Microelectrode Recording-Based Targeting for Parkinson's Disease Surgery

5

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Core Messages

- Microelectrode recording (MER) is a key technique for electrode targeting in deep brain stimulation surgery.
- MER depends on an experienced practitioner differentiating signature forming patterns of basal ganglia structures.
- The targets in Parkinson's disease are the subthalamic nucleus (STN), the globus pallidus internus (GPi), and, rarely, the ventral intermediate nucleus of the thalamus (VIM) or the posterior subthalamic area (PSA), which includes the caudal zona incerta.
- The keys to identification of dorsal STN are neuronal firing rate, firing pattern, and passive motion sensitivity.
- The keys to identification of GPi are identification of globus pallidus externus and the optic tract.
- The value of MER has been questioned and is evolving.

Introduction

Microelectrode recording (MER) has a long history in neurosurgery and has paralleled the development of stereotactic targeting of subcortical structures. MER is a critical step in mapping subcortical structures. It is accomplished by comparing the

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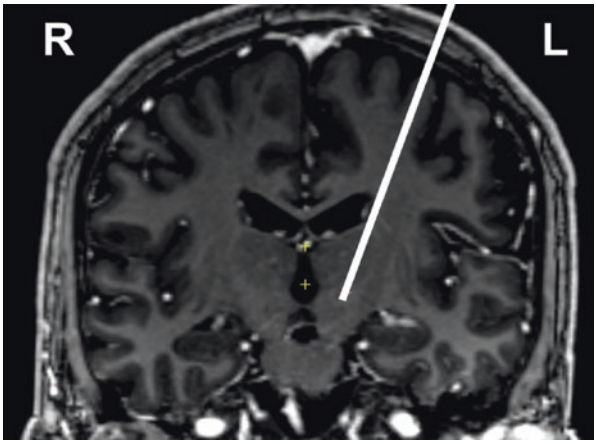

Fig. 5.1 A typical trajectory to subthalamic nucleus. Care is taken to enter a gyrus rather than a sulcus. We typically begin mapping 10–15 mm above target. The thalamus can be seen adjacent to the third ventricle. (Figure is from Camalier et al. 2014)

basal firing rates and response properties of detected structures to the known regional anatomy. Done correctly, MER thus provides a detailed understanding of both the anatomy and physiological function of circuits relevant to movement disorders. For instance, the identification of tremor cells in the subthalamic nucleus (STN) both suggests that the identified location is likely to be an effective location for permanent placement of the deep brain stimulation (DBS) electrode and hints at the pathophysiology of tremor in Parkinson's disease (PD) [1]. Despite advances in intraoperative neuroimaging that have called its use into question [2], MER's ability to physiologically verify DBS targets continues to have broad application among functional neurosurgeons (Figs. 5.1 and 5.2).

In this chapter we will briefly explore the history of MER before describing the technical basics of MER, as practiced in 2018. We will discuss the relevant subcortical anatomy of the STN and the globus pallidus internus (GPi), the most frequent surgical targets in PD, as well as discuss some less frequently used targets. We will close with a discussion of novel techniques in MER, including automated target detection and closed-loop systems.

History

Spiegel and Wycis developed frame-based stereotaxy for the treatment of psychiatric disease and reported this advance in *Science*, in 1947 [3, 4]. However, they quickly realized that individual anatomy was variable and looked for techniques to improve the precision of targeting [5]. Albe-Fessard was the first to use MER to map the human thalamus [6], but her papers were mostly published in French, and her findings did not reach a wide, English-speaking audience. However, in the 1980s, DeLong and colleagues applied these techniques to primate basal ganglia physiology [7] and used insights gained in this manner to develop a detailed map of the functional organization of the human STN and pallidum [8]. These techniques were then applied by Kelly and others to create reproducible lesions of the thalamus

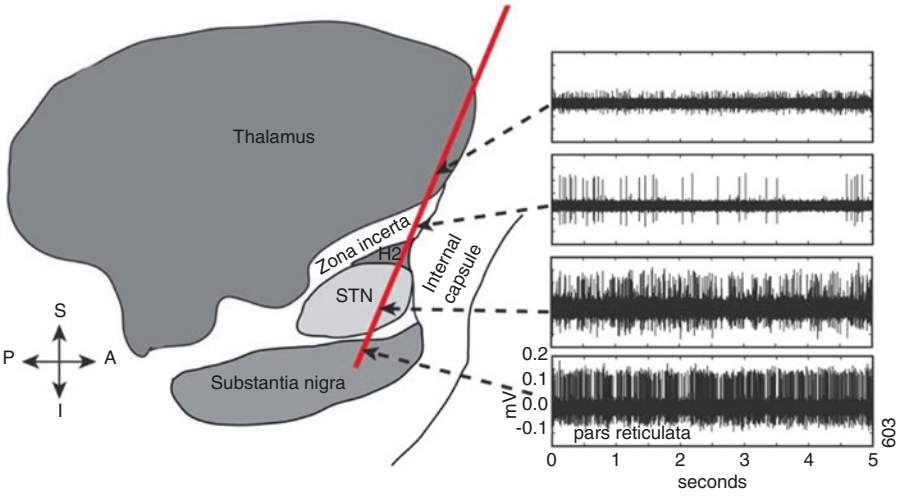

Fig. 5.2 Multiunit activity in subcortical structures has distinct firing rates and patterns. In the thalamus, firing rates of 15–25 Hz, including both bursting and nonbursting cells, are typical. There is rarely neuronal activity in the zona incerta. STN is identifiable by its marked increase in background and firing rates from 35–45 Hz. Finally, the substantia nigra contains tonically active cells firing at variously reported rates from 30–70 Hz. (Figure is from Camalier et al. 2014)

[9] and pallidum [10]. Roughly contemporaneously, Alim Benabid in Grenoble observed that high-frequency stimulation could have clinical benefits similar to lesion generation in both PD and ET [11]. Alim Benabid's group eventually used MER to guide DBS surgery of the thalamus [12], as well as STN surgery [13]. Indeed it was the use of intraoperative stimulation used for mapping that led to the observation that high-frequency stimulation could "create a functional lesion" and led to the advent of DBS. At present, MER is widely used in these surgeries.

Advantages of MER

Stereotactic targeting is a messy business, as there remains significant disagreement on how and where to target standard BG structures. Indirect methods with averaged coordinates as well as "direct" targeting of MRI-identifiable structures are available [14]. MER provides the ability to directly identify neuronal populations with defined characteristics, including firing rate and bursting behavior. Moreover, somatotopic features of STN, ventralis intermedius (VIM) nucleus, and other targets can be used to confirm that the targeted region subserves parts of the body that are afflicted by bothersome symptoms, like tremor or dyskinesia. For instance, in the treatment of hand tremor by VIM stimulation, it is believed that the best treatment efficacy results from stimulating parts of VIM that respond to passive hand or wrist movements [15]. Although this confirmatory function can be somewhat replicated without MER by placing the permanent electrode and stimulating it, or performing

macrostimulation of the cannula, there is appeal to using the smaller MER electrodes before passing the larger cannula or test electrode. As above, there is no class I evidence to confirm this suspicion.

A second advantage of MER is that a second practitioner may be engaged in the surgery. Many successful DBS programs include a neurologist who performs the intraoperative neurophysiology, as well as grades the response to test stimulation intraoperatively. In our experience, two heads are better than one in DBS, and a second experienced physician or neurophysiologist can often confirm clinical suspicions or detect subtle abnormalities that the operating surgeon would fail to detect during the procedure. This collaborative approach with the movement disorders neurologist can provide more comprehensive consideration of the patient's symptoms and is appreciated by the patient. Often this practitioner is interested in MER from a research perspective, as well.

A third advantage of MER (which accrues to society) is the research that has been conducted on neural structures targeted in DBS. Our understanding of how cortical-basal ganglia loops contribute to behavior in normal and pathological states has been greatly expanded by insights from DBS surgery. More recently, studies interrogating the anterior cingulate gyrus [16] and the prefrontal cortex [17] in behaving patients have been possible. While individual patients rarely directly benefit from the MER research in which they participate, new therapies are being developed using signals identified in DBS. This would not have been possible without MER.

Disadvantages of MER

Obvious downsides of MER are (1) the additional time required, (2) the additional passes through the brain with the microelectrodes, and (3) the cost of the equipment, neurophysiology personnel, and OR time needed for mapping. However, whether these issues are themselves associated with risk remains unsettled. To be sure, time of the operation has been associated with infection in one large series [18], but this has not been uniformly reproduced [19]. It is not clear, additionally, that image-guided surgeries are significantly faster; in one recent report of asleep, CT-guided surgery, operative time was somewhat longer than the time needed for more traditional, MER-guided surgery (190 versus 145 min [20]. Yet it is certain that long procedures are taxing for the patient as well as the practitioner. Whether long duration is itself associated with medical risk is not clear.

The risk associated with multiple penetrations through the brain seems self-evident, but the actual numbers are not clear. In one report, multiple penetrations were associated with hemorrhage risk [2], a finding that has been reproduced in some [21] (in one case not at the 0.05 p value level) [22] but not all reports [23, 24]. Some of the discrepancies may be due to differences in cannula size used by some centers employing MER (i.e., smaller MER cannulas may not engender the same risk as the larger DBS lead cannula). Eskandar and colleagues reported improvement in

hemorrhage rates when the electrodes were redesigned, so that only the microwire tip is advanced through the brain rather than the microelectrode along with its protective sleeve. However, a recent systematic review did conclude that MER increased hemorrhage risk [25] and concluded that image-guided techniques are therefore preferred. This claim is highly controversial, given the long history of MER use and the lack of strong evidence that imaging-based targeting is superior [26]. Nonetheless, it is beyond dispute that MER is associated with some risk of hemorrhage.

MER Basics

MER depends upon identifying and recording subtle changes in membrane potential that are characteristic of action potentials and postsynaptic potentials in local neuron populations (including the typical DBS targets). This is typically done with thin, tungsten-coated electrodes attached to a differential amplifier, which is accompanied by various bells and whistles, depending on the manufacturer. These signals are typically unique to different brain regions, and trained neurophysiologists interpret these signals as "fingerprints" of subcortical structures, including the STN, GPi, thalamus, and so on. After a structure is identified, its response properties can also be determined, including its response to active or passive joint movements, sensory input, flashing lights, and so on. Taken together, the neurosurgeon can use this information to assemble a detailed picture of the anatomy and physiology of the interrogated region.

Neurophysiological Signals Relevant to DBS

The signal most commonly used to guide mapping for DBS surgery is high-frequency activity (>300 Hz) corresponding to multiunit activity (MUA). MUA corresponds to the action potential firing of a local group of neurons, and its frequency and pattern are characteristic of the STN, thalamus, substantia nigra, and other subcortical structures. A variety of tricks are used to amplify it over the rest of the broadband signal, especially hardware high-pass filtering. The signal amplitude itself is quite modest (as one would expect from individual neurons!), and is easily drowned out by electrical or mechanical noise, if care is not taken in the recordings. Nonetheless, with care, attention, and the right equipment, it is straightforward to detect and characterize MUA.

A second signal that is robustly identified is referred to as the background. The background appears to represent synaptic activity and distant action potential firing that is still identifiable despite the use of filtering and high-impedance electrodes that only detect a small area. A marked, sudden increase in amplitude of the background characterizes the STN [27], and attempts have been made to detect this phenomenon in an automated way [28].

Hardware Needed

Modern neurophysiology equipment consists of four parts: recording electrodes (typically made of tungsten), a headstage containing a preamplifier (and sometimes a hardware high-pass filter), an analog-to-digital conversion board, and a computer where the digital signals are turned into sound and visual representations for interpretation by a neurophysiologist. Commercial systems to do this include the Neuro Omega™ by Alpha Omega (Nazareth, Israel) and the Guideline 4000 LP+™ by FHC (Bangor, ME). These systems are essentially similar in capability and pricing.

Personnel Needed

In addition to a neurosurgeon, a trained neurophysiologist is typically needed to interpret the MUA and background signals to construct a detailed, three-dimensional map of recorded structures. There is no accepted, standard training for DBS neurophysiologists; they may be engineers, PhD neuroscientists, or physicians (neurosurgeons or neurologists typically with experience in a basic neurophysiology research laboratory). However, only a physician may bill insurers a professional fee, in accordance with federal guidelines, and the fee for MER interpretation cannot be billed by the neurosurgeon who is billing for the surgery. Other professionals may collect reimbursement out of the hospital's diagnosis-related group fee. The neurophysiologist will typically have a detailed understanding of the regional anatomy being interrogated. He or she will also have experience in the technical aspects of neurophysiology, especially in understanding how to improve the signal-to-noise ratio. Finally, this team member must be comfortable in the operating room, sometimes for lengthy periods, while mapping is underway.

Targets in PD

Typical targets for the treatment of PD include STN, GPi, and, occasionally, VIM thalamus, as well as investigational targets including the posterior subthalamic area (PSA), which includes the caudal zona incerta, and the pedunculopontine nucleus (PPN).

STN MER

Basic Procedure for Identifying STN The surgeon will generally create a stereotactic plan, which is implemented using frame-based or frameless stereotaxy. A tract is planned that typically passes through striatum, thalamus, zona incerta (ZI), STN, and substantia nigra. Using the surgeon's preferred technique, a burr hole aligned with the planned trajectory is created, and a cannula is passed to some fixed distance

(typically 25, 15, or 10 mm) above target. Longer trajectories take longer to map, but may provide more detailed anatomical information. The microelectrode(s) (from one to five electrodes) is/are then passed downward to and through the target. After identification of STN (or whatever structures happen to be identified), a decision is made about whether to pass the microelectrode(s) along an additional track or tracks or to place the stimulating electrode in the identified target. If the decision is made to attempt a different trajectory, the cannula or cannulas will be reintroduced, usually 2 mm away from the prior track(s), and the process is repeated. Many centers incorporate macrostimulation (of the guide sleeve) or microstimulation (of the tungsten microelectrode) into this paradigm.

Neurophysiology of the Ideal Tract In the ideal pass, the striatum, thalamus, ZI, STN, and substantia nigra are all encountered at the expected depths.

Before Encountering STN In a typical tract, started 10–20 mm above target, the neurosurgeon will encounter the lateral part of the thalamus. Its neurophysiology is characterized by two cell types, bursting and nonbursting cells, at a density of approximately two cells per millimeter, and an overall mean firing rate between 15 and 25 Hz [29]. More specifically, the bursting cells are reported to have a mean firing rate of ~15 Hz, and the nonbursting cells fire at ~28 Hz [30]. These are reported to correspond to the reticular, ventralis oralis anterior, or lateropolaris nuclei. Background activity is relatively low. The ZI is encountered next. The ZI is a thin rim of gray matter between the thalamus and subthalamus which may treat tremor when stimulated [31, 32]. However, it is identifiable by its paucity of neuronal activity.

STN After the ZI is traversed, there is typically a massive increase in action potential firing and background activity. This marks the superior boundary of the STN. Sources vary about the mean firing rate, reported between 35 and 45 Hz, but agree that a variety of regular and irregularly firing neurons are present [27, 29, 30]. Recordings are continued until there is a decrease in background activity, corresponding to exit from the STN [29]. Subsequent to this, the substantia nigra pars reticulata (SNpr) is identified. SNpr is distinctive because of its tonic pattern of discharge variously reported between 30 and 70 Hz [27, 30] and has been compared to the sound of rain on a tin roof (Okun M, Personal communication). SNpr lacks kinesthetic responses and is not typically mapped in detail.

STN has extensive kinesthetic responses, especially rostrally and dorsally. This anteromedial location is believed to be the most effective location for stimulation therapy and corresponds to the sensorimotor territory of the STN [33]. In general, STN cells respond to movement of contralateral limbs across one or two joints, and responses tend to be relatively clear. The proportion of STN cells reported with kinesthetic responses varies between 26% and 40% in the literature [27, 30]. These responses are absent from SNpr, which also indicates exit from STN.

Stimulation Testing While it is good to identify efficacy with intraoperative testing, a variety of issues prevent full assessment of clinical efficacy in the operating room, including patient comfort and the use of sedation. In a responsive patient, however, significant improvements in rigidity or tremor are good signs of an effective placement. It is important to note however that while immediate effects may be a good predictor, they are not invariably identical to the effects of long-term stimulation.

If side effects are detected at low stimulation amplitude, the electrode should be moved. The STN is bordered anteriorly and laterally by motor fibers from the internal capsule, medially by fibers in CN III, and posteriorly by the medial lemniscus. Therefore, face pulling or dysarthria should prompt posterior or medial movement. Eye movement abnormalities indicate too medial a trajectory. Contralateral paresthesia should prompt movement forward. If some clinical benefit is identified, and there are no side effects, the electrode should be fixed into place.

Debugging a Suboptimal STN Recording Suboptimal recordings are either (1) technically bad or (2) fail to detect adequate STN. From a technical standpoint, the most common issue is line noise, from any of numerous sources in the operating room, especially the cauteries and the electric drill. These should be unplugged. Loud, repetitive noises known as "ground loops" are a consequence of high-amplitude signals oscillating in the amplifier. Ensuring adequate grounding prevents this issue. Other technical issues should be discussed with the MER equipment manufacturer.

When not enough (or no) STN is detected, Bakay has developed an algorithm, depending on the other MER findings, and microstimulation [33]. If microstimulation triggers the above events, the appropriate maneuvers should be made. If microstimulation is not available, or has no acute effect, the length of time spent in the thalamus should be considered, as well as the distance between the thalamus and STN. If the thalamic pass is long, one is either medial or posterior, as distinguished by the distance between the thalamus and STN. If this distance is long, one is posterior, and if it is short, medial. Alternately, if the thalamic pass is short, one is either anterior or lateral, possibilities which are again distinguished by distance between the STN and thalamus (long distance is consistent with an anterior tract, and short is probably lateral). If no STN is encountered, one is either anterior or posterior, possibilities again distinguished by how much thalamus was recorded.

GPi MER

For a variety of reasons, including mood disorders and cognitive disorders, a GPi target may be considered in some patients [34]. MER for GPi is straightforward but does have some technical nuance. Most passes begin in the striatum, which exhibits tonic firing at 4–6 Hz. Subsequent to this, the globus pallidus externus (GPe) is entered. GPe is characterized by two types of units: high-frequency bursting neurons, separated by pauses (60 Hz), or lower-frequency neurons (10–20 Hz) with periods of bursting [35, 36]. There is typically a 1–2 mm area characterized by decreased activity or border cells (firing regularly at 20–40 Hz) corresponding to the medial medullary

lamina that is encountered before the GPi is encountered [35]. GPi neurons have a firing rate (80–90 Hz) a bit higher than GPe, which is qualitatively similar to STN [35, 37], with high cellular density. The sensorimotor territory of GPi is found posteroventrally. Approximately 25% of neurons in this area have kinesthetic responses, which should be looked for [35]. Below the inferior border of GPi is the optic tract. Visual evoked responses are often seen in this location and should be considered confirmatory of a good pass. The final target should have the first contact of the DBS electrode just over the optic tract, with the other contacts in the posteroventral GPi.

Debugging a Suboptimal GPi Recording Technical issues should be addressed as above. We adapt another algorithm from Bakay, if little or limited kinesthetically responsive GPi neurons are identified. GPi is bounded anteriorly and laterally by GPe and posteriorly and medially by the corticospinal tract. If microstimulation elicits contralateral movements, the length of the GPi pass should be considered. If GPi itself was short, one is probably posterior and should move 2 mm anterior. If no movements are elicited by microstimulation, the width of the medial medullary lamina should be considered. If it was long (4–6 mm), one is probably too lateral and should move 2 mm medially. Otherwise, it is likely one is anterior and should move posteriorly. Anterior tracts may detect basal forebrain cells that have a high tonic firing rate and no kinesthetic responses.

Other Targets in PD

VIM nucleus of the thalamus is the oldest target for PD tremor, and it is still a reasonable choice for tremor-dominant disease [12]. Many centers place VIM electrodes without MER, but if MER is desired, the essential step is to identify sensory thalamus (Vc thalamus) and place the electrode 2–3 millimeters anterior [33]. PPN is an investigational target for treatment of freezing and gait disturbance in PD. It consists of populations of cholinergic and glutamatergic neurons, which are responsible for gait initiation and voluntary movement initiation, respectively [38]. PPN is located medial and inferior to SNpr and is usually approached almost directly from a lateral angle. Its units have a firing rate around 15 Hz and some subtle kinesthetic responses [39]. PPN surgery is best performed under an institutional review board protocol, under the guidance of physicians from an experienced center. The posterior subthalamic area is a location that includes caudal zona incerta, and has been stimulated in tremor syndromes that are not traditionally responsive to VIM stimulation, including postural tremors that occasionally accompany PD [40].

Future Directions in MER

In the setting of advancing neuroimaging technology, there are strong incentives to prove the usefulness of MER in the operating room. Several recent developments have demonstrated potential new directions for MER in stereotactic

surgery. One promising technique is performing MER under light general anesthesia. The efficacy of this technique may be comparable to awake surgery [41]. Along these lines, there is experience using automated techniques to detect boundaries of the STN, which may take the human error out of neurophysiology [42]. Finally, use of field potentials, rather than MUA, has permitted the development of closed-loop systems that stimulate in response to brain activity rather than in a continuous fashion [43]. The coming years will no doubt bring further advances of this kind.

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