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Applying Microelectrode Recordings in Neurosurgery

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Many techniques can be employed to carry out functional stereotactic procedures within the standard of care, and both radiologic and physiologic landmarks are usually used to localize the target accurately (1-4). Many surgeons have employed radiologic localization of the anterior commissure posterior commissure (ACPC) line, or direct targeting of subcortical structures using both computed tomography (CT) or magnetic resonance imaging (MRI). Others refine the radiologic estimate of location by microelectrode physiologic localization and then carry out deep brain stimulation (DBS) electrode implantation or radiofrequency lesioning (1;5;6). Alternate approaches are to localize radiologically using CT or MR jointly or with fusion techniques (7). Using these estimates, further localization can be carried out physiologically using semi-microelectrode recording or macrostimulation (8). The relative efficacy and safety of these different techniques have not been examined systematically.

Radiologic Localization

Radiological targeting can be used to determine the location of the anterior commissure (AC) and posterior commissure (PC) by ventriculography, MRI, or CT. AC and PC predict the locations of the different subcortical nuclei in stereotactic space. The coordinates of the ventral caudal (Vc) nucleus of the thalamus, just posterior to the ventral intermediate (Vim) nucleus of the thalamus are estimated with reference to the AC-PC line. In this approach the thalamic nucleus Vc was 3mm anterior and 14mm lateral to PC and 2 mm above the line. Alternately, the lateral plane of the target in Vim can be estimated as lying between the internal capsule and the T2 intense medial dorsal nucleus of the thalamus (9).

The globus pallidus interna (GPi) was estimated as 3mm anterior, 3mm inferior and 20-22mm lateral to the mid-commissural point. Direct targeting can be carried out on an inversion recovery series. On an axial cut through the AC-PC line the anterior posterior coordinate is the mid-commissural point and the lateral coordinate is 4 mm medial to the external lamina separating the internal from the external pallidal segment. The vertical axis can be targeted from the location of the optic tract and GPi on the coronal cut through the mid-commissural point.

The location of the subthalamic nucleus (STN) can be estimated as 4 mm posterior and 4 mm inferior to the midcommissural point (MC) and 12 mm lateral to the midline (4;10).

STN can be directly localized on 2mm, axial T2 weighted scans and coronal scans through the thalamus and midbrain. Fusion with other MRI series or CT can then be used to estimate the location of the STN (4). The target is then selected in the dorsal part of the posterior third of the STN. Another approach is to localize the STN by a fusion process based on a volumetric gradient echo T2 and a fast spin-echo sequence. Finally, the STN can be localized 7 mm lateral and 4 mm anterior to the center of the red nucleus (11).

Physiological confirmation of the radiologic estimate is carried out by stimulation or recording at and around the target. In our institution, a map is made to the same scale as a set of transparent atlas maps from the sagittal sections of the Schaltenbrand and Bailey atlas (12). The 13.5 mm lateral atlas map is used for Vim procedures, 21 mm for GPi procedures, and 11 mm for the subthalamic nucleus.

Ventriculography can be used as a means of locating the AC-PC line (13;14). However, it has largely been replaced by CT and MRI scanning. CT is as accurate as ventriculography (15) and does not carry the risks of ventricular puncture and instillation of air or contrast media into the ventricles. MRI is slightly less accurate than CT, with errors of approximately 2mm on average and 4mm at maximum (16;17) (18). This error is due to artifacts related to inhomogeneities in the magnetic field and non-linearities in the gradient field – the position dependent strength in the magnetic field (19). These artifacts can be induced by metal or magnetic susceptibility artifacts – produced at the interface between materials (e.g. air and bone) which have different tendencies to affect the magnetic field in a region.

Attempts to decrease errors in from MR imaging due to these artifacts include software modifications and overlapping (fusion) of the 3D MRI image with the CT image, which is not prone to these types of artifacts (20). Targeting in thalamotomy can then be accomplished by computer programs which relate atlas maps of anatomy to the radiologic anatomy. These maps display atlas maps transformed either to match the AC-PC line in isolation (21) or to match the AC-PC line and other structures, such as the margins of the third ventricle or the internal capsule(22).

II.2. Physiologic Localization

Radiologic targeting should be verified by identifying the different structures (GPi, STN and Vim) on the basis of their electrophysiologic properties. These properties are defined by recording spontaneous activity, and neuronal response to passive and active movements. Nuclear properties are also defined by microstimulation (< 100µA), evoked sensations, motor effects such as muscular contractions, and alteration in the movement disorder, e.g. decreased tone or tremor. Physiologic localization has been carried out by stimulation using a macroelectrode (impedance < 1000 Ohms), or by stimulation and recording using a semi-microelectrode (impedance < 100 Kohms) or a microelectrode (impedance > 500 Kohms).

II.2.A. Microelectrode Localization

Microelectrodes for physiologic monitoring and recording are designed to isolate single action potentials (23-25). In addition, the electrode must be durable to withstand

microstimulation which degrades the glass insulation. Typically these characteristics are achieved by constructing electrodes from a platinum-iridium alloy or from tungsten, producing a tapered tip and insulating with glass (23;26;27) (25;28;29). The electrode impedance is usually (3) greater than 500 Kohm. (23;24). A high impedance microelectrode is required to isolate single units (23). Passing current through the electrode during microstimulation will degrade insulation and lower impedance which makes it harder to isolate single units.

The assembled electrode is attached to a hydraulic microdrive and mounted on the stereotaxic frame. Some microdrive systems incorporate a coarse drive so that overlying structures can be traversed quickly. The tip is then retracted into a protective cylindrical housing while the whole assembly is advanced to a new depth (30). The microdrive may then be employed from this new depth for detailed exploration of deeper structures. Another option is to use the microdrive throughout the trajectory by advancing it each time it reaches the end of its traverse (23).

The signal from the microelectrode is amplified and filtered. Multiple neuronal discharges of varying sizes may be seen on an oscilloscope and heard by use of an audio monitor. Action potential signals of constant shape and amplitude will be produced from any one neuron and can be discriminated with a level-window discriminator to isolate single neuron activity.

Semimicroelectrode recordings are carried out using a low impedance microelectrode (<100Kohms). The semi-microelectrode signal is often amplified against a concentric ring electrode which is located at a radius of .4mm around the microelectrode (8;31;32). Bipolar stimulation through a concentric ring electrode can be used alone or in combination with recording through a semi-microelectrode (33-35).

Localization of Vim

Microelectrode penetrations toward the radiologic target are made from a coronal burr hole about 25 mm from the midline. The ventral intermediate (Vim) and adjacent nuclei show a characteristic pattern of neural activity. Sensory cells responding to sensory stimulation in small, well defined, receptive fields are found in the ventral caudal nucleus (Vc), posterior to Vim (see figure 1) (36). Some have described a medio-lateral somatotopy within Vc (24;36) proceeding from representations of oral structures medially to leg laterally. In anterior Vc and further anterior, in Vim and the ventral oral posterior (Vop), thalamic neuronal firing is correlated with active and passive joint movement (voluntary cells)(37;38).

The movement-related activity of most cells in Vim and Vop is preferentially related to the execution of particular movements with a somatotopy parallel to that of the Vc nucleus of the thalamus (38). As shown in figure 2 some neurons respond both to active movement and to sensory stimulation such as joint movement (combined cells) (38;39). Many sensory, combined, and voluntary cells have activity correlated with EMG activity during tremor (40-42), as shown in figure 4.

In addition to recording, microstimulation of subcortical structures through the microelectrode may be employed in physiologic localization. Typically, microstimulation is

delivered in biphasic, square wave pulse trains of 0.1 to 0.3 msec pulses for times up to 10 seconds at a frequency of 300 Hz (43). The current used in stimulation determines the amount of local current spread. Stimulation in Vc will evoke somatic sensations (44) while stimulation in Vim may alter the ongoing tremor or dystonia(45).

Thalamic semi-microelectrode recordings (8) (28;32) reveal patterns of neuronal activity parallel to those of microelectrode recordings. Macrostimulation through a low impedance electrode (impedance often less than 1000 Kohms) can reliably identify the capsule by stimulation-evoked tetanic contraction of skeletal muscle at low threshold (33;34). Stimulation of intralaminar nuclei, medial to Vc or Vim may evoke the recruiting response – long latency, high voltage, negative waves occurring over much of cortex at the frequency of stimulation (usually less than 10 Hz). The target area in Vim can be identified by stimulation evoked increase or decrease in the amplitude of tremor (34).

Localization of GPi

During pallidal procedures, initial coordinates of GPi are calculated from the midcommissural point (46). Microelectrode penetrations toward the radiologic target are made from a coronal burr hole about 25 mm from the midline. Striatum, GPe, and GPi each have a characteristic pattern of neural activity (Figure 3)(3;30;47). Striatal cells are characterized by broad action potentials and a slow firing rate (approximately 1 Hz), often with long silent periods. Cells in GPe have narrower action potentials and fire either at high frequency (approximately 50 Hz) with intermittent pauses (pause cells) or at lower frequency (approximately 20 Hz) frequency with intermittent bursts (burst cells). Cells in GPi fire with tonically at high rates (60-80 Hz). Cellular activity is also recorded during passive movements of upper and lower extremities both ipsilateral and contralateral to the recording site to identify the cellular receptive field.

Characteristically, the optic tract is about 1mm below GPi. The optic tract can be identified by the hissing sound resulting from the firing of multiple myelinated axons. This sound increases in response to a flashing light (visual-evoked potentials) and microstimulation in the optic tract evokes multiple coloured points of light. The same axonal sound and microstimulation-evoked muscle twitches can be evoked by stimulation of the internal capsule which is immediately behind this portion of GPi. These data are used to generate a functional map of the target zone in sagittal section.

Localization of the subthalamic nucleus

During the subthalamic exploration trajectories are made from a coronal burr hole about 30 mm from the midline. Striatum, and Voa thalamus each have a characteristic pattern of neural activity (48). As the electrode approaches the STN from anterior and dorsal, striatal cells are often encountered and are characterized by broad action potentials and a slow firing rate (approximately 1 Hz), often with long silent periods. When the thalamus is entered the action potentials become narrower and often occur in bursts of the LTS type. LTS bursts are preceded by a silent period of 20-100 ms and consist of a interspike interval of less than 6 msec followed by interspike intervals of less than 16 msec (49;50). A relatively acellular gap

of 1 to 6 mm is observed below the thalamus and above the subthalamic nucleus, depending upon the anterior-posterior location of the trajectory.

The subthalamic nucleus is characterized by multiple spike trains recorded from closely packed neurons, each with a mean rate of about 20 msec. Microstimulation evokes paresthesias posterior to STN, muscle contractions lateral to STN, and decreases in tremor or tone within STN. The single lesion may be made dorsolateral to STN (4) or two lesions may be made within STN but located 3 mm apart in the medial lateral plane (51) with much different results (see below).

Tremor related activity

The activity of neurons in the thalamic nucleus Vim, and GPi and STN have been found to be related to tremor (52-55). Figure 4 shows thalamic single neuron activity and simultaneous forearm EMG activity. These studies indicate that thalamic cells have tremor frequency firing patterns that are linearly related to forearm EMG signals during essential tremor (tremor-related activity). One-third of cells with tremor-related activity responded to sensory stimulation. Three models could account for this correlation: that thalamic activity drives EMG activity; that thalamic activity is driven by sensory input generated by tremor movement (for one-third of cells); or that an oscillator outside the thalamus drives both thalamic and EMG activity. Surgical lesions in the thalamus abolish essential, parkinsonian, and cerebellar tremor (14;56-58).

The correlation between thalamic activity and EMG activity in tremor is found in parkinsonian, essential and cerebellar tremor. It seems likely that thalamic activity in parkinsonian tremor is driven by sensory input which is itself generated by tremor movement, in a feedback loop (39). Thalamic oscillations in essential tremor seem to be facilitated by motor circuits through the thalamus that enable tremor-related thalamic activity during voluntary movement. (59). Cerebellar intention tremor may result from deafferentation of neurons in the cerebellar thalamus which leads to a phase lag relative to tremor that is not found in normal oscillations during active movement or in tremor related activity in Vo (60). The involvement of Vim in these three mechanisms may explain the effectiveness of Vim thalamotomy and Vim-DBS in these three types of tremor (14).

Controversies

The role of microelectrode recording and stimulation as an aid in target localization for DBS implantation remains an area of debate, although it is very widely used. In a review that compares modern techniques with the older unguided lesioning procedures of the 1960s,⁹³ Hariz argues that the technique of multiple microelectrode passes for localization results in more intracranial hemorrhages but no significant difference in outcome. Studies have shown good correspondence between the proposed electrophysiology-derived map with the MRI-defined target, indicating that the electrophysiology might not be essential(30;61;62).

In one report microelectrode recording led to a change in final location for lesion placement in 14/20 (70%) cases (63) with an average change of 3.5 mm. In another, 75% of cases were within 3 ± 1 mm of the final lesion site, while 25% (4/10) were > 5 mm away (64). Still a

third reported a rate of target change based upon microelectrode recording which was considered too high to support pallidotomy without microelectrode recording (65). Although the accuracy of targeting without the microelectrode may be quite good in many cases, the high incidence of changes in final lesion location reported in these studies suggests that microelectrode recording provides for improved target localization. Although these reports suggest improved accuracy with microelectrode mapping there remains no consensus regarding the effect of microelectrode mapping on long-term clinical benefit. We conclude that precise mapping using the microelectrode is at present the best way to define the boundaries of the target and optimize lesioning and that improvement in the accuracy of lesion placement is likely to improve long-term outcome.

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Figure 1.

Photographs of oscilloscope traces showing single-unit activity elicited by sensory stimulation in two neurons. The lower oscilloscope tracing in each section demonstrates the neuronal responses evoked during sensory stimulation. The approximate duration of somatosensory stimulation is indicated by horizontal bars beneath the track. The dots above each spike train indicate the occurrence of discriminated action potentials having the shape displayed at high sweep speed in the upper trace. The receptive field for each cell is

indicated in the figurines located to the right of the upper traces. Horizontal calibrations for upper and lower traces are as marked in A. Adapted from Figure 1 in (36).

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Figure 2.

Combined cell exhibiting activity related both to active movement and somatosensory stimulation. A illustrates the location of this cell (arrow). In relation to the trajectory along which it is recorded (oblique line) and the intercommissural line, indicated by the posterior commissure (PC) and the midcommissural point (MC) and the midcommissural point (MC). The patient number (b4), parasagittal plane 14 mm lateral to the midline and the scale are indicated in this panel. B illustrates the response of the cell to passive elbow movement. The time scale is as indicated. Lines below the spike train in the lower panel of B indicate the approximate interval of the elbow flexion and hold or extension and hold passive movements, as labeled. C shows the raster and histogram for the activity of this cell during active elbow extension. Adapted from Figure 3 in (38),

Figure 3.

Examples of characteristic spike trains of neurons recorded in the basal ganglia of patients with Parkinson's disease. Each panel includes the label of the type of cell recorded (upper left). The shape of discriminated action potentials included in the spike train is shown to the right of the label. The spike train is shown in the line below the label. The scale is as indicated below the lowest spike train. Adapted from Figure 14-1 in (5).

Figure 4.

Simultaneous recording of thalamic single neuron activity and peripheral EMG during tremor in a patient with essential tremor. A, digitized spike train (upper trace) and EMG channels (lower two traces). B, Autopower spectrum of the spike train illustrated in A. C and D, Autopower spectra for EMG 1 and EMG 2. E, F, G. Crosspower spectra Spike $\times$ EMG 1, spike $\times$ EMG2, EMG1 $\times$ EMG2. H, I, J. Coherence spectra Spike $\times$ EMG 1, spike $\times$ EMG2, EMG1 $\times$ EMG2. The autopower spectrum measures power or the intensity of the signal as a function of frequency. The coherence is a statistical function used to estimate the probability that two signals are correlated at a given frequency. As computed by this method, a coherence 0.42 indicates significant probability ($P < 0.05$) of a linear relationship between the two signals (66). This figure adapted from reference (41), with permission.