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Review Article

# Stimulus techniques and microelectrode recordings of subthalamic-nuclei neurons in Parkinson‘s during functional-neurosurgery

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ABSTRACT

This study discusses the various procedures and issues involved in the acquisition of microelectrode recordings (MER) signals of subthalamic nucleus stimulations with induced deep brain stimulation electrodes very rigorously. Bellicose-invasive physiological detections through the methods of sub cortical physio logical detections, electrical induced stimulations and micro electrode recordings, stereo-tactic technique, macro-stimulation, stereo-tactic functional neurosurgical technique, stimulations such as macro and micro, induced stimuli with current and microelectrode recordings, impedance information monitoring, micro injections of test substances, evoked potentials, biomarkers/local field potentials, microelectrode fabrication methods and setups, sub cortical atlas-mapping with micro recording/microelectrode recording (M.E.R.). Thus, the study is very significant to the electrophysiological neurosurgical point of view and is very useful to the field of microelectrode recording and functional neurosurgery. This study is concerned with invasive physiological detection of deep brain structures with micro- or macro-electrodes prior to surgery followed by imaging techniques and their use in cortical and subcortical detection; detection relevant to the superficial cerebral cortex regions.



## 1. Introduction

During functional neuro surgical procedure, a target or imperils a significant adjoining structure which cannot be found or conspicuously imaged interventionally, intra operatively, hence, a kind of invasive physio- logical detection method is necessary to ensure the accuracy and safety.[1] Although anatomical structural organization provide some clues as to what the function of basal ganglia circuits in PD patients might be, albeit the inference of function from anatomical structure is exploratory.[1–12] One investigative approach to studying-the-function of an area-of-the-CNS substantia-nigra (SN) is to acquire the STN neurons with extracellular MER in locally anesthetized PD patients. Other approaches involve inferences of neuronal signaling from imaging studies of blood flow and metabolism, or of changes in gene expression. By sampling the signal of a part of the brain during behavior, one can gain some insight into what role that part might play in behavior. Neurons within different basal ganglia nuclei have characteristic baseline discharge patterns that change with movement.[13–17] In this study, we followed the M.E.R approach. Keeping this in mind, a retrospective study was carried out at tertiary care N.I.M.S Hospital and research center (Hyderabad, Telangana State TS, South India) with a dedicated movement disorder unit in Neurology department of N.I.M.S and biomedical engineering. Twenty-six subjects with diagnosis of PD as per United Kingdom Parkinson

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disease society brain bank criteria are included in the study.

At times occasionally, a whole structure cannot be visualized clearly (such as STN); on other occasions, the gross structure can be imaged but its important functional subdivisions cannot (such as the case with motor thalamus), even with the highest-quality magnetic or functional magnetic resonance im-aging (M.R.I.). In both circumstances, the structure must be penetrated, and its identity must be established by functional means. This study is concerned with invasive physiological detection of deep brain structures with micro- or macro-electrodes prior to surgery followed by imaging techniques and their use in cortical and subcortical detection; detection relevant to the superficial cerebral cortex regions and to surgery for epileptic-seizures (epilepsy-seizures).

There is still a need for invasive physiological detection despite any shortcomings since functional stereotactic imaging still does not allow accurate visualization of all stereotactic targets that the surgeon can manipulate. The current consensus is that imaging techniques are still not sufficiently accurate to achieve the best results in most functional stereotactic procedures. If every brain were identical, it would be expected that any target structure would bear a fixed 3D three-dimensional relationship in space to brain landmark structures such as the anterior and posterior commissures (A.C and P.C). The fact that this is not so is well known from cortical mapping. For example, a given site on the postcentral gyrus a fixed distance from the midsagittal line may in one patient rep- resent the face, in another the arm, and in yet another the leg.[2–4] However, it is clear to those who routinely perform subcortical mapping, that there is ongoing variation in initial or image-based targeting due to errors from various sources as revealed by the selection of the final target (taking into) considering the mapping results.

Authors.[7–17] conducted the study on microelectrode-signal-recording (MER) in targeting subthalamic-nuclei (STN) in 40 Parkinson candidates (i.e., Parkinson diseased subjects). The predicted location (with the preoperative deep brain stimulation with the magnetic resonance imaging, DBS MRI) was used in 42% of the cases; however, in the remaining 58% of the cases it was modified through MER (MER with STN-DBS). By applying MER technique, an average pass through the subthalamic-nucleus (STN) of 5.6 mm was attained and evaluated to 4.6 mm if the central-tract was selected as per the MR-imaging.

Application of microelectrode-recording augmented the path through the subthalamic-nuclei by 1 mm, increasing the likelihood of implanting the microelectrodes with the deep brain stimulator squarely in the STN, which is relatively an elfin or petite target. Bour et.al studied the outcome of MER in 57 PD patients with STN-DBS and deduced the following inferences. For the subthalamic-nucleus, the central-trajectory was chosen for inserting-microelectrodes in 50% of the cases, the channel selected had the longest segment of STN with the MER activity in 64% of STN DBS cases. In case the central electrode was selected for embedding the innocuous micro electrode, this was also the channel with the best micro recording in 78% for STN. The final electrode-position or electrode-point in the STN, if not placed in the central-channel, was often more lateral than medial to the computed—evaluated target ten percent (10%, i.e., 10 patients / 98 patients) lateral; six percent (6%, i.e., 6/98) medial and frequently more anterior 24% (i.e., 22/98) than posterior 10% (10/98). The mean and standard deviation (SD) of the deepest contact-point with respect to the magnetic resonance imaging (MRI)-based target for the STN was 2.1 mm ± 1.5mm.

Some of the available techniques for invasive physiological detection. The most important are microelectrode recording, and electrical stimulation using micro- and macro- electrodes, which will be covered in some detail first. electroencephalography (E.E.G), electrocorticography (E.Co.G), are used mainly during epilepsy surgery but results from “deep EEG” studies were at one time used for functional detection of deep brain structures.[1–8] The deep E.E.G technique can be considered, to be reinvented, since more and more centers are also recording L.F.P activity from micro- and macro- electrodes intraoperatively as well as in the immediate post-operative period from D.B.S. electrode contacts. The characteristic oscillation frequencies such as the S.T.N beta band activity in PD patients off medication indeed helps to confirm S.T.N detection. In a similar way, evoked potential recording has been used as a detection method in the past, and recently our group has used focal microelectrode evoked potentials with some further insight into physiological detection. Finally, impedance monitoring is rarely used for detection and the techniques of microinjection of test substances are only occasionally used for specific indications or investigations.

## 2. Electro-neuro Bellicose-Invasive Physiological Detection with Various Methods of Invasive/Noninvasive and Minimally Invasive Techniques

Microelectrode recording (M.E.R), stimuli with current, i.e., electrical stimulation which includes micro and macrostimulations, recording of local field potentials/biomarkers, electroencephalography (E.E.G), electrocorticography, noninvasive magnetic resonance functional imaging, evoked potential recording, impedance monitoring, semi-M.E.R, neural noise recording, microinjection of test substances (locally anesthetized or muscimol, optical imaging of cerebral cortex.

### 2.1. Stimuli with electrical current and micro recording system

Currently, stimulation and recording are the most widely used techniques for the physiological localization of subcortical structures. Recording can be done with fine tipped microelectrodes capable of discriminating single cells[7–16] or with semi- microelectrodes that cannot.[17–22] Stimulation can be done with a large tipped electrode (macro- stimulation)[3–6,17,23–29] or a microelectrode (macrostimulation).[7,8,12] Each technique has its advantages and disadvantages.

In its simplest form, physiological detection can be reduced to observing the effects of macro- stimulation on motor and sensory function. In peripheral nerves, roots, and certain long tracts, low-frequency (often 2 Hz) stimulation is used to search for motor twitches and higher-frequency (30–300 Hz) stimulation is used for both sensory and motor effects, the latter in the form of tetanization. A correlation between the effect observed and the parameters used allows, with experience, a reasonable estimation of the distance of the stimulation probe from the target structure. Somato-topographic features also can be obtained, as in exploration of the trigeminal nerve, in which selective manipulation is desired. Similar macrostimulation techniques can be used for selective lesioning of the lateral spinothalamic tract.

However, in most subcortical explorations, matters may be a little more complicated. Fritsch and Hitzig are said to have been the first to elicit motor responses by stimulating the motor cortex in experimental animals; Bartholomew was first to do so in humans, while Cushing was the first to elicit sensory effects in humans.[19,29] Macrosti mulation was employed for confirmation of probe position in early functional stereotactic procedures[6] only after a probe was thought to have reached the appropriate target site. However, macrostimulation also can be done systematically at fixed intervals as the probe is passed into the brain, allowing the results to be plotted in "figurine charts" of the type used by Woolsey in the laboratory.[29] Such mapping provides more comprehensive localization data that are more easily assessed visually; in addition, it provides information about normal and abnormal brain organization, especially if each electrode trajectory is contained in the same sagittal plane. Wetzel and Snider[29] are said to have been the first to use microelectrode recording in humans in 1958 during a pallidotomy, but the technique did not come into common use until after the intro- duction of thalamotomy for Parkinson's disease.[2,9–11,18,19,21,22,28] The earlier work in the thalamus was done with semi-microelectrodes, while later on true microelectrodes were employed. Semi-microelectrodes can more readily monitor neural "noise" as the electrode progresses along its trajectory, with the "noise" being sufficiently characteristic in some regions of each structure traversed to allow its recognition.

### 2.2. The stereotactic procedure

Stereotactic techniques have been described else- where and will be reviewed briefly here.[1–18] The Leksell G frame is applied to the patient's head under local anesthesia in the ward or radiology department. A stereotactic MRI is carried out, and the coordinates of AC and PC are determined. There are two general approaches, the more established procedure is to obtain a tentative target using a customized atlas reference to AC-PC and the second is to directly target the structure of interest, given that MRI sequences are performed that enable visualization of the target. For the first procedure,[17] a series of sagittal brain diagrams are generated using a customized program containing digitized plates from the atlases of Schaltenbrand and Bailey[27] and Schaltenbrand and Wahren[27] that are reformatted to conform to the A.C-P.C distance in each patient. These diagrams are also ruled in a millimeter grid in stereotactic coordinates, reflecting the position of the frame on the patient's head. The program is also capable of overlaying the position of electrode trajectories and mapping the physiological data. A burr hole or twist-drill hole is now made in the same sagittal plane as the expected target so that all electrode trajectories will lie in the same sagittal plane if possible, facilitating the evaluation of physio-logical data. With regards the second method of direct targeting, this is obviously best for targets easily recognized on M.R.I, such as the cingulum or subgenual cingulate cortex, allowing its coordinates can be read directly from the scan. In our opinion, targets such as the globus pallidum internum and the subdivisions of lateral thalamus (i.e., Vim, Vop. Voa, Vc) cannot be recognized in this manner; their expected coordinates must be extrapolated from the computer- generated map and confirmed physiologically with an electrode to identify structures with motor and sensory properties respectively (see next section for details).

### 2.3. Macro stimulus procedure

Several studies[17,23] have measured the variations in the locations of deep brain structures identified by macrostimulation from their locations predicted from ventriculography. In each of those studies, discrepancies of 1 mm or more were found in a significant percentage of patients (15, 43, 42, 56, 45, 35, and 5%, respectively; mean, 34%) and discrepancies greater than 2 mm in 50, 32, 33, 23, 16, 13, and 22%, separately (mean, 27%). A 2-mm discrepancy can lead to surgical failure or complications. We compared the actual locations of tactile neurons in the thalamus with those predicted from computed tomography (CT) imaging, finding no discrepancy in 62.7% of patients in the medio- lateral, 63.4% in the dorsoventral, and 44.6% in the anteroposterior dimension; over a 2-mm discrepancy was seen in 10.8, 12.0, and 19.2% of these dimensions, respectively.[9] The largest discrepancies occurred in patients

who had previously undergone craniotomies or had suffered massive damage to the brain from multiple sclerosis or stroke. Macrostimulation can be done with a mono- or bipolar electrode, with the latter resulting in a little less current spread than the former.[17] Even so, with a 1.1-mm-diameter concentric bi- polar macroelectrode employing a 0.5-mm tip insulated from a surrounding ring by a 0.5-mm insulating band (Diros Techno- logy, Toronto, Ontario, Canada), current may spread to involve up to a 3- to 4-mm sphere. We employ trajectories 2–3 mm apart and stimulate at threshold from about 10 mm above to 10 mm below the target in 2-mm steps, using manually controlled trains of 60-Hz monophasic dampened sine wave pulses of 3-ms duration.

*2.3.1. Impedance monitoring and information*

Impedance monitoring can readily distinguish normal from pathological brain tissue. Collections of cerebrospinal fluid (CSF), abscesses, hematomas, and malignant and soft benign neoplasms have an impedance value of about 400 ohms, while pathological capsules and hard lesions have a much higher impedance. However, the technique is not sufficiently sensitive to reliably distinguish the differences between normal brain tissues. Though dense fiber tracts traversed perpendicularly by a probe may record an impedance as high as 1,600 ohms, the values in different fiber tracts or nuclear masses are not usually sufficiently distinct to pro- vide the sharpness of detection required in stereotactic surgery.

*2.3.2. Micro injections of test substances*

Test microinjections of substances that block, enhance, or otherwise alter neurological function can potentially help confirm an electrode's position at a target site and may constitute a promising technique for the future for some sites, when a more diverse "library" of injectable substances will become available. Meanwhile microinjections of lidocaine [61] have proved useful in the selection of the thalamotomy target site for the control of tremor but are not routinely used in our group due to time constraints.

## 3. Evoked Potentials

Recording of evoked potentials was employed from the previous procedure of stereotactic surgery but in its conventional use is now very rarely employed. Hassler et.al[23] acquired the evoked potentials cortical, especially in the pre-central cortex, through the stimulations of the anterior ventral oral nucleus of the thalamus (V.O.A) and / or the posterior ventral nucleus (V.O.P). stimulations of V.O.A at a frequency of 4Hz to 8 Hz induced a recruiting response that allowed the European France/French personnel[22] to detect the passage of a probe into the ventrolateral nucleus. Authors [63] evoked an augmenting response in monitor and premotor cortex when they stimulated V.O to 6Hertz but not from the ventral intermediate nuclei (V.I.M.) of the thalamus. The latency of the of initial wave was 20 milli sec to 30 milli sec (negative direction, i.e., -Ve peaks). Similarly, authors[18] connected different patterns of cortical evoked potentials, depending on the site in thalamus stimulated. Sano et.al., were able to determine which part of the internal medullary lamina of the thalamus they were stimulating by virtue of the pattern of ipsilateral scalp evoked potentials produced. Also, authors,[19] and authors[25] showed the changing patterns of evoked potentials acquired through the micro electrodes from the different thalamic nucleus response to peripheral stimuli. We did micro electrode recordings which has allowed a new technique to be used, that of focal micro electrode evoked potentials within the nucleus. In this technique open filter recordings are made from the one electrode while stimulating with single electrical-pulse-widths from the other one electrode and 1 milli meter away at a similar vertical depth. In the single pulses, evoked potentials are routinely found in subatsntia nigra pars reticulata (S.N.p.r) however not from the subthalamic-nuclei, therefore, this technique conforms that the detection of S N r that might sparsely populated with spontaneously firing neurons with characteristic properties. The positive going fields are likely of G.A.B.Aergic origin and can be used as tool to examine activity and dopamine/dopaminergic dependent synaptic plasticity at this basal ganglia output station. Within the sub thalamic nuclei a field might also be evoked but with burst stimulation, and it remains to be perseverance if this is a focal sub thalamic nucleus due to G.A.B.Aergic afferents from the pallidal neurons i.e., global pallidus externa or a far field contamination from S N r.

## 4. Microelectrode Fabrication Setup

The techniques for the design of electrodes are briefly explained here for the sake of completeness, however, several institutions now prepare long electrodes that are suitable for use with stereotactic tubes. Commercially available parylene-C-insulated tungsten or platinum-iridium microelectrodes are used with tip sizes ranging from 15 to 40 mm (height of cone) with initial impedances before plating of 1-2 Meg Ohms. the lengths of these electrodes are in the range of 50-70mm, so they need to be extended for use with deep brain structures. If present, the connector pin is cut-off the electrode and the insulation is stripped from the cut end, so that the shaft makes good electrical contact with a stainless-steel extender tube. Kapton tubing insulates the extender tube and is glued to the insulation of the electrode shank to make a contiguous seal.[12] The microelectrodes are plated first with gold and then with platinum to reduce their impedance to about 0.5 Meg Ohms. The electrodes are tested for adequacy of the insulation by suing an electrolytic bubble test, and / or observing constancy of the tip impedance measurement as it immersed

deeper in the conducting saline. The electrode apparatus is assembled on a table under sterile conditions by using a protective carrier tube that fits inside and is the same length as the outer reinforced guide tube. The outer guide tube is passed through the electrode holders mounted on the stereotactic frame and into the brain a sufficient distance to direct the carrier tube accurately to the target but not as far as the area of the brain that is to be studied. The zero reading is obtained by fixing the top of the microelectrode shaft to the hydraulic Microdrive at a point where the tip is visually observed to be flush with the tip of the carrier tube. The inner guide tube containing the micro electrode is then inserted into and fixed with a set screw to the outer guide tube already in place in the brain.

## 5. Sub cortical atlas/ planning with MER Machine

The micro electrode is then extruded with a manually driven hydraulic Microdrive. Continuous recording begins as soon as the microelectrode extrudes into the brain, usually 10mm to 15mm above the target site, and is continued along the trajectory through the target and a variable distance 5mm to 10mm beyond that. Micro stimulation is done each 1.0mm along the way. Currents of up to 100 milli Amperes do not damage the electrodes. Physiological data and a voice channel are recorded for off-line analyzing using a commercially available digital interface C.E.D 140‘ m k II that saves two channels of electrode data, 5E.M.Gs, and 2accelerometers traces and E.O.G or any other stimulus triggers as required. These are collected continuously into digital files. Similarly, a digital video-camera saving direct to digital versatile disks (D.V.D.s) is used to monitor events and patient‘s movements during the entire recording session. Responses elicited by micro and macrostimulation are similar in quality, however, the threshold and the electrical-current spread differ. The size of the projected fields at threshold current, i.e., minimal current required to evoke a sensation, usually is smaller with microelectrodes, but in some cases macrostimulation also results in small projected fields. Stimulus-frequency has a variable effect. Sensory effects may not be perceived with very low frequencies, i.e., 1 Hertz to 5 Hertz frequency or high frequency rates like above 1000Hertz rates of repetition, and for the patient to perceive a sensory effect, trains of many pulses are required rather than the single shocks. Stimulus frequency in the motoric system determines whether individual muscle jerks or tetanization will be produced, and in the extrapyramidal system it determines whether involuntary will be driven or inhibited.

## 6. Conclusion

Theis study showed the physiological atlas mappings with recording and stimulation in structures in which functional stereotactic procedures are regularly done, and describing first, the responses considered to be normal and then certain pathological ones.

## 7. Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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None.

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## Author biography

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