimize MRI visualization of DBS targets

As highlighted in Figure 1, marked improvements in direct visualization of targets when using optimized, rather than routine (non-optimized) sequences have been made. Importantly, as discussed in this review, there is little quantitative evidence favoring specific sequences for visualization of each DBS target. Generally, Table 2 seems to suggest that IR sequences, for example FGATIR, provide improved visualization for the STN, GPi, and thalamus. This is a potential option for centers that do not have the requisite expertise needed to design their own optimized MRI protocols, or implement post-processing techniques such as QSM, for each DBS target. Finally, when implementing new sequences in their surgical planning, neurosurgeons should audit their own targeting accuracy and assess for systematic errors that may have originated from geometric distortions and other sources of error.[74,75]

Future directions

Direct visualization of the most common DBS targets, namely the STN, GPi, and thalamus, has markedly improved in recent years. Further improvement may be expected as ultra-high field (UHF) MRI becomes more widely available (Figure 3a, b). Higher magnetic field strengths offer increased SNR, which in turn allows increased spatial resolution, permitting the delineation of smaller neuroanatomical structures.[76-78] UHF MRI also confers a superior CNR, improving the

ability to differentiate between two small abutting structures.[77,78] Given these advantages, it is unsurprising that UHF MRI has been shown to better visualize DBS targets than 1.5T and 3T with comparable acquisition times.[79] However, while higher magnetic field strengths may improve visualization *per se*, they are also more prone to susceptibility effects and image distortions[24,80], theoretically leading to a greater risk of mistargeting. Furthermore, UHF MRI has not been utilized in conjunction with commercially available stereotactic frames to date. This necessitates that UHF MR images be co-registered with stereotactic images acquired using another modality (e.g., CT) for pre-operative targeting, a step that can introduce registration errors.[72] Lastly, the risks of DBS systems in UHF MRI have not been thoroughly evaluated, potentially limiting the widespread clinical applicability of this technology.[81] Taking these aforementioned caveats into consideration, it is clear that further studies are needed to compare UHF MRI with conventional MRI (1.5T and 3T) for surgical targeting, with clinical outcomes being used as the primary endpoint. With the advent of image distortion correction methods[82], continued testing is required to elucidate potential benefits, obstacles, and trade-offs presented by UHF MRI.

The desire to expand the indications for DBS and improve upon traditional targets has contributed to a paradigm shift in pre-operative targeting. Rather than discrete structures, such as deep gray matter nuclei, optimal targets may include white matter pathways[83,84] or focal hubs of functional networks[85], which are entities that are not necessarily appreciated on structural sequences at any field strength. Moreover, there is a growing appreciation that optimal targets may differ between patients, reflecting both heterogeneity within specific disorders and underlying inter-individual differences in brain "wiring". To be appreciated, white matter tracts and functional networks require both highly specialized MRI sequences – diffusion-weighted imaging (dMRI) tractography and resting-state functional magnetic resonance imaging (rsfMRI), respectively – and fairly complex post-processing. While rsfMRI networks have shown to predict improvement in STN stimulation for PD, this technique remains experimental.[85] Conversely, structural connectivity profiles have been shown to retrospectively correlate with clinical outcome[60] and tractography-based targeting of the dentato-rubro-thalamic tract (DRTT) and medial forebrain bundle have already been employed as clinical treatments for essential tremor and psychiatric disorders, respectively (Figure 3c-e).[86,87] DRTT has been seldom used to prospectively guide DBS targeting.[88] However, the protocol for a randomized clinical trial comparing the efficacy of VIM-DBS (the traditional DBS target for tremor) and DRTT DBS has been published.[89] Outside of DBS, prospective DRTT targeting with MRI-guided focused ultrasound was shown to provide excellent symptom relief in patients withtremor.[90] Since many of the proposed targets trialled for psychiatric disorders, such as the medial forebrain bundle for treatment resistant depression and obsessive-compulsive disorder, are white matter structures, tractography-based targeting is required. Tractography has also been used to functionally segment grey matter targets, such as STN or thalamus, based on their white matter projections to the cortex, thereby potentially offering an alternative method to demarcate zones of clinical interest within these structures.[91,92] This method has not been thoroughly investigated in a prospective fashion. Overall, rsfMRI and dMRI tractography provide an opportunity to both refine current targets using network-centred approaches and to better visualize new or emerging targets that are not amenable to visualization with structural MRI sequences. The limitations of these emerging techniques need to be considered, particularly their validation in prospective studies is generally lacking.

Conclusion

Owing to technological advances in neuroimaging, most DBS targets can currently be visualized on MRI to some degree, providing an adjunct to indirect targeting. Progress in this field largely stems from the development of optimized sequences and acquisition parameters and has also been furthered by the increasing use of 3T MRI in clinical settings. It is expected that direct visualization will continue to improve, eventually enabling sufficient visualization of additional targets such as the pedunculopontine nucleus[93], which are thus far difficult to appreciate.

While direct visualization of DBS targets has the benefit of taking into account inter-patient anatomical variability and encouraging more individualized pre-operative planning, studies are needed to definitely establish the superiority of direct targeting over indirect targeting, and to establish which visualization techniques have the highest spatial fidelity for each target. Upcoming developments in this field are likely to relate to UHF MRI, which provides increased SNR and CNR, as well as emerging techniques such as rsfMRI and dMRI tractography, which offer the possibility of refining existing targets and discovering new targets by tapping into distributed functional or structural networks.

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Tables

Study	**Routine**	**Routine**	Senova (2016)[30]	Sudhyadhom (2009)[33]	Xiao (2015)[35]	Rasouli (2018)[28]	**Routine**	**Routine**	**Routine**	Hirabayashi (2002)[15]	Nowacki (2015)[54]	Beaumont (2019)[55]	**Routine**	**Routine**	**Routine**	Buentjen (2014)[62]	Bender (2017)[63]	Vassal (2012)[13]
Figure 1	**a**	**b**	c	d	e	f	**g**	**h**	**i**	j	k	l	**m**	**n**	**o**	p	q	r
Target	**STN**	**STN**	STN	STN	STN	STN	**GPi**	**GPi**	**GPi**	GPi	GPi	GPi	**Thal**	**Thal**	**Thal**	Thal	Thal	Thal
Sequence	**T1W**	**T2W**	FLAIR	FGATIR	T2*W	QSM	**T1W**	**T2W**	**PDW**	PDW TSE	MDEFT	FLAWS	**T1W**	**T2W**	**PDW**	MPRAGE	MPRAGE*	WAIR
Disease	**Healthy**	**Healthy**	PD	PD, ET	PD	PD	**Healthy**	**Healthy**	**Healthy**	PD	PD 6, DYT 7	Healthy	**Healthy**	**Healthy**	**Healthy**	Healthy	Healthy	PD, ET
Number of patients	**1**	**1**	10	PD 2, ET 1	25	122	**1**	**1**	**1**	48	13	11	**1**	**1**	**1**	6	9	PD 13, ET 7
MRI Manufacturer	Signa Excite, GE	Signa Excite, GE	Verio, Siemens	Allegra, Siemens	Trim Trie, Siemens	Discovery MR750, GE	Signa Excite, GE	Signa Excite, GE	Signa Excite, GE	Magnetom Impact Expert,, Siemens	Magnetom Trio Trim, Siemens	Magnetom Aera, Siemens	Signa Excite, GE	Signa Excite, GE	Signa Excite, GE	**Verio, Siemens**	Trio, Siemens	Sonata, Siemens
Field strength (T)	**1.5**	**1.5**	3	3	3	3	**1.5**	**1.5**	**1.5**	1.0	3	1.5	**1.5**	**1.5**	**1.5**	3	3	1.5
Matrix	**256 x 224**	**256 x 224**	512 x 512	320 x 256	256 x 256	256 x 256	**256 x 256**	**320 x 256**	**256 x 256**	210 x 256	256 x 224 x 176	180 x 192	**256 x 256**	**320 x 256**	**256 x 256**	320 × 240 × 224	NA	NA
FOV (mm)	**NA**	**NA**	250 x 250	256 x 192	NA	25	**NA**	**NA**	**NA**	250	NA	225 x 240	**NA**	**NA**	**NA**	NA	256 × 256	NA
Slice thickness (mm)	**2**	**2**	1	1	NA	1	**1.4**	**1**	**1**	2	1	NA	**1.4**	**1**	**1**	NA	1	NA
TE (msec)	**20**	**90.36**	372	4.39	21.0	NA	**5.3**	**92.49**	**30**	15	2.48	2.32	**5.3**	**92.49**	**30**	6.7	3.4	13
TR (msec)	**450**	**3750**	6000	3000	30	43.8	**12.4**	**3600**	**2950**	4000	7.92	3500	**12.4**	**3600**	**2950**	2.91	2300	4500
TI (msec)	**NA**	**0**	2100	409	NA	NA	**300**	**NA**	**NA**	NA	NA	403/1030	**300**	**NA**	**NA**	1100	700	160
Flip angle (degree)	**90**	**90**	NA	180	23	15	**20**	**90**	**90**	NA	16	6/8	**20**	**90**	**90**	7	8	NA
Bandwidth (kHz)	**244**	**195**	781	130	450	62.5	**57**	**122**	**97.7**	NA	NA	240	**57**	**122**	**97.7**	160	130	NA
Head coil	**head receive-transmit coil**	**head receive-transmit coil**	12-channel coil	NA	32-channel head coil	NA	**head receive-transmit coil**	**head receive-transmit coil**	**head receive-transmit coil**	head coil	12-channel	20-channel head coil	**head receive-transmit coil**	**head receive-transmit coil**	**head receive-transmit coil**	32-channel head coil	32-channel head coil	NA

Voxel size (mm)	**NA**	**NA**	NA	NA	0.95 x 0.95 x 0.95	NA	**NA**	**NA**	**NA**	NA	N/A	1.25 x 1.25 x 1.4	**NA**	**NA**	**NA**	0.8 x 0.8 x 0.8	NA	0.52 x 0.62 x 2.0
Acquisition time (min)	**7:49**	**8:17**	7:00	11:14	7:05	NA	**3:13**	**11:50**	**7:50**	6:05	12:00	10:27	**3:13**	**11:50**	**7:50**	20:00	19:39	19:06

Table. 1 Optimized MRI acquisition parameters. Acquisition parameters used to optimize visualization of the subthalamic nucleus, pallidum, and thalamus as shown in Figure 1. Bolded sequences are routine (non-optimized) sequences for comparison. 2/3D = two-/three-dimensional; DYT = dystonia; ET = essential tremor; FGATIR = fast grey matter acquisition T1 inversion recovery; FLAIR = fluid attenuated inversion recovery; FLASH = fast low angle shot; FLAWS = fluid and white matter suppression; FOV = field-of-view; GE = general electric; GPi = globus pallidus internus; kHz = kilohertz; MDEFT = modified driven equilibrium Fourier transform ; mm = millimeter; MPRAGE = magnetization-prepared rapid acquisition with gradient echo; msec = milliseconds; NA = not applicable; PD = Parkinson's disease; PDW = proton density-weighted; QSM = quantitative susceptibility mapping; STN = subthalamic nucleus; T = tesla; T1W = T1-weighted; T2*W = T2*-weighted; T2W = T2-weighted; TE = echo time; Thal = thalamus; TI = inversion time; TR = repetition time; TSE = turbo spin echo; WAIR = white matter attenuated inversion recovery

	Study	Field Strength (T)	"Optimal" Sequence(s)	Other Sequences Compared	Image Quality Metric
Subthalamic Nucleus	van Laar (2016)[48]	3 / 1.5	T2W $TSE_{(3T)}$	**T2W $TSE_{(1.5T)}$**	TC, SNR
	Senova (2016)[30]	3 / 1.5	3D SPACE FLAIR	**T2W**	$C_{contour}$
	Heo (2015)[45]	3	FLAIR	T2W TSE, **T2*W FFE**	Rater, CR
	Sarkar (2015)[46]	1.5	FSTIR	**T2W FSE**	SNR
	Lefranc (2014)[42]	3	HR 3D SWAN	3D T1W + Gd, **3D T2W SE**	Rater
	Nagahama (2015)[43]	3	T2W SWAN	**T2W FSE, T2*W GRE**	CNR
	Liu (2013)[16]	3	QSM	**T2W, T2*W, R2*, Phase, SWI**	Rater, CNR
	Kerl (2012)[25]	3	T2*W FLASH2D	SWI, T2W SPACE, T1W MPRAGE, **T2W FLAIR**	Rater, CNR
	Ben-Haim (2011)[47]	1.5	T2W FSE/IR - SPGR	**T2W FSE/IR**	NA
	O'Gorman (2011)[44]	1.5	SWI	PDW FSE, PSIR, DESPOT1, IR-FSPGR, TE40 GRE, **T2W FSE**	CNR
	Sudhyadhom (2009)[33]	3	FGATIR	T2W 3D FLAIR, **T2W 3D MPRAGE**	CNR, CR
	Kitajima (2008)[32]	3	FSTIR	**T2W FSE**	Rater, CNR
	Elolf (2007)[94]	3	T2*W FLASH	**T2W TSE**	NA
Globus Pallidus	Maruyama (2019)[95]	3	T2W	PDW	CR
	Ide (2017)[57]	3	PADRE	SWI-like, **T2W**	Rater
	Liu (2013)[16]	3	QSM	**T2W, T2*W, R2*, Phase, SWI**	Rater, CNR
	Nölte (2012)[9]	3	T2*W FLASH 2D, SWI, SWI-MIP	T2W SPACE, T2*W FLASH 2DHB, **FLAIR**, T1W MPRAGE	Rater, CNR, SNR
	O'Gorman (2011)[44]	1.5	SWI	PDW FSE, PSIR, DESPOT1, IR-FSPGR, TE40 GRE, **T2W FSE**	CNR
	Sudhyadhom (2009)[33]	3	FGATIR	T2W 3D FLAIR, **T2W 3D MPRAGE**	CNR, CR
Thalamus	Li (2019)[96]	3	3D GRE / QSM	3D T1W, 2D T2W	CNR
	Grewal et al. (2018)[61]	3	HR FGATIR	HR MPRAGE, MPRAGE	NA
	Bender (2017)[63]	3	MPRAGE*	Phase, **T1W MPRAGE**	Rater
	Jiltsova (2016)[68]	1.5	STIR	**T1W MPRAGE**	NA

Table 2. Comparison of MRI sequences for visualizing common DBS targets. Studies comparing MRI sequences to optimally visualize the subthalamic nucleus, pallidum, and thalamus are listed. Bolded sequences show the reference or "standard" sequence used in each study. The metric of image quality that authors used for comparison is provided. 2/3D = two-/three-dimensional; $C_{contour}$ = contrast of the contour; CNR = contrast-to-noise ratio; CR = contrast ratio; DESPOT1 = driven equilibrium single pulse observation of T1; FGATIR = fast gray matter acquisition T1 inversion recovery; FLAIR = fluid attenuated inversion recovery; FLASH = fast low angle shot ; FSE = fast spin echo; FSPGR= fast spoiled gradient recovery; FSTIR = T1-weighted fast spin echo based inversion recovery; Gd = gadolinium; GRE = gradient echo; HB = high bandwidth; HR = high resolution; IR = inversion recovery; MIP = minimum intensity projections; MPRAGE = magnetization-prepared rapid acquisition with gradient echo; NA = not applicable; PADRE = phase difference-enhanced imaging; PDW = proton density-weighted; PSIR = phase sensitive inversion recovery; QSM = quantitative susceptibility mapping; R2* = R2* mapping; Rater = qualitative scoring by raters; SE = spin echo; SNR = signal-to-noise ratio; SPACE = sampling perfection with application – optimised contrast by using flip angle evolution; STIR = short TI inversion recovery; SWAN = T2*-weighted angiography; SWI = susceptibility weighted imaging; T1W = T1-weighted; T2*W = T2*-weighted; T2W = T2-weighted ; TC = tissue contrast; TE40 = echo time 40; TSE = turbo spin echo.

Figures

Figure 1. Examples of optimized sequences and post-processing methods for enhanced MRI visualization of DBS targets. Zoomed out and zoomed in MRI images of the subthalamic nucleus (top section), globus pallidus internus (middle section), and thalamus (bottom section) are shown in addition to the corresponding slice from Mai et al. atlas.[97] Green outline identifies MRI images from the literature aiming at improving visualization of DBS targets whereas red outline identifies routinely acquired (non-optimized) T1W (left), T2W (middle), and PDW (right) images for comparison. Details pertaining to their publication and acquisition parameters are included in Table 1. The subthalamic nucleus is shown on coronal images whereas the globus pallidus internus and thalamus are shown on axial images. Atlas slices were reprinted by permission from Academic Press, , Mai JK, Majtanik M, Paxinos G, Atlas of the Human Brain (4th Edition), 239 & 406, Copyright Elsevier (2015). C was reprinted by permission from Senova S, Hosomi K, Gurruchaga JM, et al. Three-dimensional SPACE fluid-attenuated inversion recovery at 3 T to improve subthalamic nucleus lead placement for deep brain stimulation in Parkinson's disease: from preclinical to clinical studies. *J Neurosurg.* 2016;125(2):472-480. D was reprinted with permission from Sudhyadhom A, Haq IU, Foote KD, Okun MS, Bova FJ. A high resolution and high contrast MRI for differentiation of subcortical structures for DBS targeting: the Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR). *Neuroimage.* 2009;47 Suppl 2:T44-52. E was reprinted by permission from Xiao Y, Fonov V, Beriault S, et al. Multi-contrast unbiased MRI atlas of a Parkinson's disease population. *Int J Comput Assist Radiol Surg.* 2015;10(3):329-341. F was reprinted with permission from Rasouli J, Ramdhani R, Panov FE, et al. Utilization of Quantitative Susceptibility Mapping for Direct Targeting of the Subthalamic Nucleus During Deep Brain Stimulation Surgery. *Oper Neurosurg (Hagerstown).* 2018;14(4):412-419. J was modified with permission from Hirabayashi H, Tengvar M, Hariz MI. Stereotactic imaging of the pallidal target. *Mov Disord.* 2002;17 Suppl 3:S130-134. K was modified with permission from Nowacki A, Fiechter M, Fichtner J, et al. Using MDEFT MRI Sequences to Target the GPi in DBS Surgery. *PLoS One.* 2015;10(9):e0137868. L was modified with permission from Beaumont J, Saint-Jalmes H, Acosta O, et al. Multi T1-weighted contrast MRI with fluid and white matter suppression at 1.5T. *Magn Reson Imaging.* 2019;63:217-225. P was reprinted with permission from Buentjen L, Kopitzki K, Schmitt FC, et al. Direct targeting of the thalamic anteroventral nucleus for deep brain stimulation by T1-weighted magnetic resonance imaging at 3T. *Stereotact Funct Neurosurg.* 2014;92(1):25-30. Q was reprinted by permission from Bender B, Wagner S, Klose U. Optimized depiction of thalamic substructures with a combination of T1-MPRAGE and phase: MPRAGE. *Clin Neuroradiol.* 2017;27(4):511-518. R was reprinted with permission from Vassal F, Coste J, Derost P, et al. Direct stereotactic targeting of the ventrointermediate nucleus of the thalamus based on anatomic 1.5-T MRI mapping with a white matter attenuated inversion recovery (WAIR) sequence. *Brain Stimul.* 2012;5(4):625-633.

Figure 2. 3D representation of DBS targets and relevant neighbouring anatomy. (A) The subthalamic nucleus (orange) is shown medial to the internal capsule, lateral to the red nucleus, superior to the substantia nigra, and inferior to the thalamus. (B) The globus pallidus internus (green) is shown medial to the globes pallidus externus, infero-lateral to the thalamus, and superior to the optic tract. (C) The thalamus (pink) is shown medial to the internal capsule, and superior to the subthalamic nucleus and hypothalamus. Structures are overlaid on (A and C) coronal and (B) left oblique views of T1-weighted MNI brain (ICBM 2009b nonlinear asymmetric Montreal

Neurological Institute template). Anatomical structures are derived from the DISTAL atlas[49] and visualized in 3D with Lead-DBS (www.lead-dbs.org).

Figure 3. Potential implications of expected MRI advancements on DBS surgery. (A) 7T white-matter-nulled T1-weighted (magnetization-prepared rapid acquisition with gradient echo (MPRAGE) coronal image at the level of the thalamus from a healthy individual (reprinted with permission from 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;84:534-545. (B) 7T balanced steady-state free precession (bSSFP), which is a modified fast imaging employing steady state acquisition (FIESTA) sequence, coronal image at the level of the thalamus from a healthy individual (reprinted with permission from Zeineh MM, Parekh MB, Zaharchuk G, et al. Ultrahigh-resolution imaging of the human brain with phase-cycled balanced steady-state free precession at 7 T. *Invest Radiol.* 2014;49(5):278-289. (C-E) White matter tracts derived from diffusion-weighted imaging of ~1000 healthy subjects overlaid on a 7T fast low angle shot magnetic resonance imaging (FLASH) sagittal image.[98] (C) The dentato-rubro thalamic tract, a target for tremor, is shown in green alongside a 3D representation of the thalamus (blue) derived from the DISTAL atlas.[49] (D) The medial forebrain bundle, which has been targeted for treatment of depression and obsessive-compulsive disorder, is shown in purple. (E) The cingulum bundle (red), minor forceps (yellow), and uncinate fasciculus (blue), which have been used to guide targeting of the subcallosal region for depression, are shown.

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