History of Deep Brain Stimulation in la Pitié-Salpêtrière hospital

Since the beginning of Deep Brain Stimulation (DBS) in the 80's, DBS changed very much following evolution of technologies, but also following the development of new clinical indications and their corresponding new neurosurgical targets.
Everything started in France around 1987 when chronic high frequency DBS was introduced by Pr Alim Louis Benabid, neurosurgeon in Grenoble, for the treatment of Parkinson's Disease (PD) tremor. Benabid great idea was to use an electrode and implantable neurostimulator designed for the treatment of pain by stimulation of spinal cord, in a completely different context. He implanted the electrodes in a thalamic sub nucleus called Ventral intermediate (Vim) on PD patients. The frequency of stimulation was also completely original, as Benabid used a high frequency (HF) for stimulation, actually the maximum allowed by the device at that time, i.e. 130 Hz. Vim HF stimulation definitively stopped patient's tremor. Target localization was performed using ventriculography, by injecting a radiological contrast liquid into ventricles. A stereotactic frame fixed the patient's head and allowed computing spatial coordinates of Vim radiological target, based on radiological landmarks including Anterior Commissure (AC), Posterior Commissure (PC) and thalamus height as proposed formerly by Guiot, a French neurosurgeon at Hopital Foch, Suresne, France. Guiot used Schaltenbrand atlas to compute Vim limits and measure its mean coordinates based on such landmarks. To localize best Vim target during surgical procedure, Benabid first used to perform several trajectories with the help of a single microelectrode for recording and stimulation. First trajectory was an oblique fronto-posterior parasagittal trajectory. Others were orthogonal to the first one and were used to determine best target laterality and depth. Peroperative X-rays at a distance of 5 m showed third ventricule contour, Anterior Commissure (AC) and Posterior Commissure (PC) anatomical landmarks, thalamus shape and electrode progression. Guiot diagram could be drown on profile x-rays.
Microelectrode was moved manually by a millimeter each time. Best trajectory and

functional target was chosen on clinical criteria of tremor arrest with minimal current. Later, Benabid made another innovation by using cylindric device with five holes (now best known as Ben's gun) to drive simultaneously five electrodes along vertical trans ventricular paramedial parallel trajectories.

In 1994, we used a system using a slave hydraulic microelectrode holder connected to a master micrometer powered by a step by step electrical motor, similar to the one used by Prs Tasker and Dostrovski we visited in Toronto, Canada. We however modified the device in order to make it move five microelectrodes simultaneously like Benabid did. We designed and made our own Leksell frame electrode holder device, guiding tubes, recording wires and channel switches. The amplifiers and oscilloscopes were usual research laboratory equipments for animal studies. We have asked FHC (Bowdoinham, USA) to create our own microelectrodes and modify it several times until they were perfectly adapted to our needs and easily manipulated by neurosurgeons (length adapted to the frame, more secure connectors, size of exposed tip for stimulation). The neuroradiologist used stereotactic Magnetic Resonance Imaging (sMRI) to compute AC, PC and thalamus height on an 1.5 Tesla MRI. Guiot's diagram was numerically computed for Vim coordinates estimation using an Excel program and independently a computer program with vector translation of radiological coordinates into target stereotactic coordinates (matrix translation). The first year we used a Medtronic electrode with only one contact. Then Medtronic designed a four contact electrode for DBS. Distance between contacts was 1.5 mm and each contact had a length of 1.5 mm for a diameter of 1.3 mm (3388). Newer DBS electrode model 3389 have an inter contact distance of 0.5 mm. In 1999 we decide to look for a system designed for human usage with more security specifications. We found that Medtronic Keypoint would be a good model to start with. However it was not designed for high impedance electrodes. We proposed Medtronic to perform necessary adaptation four our specific needs. After a series of test we performed with sample preamplifiers provided, Medtronic came with a

working device they called Leadpoint. It had only four channels and there was an external switching box for stimulation. Our request to add a noise blanker for limiting the signal noise and keep only spikes above a given voltage level was quickly implemented by Medtronic ingeniers.

We also later suggested Medtronic to build a Leadpoint model with more recording channels. They made it with five bipolar plus three monopolar recording channels.

In our paper published in Neurosurgery (2000), we described our DBS methodology and we understand that it is close to the standard procedure now recommended by Medtronic. FHC requested some data and advice from us in order to obtain FDA administrative clearance for using their microelectrode for DBS recordings. We reported FHC data of about 50 cases using bilateral exploration with 3 to 5 electrodes simultaneously. Later FHC requested some advice from us for manufacturing a five channel electrode micro drive. Medtronic are now delivering Leadpoint microdrive and micro recording electrodes manufactured by FHC. Our radiological procedure is with a 1.5 Tesla MRI, with two sequences, one 3D volume T1 acquisition of 120 slices, and two successive T2 acquisitions of 40 slices centered on Basal Ganglia (BG) each slice being 2mm thick and the second series being shifted by 1 mm from the other. Then both T2 sequences are interlaced by the stereotactic software we are using (Advantage Windows, General Electric). T2 sequence shows BG with a dark hypo signal aspect allowing direct measure of BG targets radiological coordinates. However thalamus Vim subnucleus is not visible. T2 weighted 1,5 T MR sequences suffer from distortion at the border of the images, preventing stereotactic software to recognize the stereotactic frame. In order to obtain target stereotactic coordinates it is thus necessary to fuse T2 with T1 acquisition that has no distortion. This fusion may be performed by image fusion or by computing a translation matrix between different anatomical landmarks (AC, PC and medial point) and target coordinates in both T1 and T2 sequences. A T1 angio MRI acquisition is also performed for visualizing the veins and arteries using Gadolinium, a contrast product. On this sequence the

neurosurgeon and the neuro radiologist can choose safe trajectories avoiding dangerous areas or vessels. We always selected trajectories outside of lateral ventricles, starting our safe trajectories search with Leksell frame of 70° for A and 70° for B angles on the right side.

In parallel with technical changes, fundamental research on animals was making progress. DBS followed closely scientific knowledge. We started with Vim HF stimulation for the treatment of essential tremor or PD tremor. Soon after, Pallidum stimulation was used to cancel abnormal movements induced by high Dopa dosage (L-Dopa Induced Diskinesia). Then in 1993 Benabid, Pollak et al. performed DBS of Sub Thalamic nucleus (STN) on PD patients with a dramatic success.

HF stimulation removed all PD symptoms: rigidity, akinesia, tremor. Soon after, Pr Philippe Coubes in Montpellier, France, saved a dying young girl aged 7-8, with Generalized Primary Dystonia (GPD) by implanting DBS electrodes into her Globus Pallidus (GP) nuclei. Since then, hundreds of GPD patients, children or adults with genetic mutations DYT1, DYT11, have been considerably improved. We observed by chance that two of our patients with PD and Obsessive Compulsive Disorders (OCD) have seen the disappearance of their compulsions after DBS of STN. And finally, our team was able to improve considerably Tourette's syndrome (TS) patients with DBS electrodes in anterior ventral part of GP, a limbic area. Nowadays, more than 100.000 patients in the world benefited of a DBS for the treatment of movement disorders.

Operating procedure

First of all, why is there a need for neurophysiological exploration during DBS ? MRI precision is limited to a voxel of around 1.5 mm^3. However, T2 sequences thickness is 2mm. Then, localization error could be plus or minus 2 mm. Electrophysiological exploration is then used for three goals : check if exists any instrumental error ; determine BG nuclei limits and identify functional target (this

target, is the area where stimulation can best improve patients symptoms); help positioning final chronic stimulation electrode contacts within 1mm of desired coordinates. We have verified that if DBS is performed on another contact than the best one, with centers only spaced by 2 mm, then clinical results are less efficient. Deep anesthesia is interfering with neuronal micro recording. When procedure is not under local anesthesia patient must be awaked before starting the recording, or at least, anesthesia should be partially removed. With deep anesthesia there is less neuronal activity. Furthermore, patients must not receive any L-Dopa medication or anxiolytics since the evening before the procedure and dopamine agonists must be removed a few days before. All these drugs can interfere with the patient clinical state, loss of rigidity, neuron silence). In order to perform good recordings it is necessary to connect Leadpoint ground lead (green) alligator on the electrode guiding tubes. Electrode impedances must be checked. If impedance is lower than 400 KOhms, then the electrode should be replaced for it means that the recording tip is too large or broken. Guiding tubes are introduced by the neurosurgeon. The microelectrodes are coaxial with a mobile inner recording part and insulated external tubing. The electrodes are introduced inside of guiding tubes with the tip retracted in order to protect them. Recording tip is made of tungsten a soft metal than can be destroyed by a simple touch. Recording parts are then pushed down and the tip is usually positioned 5 mm above the radiological target. Outside of nuclei, only background noise is recorded for white matter is myelinated with only a few ionic channels and thus no neuronal spikes produced. When targeting NST, some electrodes can record thalamic reticular nucleus neurons. The pattern of discharge is typical and can be recognized easily. Each BG has its own pattern of discharge; we call it physiological nucleus signature also depending on the kind of disease (pathology signature). STN activity is very rich in PD and has a random pattern of activity, sometime pulsating, with a rhythm synchronized with limb tremor when present.

For recording, we use five channel recording Leadpoint protocol. Each channel is identified by a label glued on the corresponding plug. We prefer letters A, C, P, M, L (for Anterior, Central, Posterior, Medial and Lateral) rather than default numbers. Windows loud speaker is set to maximum for there is usually a lot of noise in the operating room. However, loud speaker level must be set at a level where there is no Larsen effect. Neuron Action Potentials (AP, or spikes) sound like brief noises. Backround noise is suppressed by the noise limiter. When recording is done inside somatomotor area of the nucleus, it may be possible to trigger the spikes by moving the patients arm, hand, fingers, leg, etc... We can observe either an increase or a decrease of activity with movements. Recording helps to determine the precise location of nuclei on each electrode channel. Best trajectories must have more than 3 mm of STN activity. If less, it means that the respective electrode was too close to the border of the nucleus. We are evaluating average spike activities and code it with one to four crosses every 500 µm (0.5 mm). The activity is reported on a piece of paper with 5 columns, one for each electrode. At the end, it is easy to evaluate the exploration by looking at the synoptic table. Finding lower limit of nucleus is essential information. It is determined by the loss of neuron spikes. If we continue to move down the recording electrodes, another active area with sometime faster but overall more regular spikes is reached after 0.5 to 1 mm. This means that we have reached Substantia Nigra (SN) a larger nucleus we can usually record with all electrodes. This is our exploration lower limit, where we capture an X-ray in order to indicate the zero level where the surgeon will put final DBS electrode contact 0. With this choice, electrode contact 1 and 2 are inside of STN and contact 3 above. We must now choose the best trajectory. The number of millimeter inside of STN is a good parameter (at least 3.5 mm) we use when no stimulation is possible (patient under general anesthesia). Best trajectory is the one with the best HF clinical response : tremor arrest, removal of rigidity, less akynesia, dyskinesia). In order to perform stimulations, the surgeon pull central part of electrodes by 1.5 mm and we can then

move down the electrodes at the level of STN entry plus 1.5 mm where we can stimulate with each electrode at a time. Clinical evaluation is performed while stimulating with different amplitude currents from 0 to 4 mA at 130 Hz and 60 or 100 microseconds. Electrode that did not cross STN (no spikes detected) can be removed before moving down the others. This will give less pseudo lesioning effect (rigidity suppression when lowering electrodes). Clinical evaluation is based on a subset of UPDRS III (thumb-index, rigidity, open-closed hand, tremor suppression). In case of good identical clinical effects on two electrodes, it can be interesting to stimulate with higher currents (up to 8 mA) until a side effect appears : sensation of heath, dizziness, gaze limitation, face or arm fixed dystonia, III cranial nerve symptoms…). We choose the trajectory with the largest interval between current levels giving improvement and side effects. In dystonia the target is Globus Pallidus internal part (GPi). To avoid abnormal movements during procedure anesthesia cannot be avoided. Stimulations can however be performed in order to detect stimulation side effects. If fixed muscle contraction is noticed at a low current level, then it means that electrode is too close to the pyramidal tract (motor fibers). Another one must be chosen. In case of anesthesia, recording is still very useful in order to find again the limits of the nucleus, particularly, lower limit that is important for determining the location of DBS electrode contact 0. It must be at least two millimeters away from GPi limits in order to avoid pyramidal tract stimulation by current diffusion. At the end of the procedure we make a hardcopy of saved screen dump recordings, electrode by electrode. A report is edited with different informations : target coordinates, stereotactic landmark coordinates (AC, PC, M), names of recorded and stimulated trajectories, depth of DBS contact 0 as read on per operative X-ray, reference of DBS electrodes. DBS electrode is inserted in selected trajectory and at de depth indicated by end of STN nucleus recording, with the help of short distance X-Ray device. Lower contact 0 of the electrode is put at the depth level where SN recording started. When DBS electrode is inserted the patient's Parkinson's symptoms should

disappear: no more rigidity or tremor and sometime transitory dyskinesias may be seen (ballism). This is due to the large size of final electrode inducing a temporary pseudo lesioning effect, proving the correct position of DBS electrode in functional target. We always perform a CT scan immediately after the procedure without stereotactic frame in order to check if there are no complications and localize the electrodes.

In order to explore targets situated inside of non visible nuclei or subnuclei on MRI T2 and T1 sequences, we have developed at Pitié-Salpêtrière, a *BG tridimensional stereotactic deformable histologic and MRI atlas* (see bibliography *). This atlas will be available in some Medtronic products soon. The tool let us visualize BG contours on patients MRI. Thalamus subnuclei contours are also well identified. This atlas helped us to target anterior and ventral GPi part that is even less visible on MRI. This has been of major interest for patients with Gilles de la Tourette syndrome (TS). With this atlas tool we have also been able to compare data from micro electrode recordings and find that overall localization errors where within 1 mm between both methods. We also determined the location of best therapeutic contacts inside of STN nuclei of a number of patients, confirming the upper and medio lateral STN DBS target for PD.

Bibliography

Bilateral subthalamic stimulation for Parkinson's disease by using three-dimensional stereotactic magnetic resonance imaging and electrophysiological guidance
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