Controversies in Deep Brain Stimulation Surgery: Micro-Electrode Recordings

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Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) was first applied as a neurosurgical intervention technique for Parkinson's disease (PD) in the 1990s and has since become a widely accepted practice. Bilateral STN-DBS has been proven to be significantly improve levodopa-responsive parkinsonian symptoms and quality of life compared to best medical treatment alone [1, 2]. DBS is generally considered in patients only when pharmacological treatment does not respond in sufficient effect any longer or leads to unacceptable adverse effects. Stimulation of the subthalamic nucleus (STN) is the most common practice since it results in more time in well-treated 'ON-condition', though the internal segment of the globus pallidus (GPi) is also a possibility [3, 4]**.** While DBS of the STN specifically is effective for a majority of patients in relieving the motor related symptoms of PD, a fraction of patients will fail to witness such beneficial effects. Moreover, DBS patients may develop a number of side effects spanning a range of domains, from

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speech and gait impairments to cognitive decline and impulse control disorders, as well as psychiatric and emotional disturbances.

The first two concepts here are a product of accurate target identification and verification, which can be achieved via pre-operative magnetic resonance imaging (MRI) and or intraoperative microelectrode recordings (MER). This chapter will attempt to determine whether MRI with or without additional intraoperative MER-guidance is most effective method for target identification and verification in DBS via a structured literature review. Additionally, we will discuss some advantages, caveats and outstanding complications for both methods. In this chapter we will focus on STN-DBS for PD.

Originally, MER was seen as the golden standard for anatomical verification of a target. In this method, the leads are placed in the brain based on standard atlas coordinate applied on a preoperative MRI of the patient. Through macro-stimulation of functionally distinct portions of the STN along with behavioural and clinical tests, MER can spatially map out the optimal location for DBS lead placement [5].

However, the verification via MER requires that the patient be awake and tested during DBS implantation. The patient's awake response on the intra-operative stimulation regarding motor symptoms and adverse effects can influence the final lead placement. Moreover, MER signals will be influenced by general anaesthesia. This is time consuming, stressful and causes a lot of anxiety for patients. Originally controversial, but steadily gaining popularity is the use of pre-operative MRI for targeting and intra operative MRI or CT for identifying lead location, rather than MER. This approach allows the patient to be under general anaesthesia, and has been shown to be equally as effective as MER [6–8]. Despite of many studies, some contradictions stay unsolved. For example, on the one hand supporters of MER suggest optimal final lead placement can deviate from the (MRI or atlas based) planned target by using intraoperative MER [9]. While, on the other hand opponents of MER suggest image-guided and verified surgery can reduce intra-operative brain-shift and accompanying lead inaccuracy, especially in the second placed lead [10].

Relatedly, the overall success of traditional target identification and implantation still will depend on a number of factors; namely the existing knowledge of the anatomy of the STN and surrounding structures, counteracting intra operative brain shift and the use of multiple leads for MER. Furthermore, modern technical advances offer new possibilities which might positively influence the outcome of lead placement and clinical outcome, however they are bring their own considerations. Some of them are pre-operative ultra-high field MRI, multimodal image techniques such as diffusion and functional MRI, personalized stimulation parameters and calculation of surrounding tissue activated outside of the target by stimulating with directional steering leads.

The following chapter therefore consists of a literature review of *DBS of the STN in PD patients using both, or either MRI and MER*, as well as papers discussing the aforementioned factors which are deemed essential for successful DBS, though remain subject to personal preference.

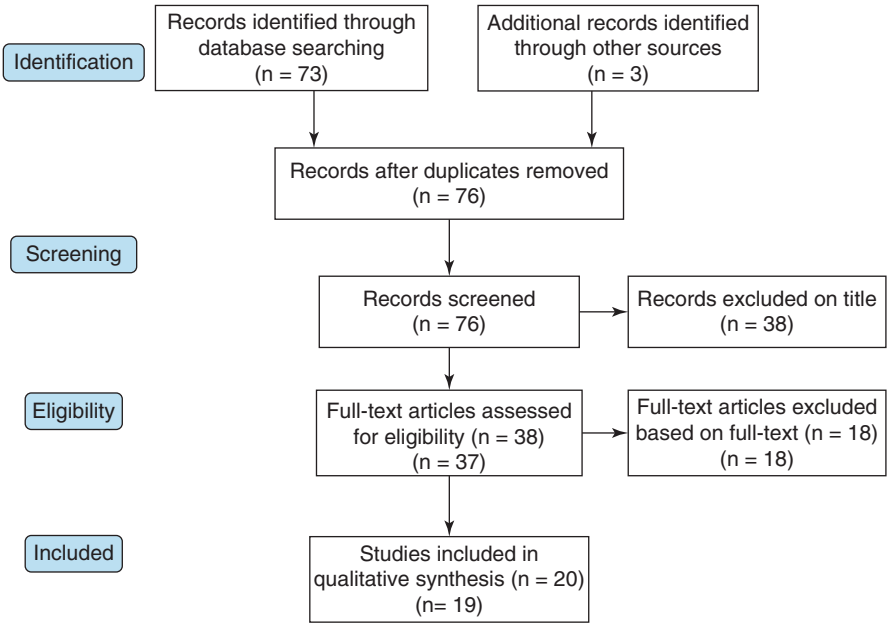
Methods

To collect relevant and recent literature we performed a literature search in the Pubmed database with the search string: "((micro electrode recording) OR (micro-electrode recording) OR MER) AND (MRI OR MR OR (magnetic resonance imag*)) AND (DBS OR (deep brain stimulation)) AND (STN OR (sub thalamic nucleus) OR (subthalamic nucleus))" on 18-07-2018, with a limitation of publication date within 10 years, which gave us 73 potential articles. We included three papers from cross-references.

We excluded 38 papers based on title. From the 38 full-articles, we excluded 18 articles because they had non-human subjects, described alternative methods besides conventional MRI-guided or MER-guided stereotactical DBS surgery, used non-STN targets or were non-original articles.

We included 20 articles for the qualitative evaluation we describe in this paper. Included articles are rated following the GRADE criteria for quality of evidence (https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/). Since this literature is very heterogenic, we did not perform a quantitative meta-analysis on clinical outcome, e.g. UPDRS or quality of life sores, or on anatomical outcome, e.g. millimetres deviation per MR-field strength or percentage of central MER-recordings used for final lead-implantation.

PRISMA Flow Chart



Results

We formatted the results section as two tables, comparing the included literature which is arguing in favour and against the additional use of intraoperative MER. Besides, we give an overview of current literature on the role for new techniques and modalities in improving MRI-guided targeting. Since different endpoints are used as outcome parameters in the literature, and most studies use different methodologies, we give a comprehensive, tough understandable, overview of the current opinions and evidence on this topic. We tried to summarize the concluding decisive of the authors in comparable arguments in order to enable a quick comparison of the actual opinions.

In favour of MER-guided targeting, using 1.5- or 3-Tesla MRI

References	Study design	Arguments
Amirnovin et al. [11]	Comparing 1.5T-MRI coordinates with final placement based on MER and intraoperative testing	– 58% of locations changed based on MER and testing
Temel et al. [12]	STN DBS with single (n = 32) vs. multiple (n = 23) intraoperative MER electrode recordings	– Multiple MER trajectories lead to better postoperative rigidity and tremor without more complications – Multiple MER trajectories induced mild declines in memory function
Bour et al. [9]	Comparing central MER trajectory (based on 1.5T-MRI) with final electrode trajectory	– Final trajectory was according MRI in 50%, final depth was within 1 mm range of MRI-target in 57% – 64% of final channels was channel with best MER activity
Schlaier et al. [13]	Comparing posterior STN-border based on 1.5T-MRI vs. MER	– 44% of MER STN volumes were larger than the MRI STN volumes – 46% of MER STN being incompatible with the MRI STN
Reck et al. [14]	Comparing DBS STN surgeries with 1.5T-MRI targeting and MER-guidance with (n = 32) vs. without (n = 10) intraoperative stimulation	– Significant better UPDRS III outcome in MER vs. non-MER – In 27% MER-guidance lead to trajectory adjustment
Schlaier et al. [15]	Comparing 1.5T-MRI defined STN vs. location defined as STN based on MER	– 16/42 active contact points beyond MRI defined STN borders
Longhi et al. [16]	Comparison of accuracy of 1.5T- vs. 3T-MRI in predicting final electrode location	– 1.5T: 2/12; 3T: 21/28 – Better clinical performance in 3 T group – MER to determine lead deepness and prevent adverse effects
Rabie et al. [17]	Direct targeting based on 3T-MRI vs. indirect targeting based on stereotaxic atlases and comparing MRI-coordinates with final implantations	– Significant different Euclidian distances between 3 T-MRI coordinates and final coordinates based on MER and intra-operative testing – MER has increased spatial resolution
Nowacki et al. [18]	Comparing targeting accuracy of 3T-MRI in 78 MER-verified implanted DBS electrodes	– Average difference between STN crossing lengths: 0.28 mm – In 43% the deviation was more than 1 mm

References	Study design	Arguments
Lozano et al. [19]	Evaluation of 100 consecutive DBS STN surgeries: comparing direct and in-direct targeting (1.5T-MRI) and MER-guided target adjustments	– 18% corrected based on MER in first side, 20% corrected in second side – Intraoperative electrophysiology or MRI is needed next to MRI-targeting

In favour of MRI-guided targeting, without additional MER, using 1.5- or 3-Tesla MRI

Reference	Study design	Arguments
Foltynie et al. [20]	Description of cohort one-year after 1.5T-MRI-guided STN DBS, without additional MER (n = 79)	– Mean UPDRS during off-medication: 28 points, 52% – Dyskinesia severity from 3.2 to 1.6 points (UPDRS IV) – Mean levodopa reduction 39% – Mean DBS: 3.0 V, 60 microseconds, 139 Hz
Nakajima et al. [6]	Comparison of two cohorts: local anaesthesia with MER and clinical testing (n = 68) vs. general anaesthesia without MER or intraoperative stimulation (n = 14)	– Comparable improvement of UPDRS-III (general: 52.8% vs. local: 50.8%) and LED reduction (general: 50.8%, local: 60.2%) – No comparison on DBS settings
Aviles-Olmos et al. [21]	Same cohort as Foltynie et al. [20]; 5 year followup (n = 41) and 8 year followup (n = 12)	– Off-medication UPDRS improvement remained 70% for tremor, 50% for rigidity and bradykinesia improvement decreased from 46% to 23%
Liu et al. [22]	Comparison of two retrospective cohorts: implantation without MER based on 1.5T T2 MRI (n = 61) vs. implantation with MER guidance (n = 76)	– Similar improvement after 1 year in off-medication UPDRS (resp. 65% vs. 66%) and quality of life (resp. 44% vs. 50%); similar levodopa reductions
Brodsky et al. [23]	Comparison of two cohorts (STN subgroups): asleep implantation without MER (n = 7) vs. awake implantation with MER (n = 18)	– No significant difference in UPDRS II and III improvement, no subscores for STN/GPi seperately – Asleep cohort was superior on quality-of-life, cognition and communication/speech outcomes
Lee et al. [24]	Evaluation of 45 consecutive DBS STN surgeries: either asleep without MER and intraoperative testing, or MER-guided DBS with intraoperative testing	– Side effect thresholds during initial programming were slightly lower in the MER group – No significant difference in the reduction of clinical symptoms or medication dosage was observed

Studies using alternative MRI techniques as ultra-high field MRI and susceptibility weighted sequences

Reference	Study design	Arguments and conclusions
Polanski et al. [25]	Comparing 182 MER trajectories from 42 STN's vs. T2, FLAIR and SWI 3T-MRI	– Recommendation for SWI MRI based on sensitivity, specificity and negative pred. value – Reserved to advise DBS without MER
McEvoy et al. [26]	Comparing 3T MRI SWI STN-SN border on coronal plane with MER activity in 7 DBS STN surgeries	– SWI MRI demonstrates reliable STN delineation
Verhagen et al. [27]	Comparing dorsal and lateral STN borders on 1.5T, 3T and 7T T2 MRI vs. computational MER-STN model	– 7T decreased variance between dorsal + lateral MRI and MER borders – 3T and 7T STN borders more dorsal than MER – 7T SWI should be explored besides 7T T2

Reference	Study design	Arguments and conclusions
Bot et al. [28]	Comparing STN targeting based on T2 and SWI 1.5T and T2 3T with MER STN activity	– MER STN activity in 84% of MRI target trajectories – 1.5T SWI inferior to 1.5T T2
Bus et al. [29]	Compare STN activity in MER trajectories (visualized with intra-operative CT) vs. 3T T2 and SWI MRI	– Low correspondence of ventral and dorsal MRI STN borders with MER STN activity – 3T SWI MRI decreases false-positive MRI-based STN targets – Only 42% of central SWI-based trajectories targeted final electrode placement

Discussion

While advancements in MRI acquisition and analysis techniques such as ultra-high field and diffusion tractography have greatly advanced and have the potential to be used for neurosurgical purposes like DBS, their application within the clinics has been severely limited [30–32]. The combined literature fails to provide a single favourable approach for DBS targeting. This is in part due to the differences in both the method and the outcome determinant. For instance, some studies report differences in the planned target in relation to the actual location as determined on CT, or by the deviation identified with MER. Others determine treatment efficacy by differences in pre and post-operative LED response and UPDRS scores. The manufacturers of both software and hardware used for surgical planning (e.g. Medtronic, Abbott, Boston Scientific) differs across DBS centres, as do the number of MER test electrodes used, types of MRI (e.g. 1.5T, 3T, 7T), vendors (e.g. Siemens, Phillips, GE), sequences and scan parameters (e.g. contrasts, voxel size). The number of patients also differs greatly across studies, which is a threat to statistical power in group-based analyses. Different surgeons can even be a confounder in such cross comparisons.

Some studies suggest that intraoperative MER can significantly improve the outcome of DBS of the STN [33]. Whereas others will argue that while targeting through standardized atlases are unreliable, the addition of MER fails to significantly improve STN DBS [34]. Following the trend of individualized and personalised medicine, direct targeting is certainly preferred over indirect targeting in MRI, though this does not necessitate that MER is no longer required. Instead, the increasing success of DBS will most likely depend on implementation of advanced MRI techniques within the clinics. Relatedly, advancements in lead and electrode hardware, such as the use of directional steering might play a role in the elimination of MER in DBS surgeries [35].

Regardless, the clinical relevance attributed to MER by many authors cannot be neglected. On one hand, it enables to measure nucleus specific neuronal activity, for example, the beta activity of the STN which can be helpful in identifying the dorsolateral boarders, reflecting the motor portion of the target. Additionally, MER allows for direct behavioural testing, optimization of stimulation parameters and assessment of potential side effects, which in theory collectively result in minimizing the occurrence of post-operative side effects and maximising clinical benefit [36]. Obviously, the

latter is no insurance for the absence of adverse effect though. However, identification of specific nuclei and their subcomponents through MER was only necessary due to the limitations of conventional MRI techniques, which traditionally lacked the contrast and spatial resolution required for the desired level of anatomical accuracy [25, 37, 38]. Moreover, DBS surgeries still heavily rely on the application of standardized coordinates and atlases, referred to as indirect targeting. Such an approach is erroneous given the well documented heterogeneity of deep brain structures. For instance, the STN is known to shift in the lateral direction with age as well as decrease in volume with disease; such alterations are not captured with stereotaxic atlases which can lead to suboptimal placement of electrodes.

However, the application of ultra-high field MRI and advanced multi modal approaches has the potential to revolutionize current practices. The increased signal and contrast offered by UHF MRI allows for sharper and more accurate visualisation of deep brain structures within a clinically feasible time frame [39–46]. The combination of diffusion tractography and functional MRI allow for the identification of both functional and structural networks which can provide additional information in relation to optimal DBS placement, which can additionally be used to inform on the potential volume of tissue activated and with connected networks, which is useful for predicting clinical outcomes. Relatedly, novel contrasts that exploit the paramagnetic properties of iron rich basal nuclei such as susceptibility-based contrasts and quantitative maps can be used to better visualize such DBS targets on 7T compared to 3T [22, 47–53].

Moreover, low field strength intra operative MRI (iMRI) can be used to monitor in real time the location of DBS leads. Although that low field strength MRI is notorious for suboptimal visibility of the STN, there are positive reports on the use of iMRI during DBS. Improved motor symptoms comparable to MER-guided DBS are reported for DBS using 1.5-T-iMRI techniques [54]. Reliance purely on radiological and neuroimaging techniques in theory leads a reduction in the additive surgical risks of MER usage, decreased operation time and increased perioperative patient wellbeing since surgery can be performed under general sedation and pre-operative dopamine-withdrawal can be excluded [55, 56]. The statement whether major surgical risks such as bleeding will decrease is debatable, since the use of multiple MER trajectories did not increase surgical risks compared to the use of a single MER trajectory [12]. However, leads placed in a single penetration, in a faster time frame, when based on MRI, can potentially limit the occurrence of brain shift by reducing CSF loss [24]. Further, a cost analysis showed MER more than doubles the price of a bilateral STN DBS surgery in the United States [57].

However, the use of UHF MRI in DBS should be applied with caution. Firstly, the deep brain structures like the STN are located in the middle of the brain, which means that the signal to noise ratio is substantially lowered compared to the cortex [44, 58–60]. This is important when considering the requirement of acquiring scans in a clinically feasible window especially for PD patients, given the potential for accumulative movement artifacts, though methods do exist for motion correction [61]. Secondly is the requirement of post processing techniques and expertise outside of a standard clinical setting, which is especially true for tractography and functional MRI [62]. And thirdly, the

absolute requirement of an accurate co-registration between pre, intra and post-operative MRI-MRI and or MRI-CT. Therefore, error can occur during the initial targeting on MRI and transformation to a stereotaxic coordinate system on CT, and during the intra and post-operative MRI and or CTs acquired for lead localization. This argument exists still for 1.5 and 3T clinical scans though appears to be more difficult to account for at 7T. Suboptimal fusion can lead to geometrical errors of up to 3 mm [63]. If we rely purely on neuroimaging, these errors cannot be accounted for.

A reasonable conclusion would be that when MRI based targeting does not result in an intraoperative deviation significantly more than when based on targets are based on MER, MRI should be preferred [64]. This doesn't suggest that MRI is significantly better than MER but rather it is a viable and attractive alternative given MRI guided DBS allows the patient to be fully anesthetized, and eliminating the need for behavioural feedback and intra operative testing [54, 65–73]. What remains so far unanswered is whether direct targeting via MRI guided DBS reduces the risk of reimplantation compared to DBS preformed with MRI and or only MER.

Conclusion

Literature is inconclusive regarding the added value of intraoperative MER during DBS surgery. Studies in favour of this technique use different endpoints then studies which do not find added value. This chapter provided an overview of these various arguments. For the near future, we expect decision making regarding "awake MER" versus "asleep MRI-guided" DBS to be made on an individual patient level, taking in to account the clinical presentation, MR imaging characteristics, experience with directional steering, and patient preference. Clinical trials comparing both methods will be needed to address this issue further.

Summary Box

What is known?

Supporters of MER suggest optimal final lead placement can deviate from the MRI-based planned target by using intraoperative MER**.** Opponents of MER suggest image-guided and verified surgery leads to satisfying post-operative results and can reduce intra-operative brain-shift and accompanying lead inaccuracy, especially in the second placed lead.

Technological developments in imaging and stimulating electrodes might influence this discussion.

What is new?

Available literature is still inconclusive regarding the added value of intraoperative MER during DBS surgery and consists of heterogenous studies using different endpoints.

Image guided and verified DBS surgery is not significantly better than DBS surgery using intra-operative MER but rather it is a viable and attractive alternative which allows the patient to be fully anesthetized.

Modern MRI techniques, for example ultra-high field imaging, are not used on a scale yet that they can contribute to the regular care in most hospitals.

What are the consequences for clinical practice?

Decision making regarding "awake MER" versus "asleep MRI-guided" DBS will vary per individual patient, taking in to account the clinical presentation, MR imaging characteristics and patient preference.

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