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Implantation of human pedunculopontine nucleus: a safe and clinically relevant target in Parkinson's disease

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The peduncolopontine nucleus modulates locomotor activity and dysfunction in this nucleus may be responsible for the gait and postural impairments seen in Parkinson's disease and other movement disorders. We report the first surgical exploration and implantation of deep brain stimulating electrodes of the peduncolopontine nucleus area in two Parkinson's disease patients to examine the safety and the potential benefit of chronic electrical stimulation at this site. Under local anesthesia, the peduncolopontine nucleus was approached from a coronal burr hole using a trajectory that was 78–80° and 62–64° on the coronal and sagittal planes. Microrecordings helped to identify neurons in peduncolopontine nucleus and the adjacent substantia nigra pars reticulata. Chronic deep brain stimulating electrodes were implanted within the peduncolopontine nucleus in a manner similar to that practiced with deep brain stimulating surgery at other targets. Peduncolopontine nucleus neurons were characterized by small and broad multiunits (230 μV, 2.5 ms, 14.6 Hz). Caudal to this area, neurons firing at higher frequency, approximately 70 Hz, characteristic of nigral neuronal discharges, were encountered, followed by 2 mm of cells similar to those recorded in the dorsal peduncolopontine nucleus area. After deep brain stimulating electrodes implantation, acute intraoperative stimulation (up to 3 V) was performed with two stimulation frequencies in each session. Stimulation at 80 Hz has little discernable effect. On the other hand, stimulation at 10 Hz fostered a subjective feeling of 'well-being' and a time-locked amelioration of the clinical scores. These findings demonstrate that the stereotactic approach of peduncolopontine nucleus is safe. The target may reliably be identified by microrecordings. Low-frequency stimulation may produce acute improvements in motor function. - *NeuroReport* 00:000–000 © 2005 Lippincott Williams & Wilkins.

Keywords: deep brain stimulation, intraoperatory microrecordings, Parkinson's disease, peduncolopontine nucleus, subthalamic nucleus

Introduction

The implantation of chronic deep brain stimulation (DBS) electrodes in the subthalamic nucleus (STN) to treat advanced Parkinson's disease (PD) has become a well-established surgical procedure with approximately 30 000 patients operated to date. While STN-DBS produces striking clinical improvements in motor disability and quality of life [1–5], it can be associated with a number of adverse events and therapeutic limitations [6,7]. One of the problem areas is the relatively modest and unsustained benefit in gait and postural disability in patients. The improvements in these domains after STN-DBS surgery may be lost within a short period of time as the disease progresses. Clearly, there is a need to develop novel therapeutic strategies for PD patients who continue to have disabling gait and postural disturbances despite optimal medical and surgical treatment [2,6,7].

The peduncolopontine nucleus (PPN) is an integral component of the midbrain locomotor region and plays an important role in the initiation and maintenance of walking behavior. An abundant literature on PPN has shown its functional interactions with basal ganglia and cortico-spinal circuits (for reviews, see [8–10]). It is therefore logical that modulation of PPN activity could modulate motor functions in patients with gait and postural disorders. Indeed, PPN stimulation, depending on the electrical parameters setting, may facilitate or worsen locomotion. In normal macaques, for instance, PPN stimulation at frequencies above 45 Hz produced severe akinesia [11]. In MPTP-intoxicated primates, however, Nandi *et al.* [12] demonstrated that PPN

activation with the locally applied GABA antagonist bicuculline improved the motor score. These findings suggest that driving PPN in parkinsonian states may improve locomotion while presumed blockade at high frequencies may produce akinesia. This possibility was supported by the observation that in a single 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated macaque PPN stimulation at 2.5, 5 and 10 Hz dramatically increased movement [13].

Thus, we sought to determine whether PPN implantation might be feasible and beneficial in human PD. To accomplish this goal, we selected two PD patients with a long history of postural instability and falls due to ON freezing relatively insensitive to the standard l-DOPA-centered therapies. The routine utilization of our double-arch Maranello system [14–16] allowed to target simultaneously, in the same surgery session, PPN and STN. Preliminary excerpts were presented at World Society for Stereotactic and Functional Neurosurgery [7].

Participants and methods

Participants

Two patients (C.D.F. and E.C.) were enrolled in this study for surgical treatment in the PPN and the STN. They had suffered a 12 and a 11-year disease history, respectively, with disabling freezing of gaits since 2002 and global Unified Parkinson's Disease Rating Scale (section III, in CAPIT) of 76 and 82. The patients were operated using local anesthesia in the medication-off state (drug withdrawal of 5 days).

The patients were clearly informed by neurologists and neurosurgeons of the surgical risks due to the procedures, including bilateral implantation of both PPN and STN. Written, informed consent was obtained from both patients. The local ethics committee approved the protocol and consent form describing the risks and potential benefits of the study.

Neurosurgery

Our complete surgical procedure, including ventriculography, is described elsewhere [14–16]. Briefly, electrode implantation was performed inside two contemporary target areas for each hemisphere (first STN followed by PPN, each implanted with definitive Medtronic 3389). For STN, however, the angle was 85–90° in the sagittal plane; and 75–80° in the coronal plane, to obtain an extra-ventricular and extra-capsular trajectory. The coordinates for the STN target were, at the AC–PC/2, 12 mm lateral to the midline of the third ventricle and 4 mm below anterior–posterior commissural plate (AC—PC). For PPN, the angle was 62–65° in the sagittal plane, to obtain a trajectory parallel to the aqueduct, and 78–80° in the coronal plane. The coordinates for PPN were 13 mm lateral to the midline, 12.5/13 mm below CP; y=CP. After surgery, the definitive electrode locations were verified by brain magnetic resonance imaging [7].

Microrecordings

Intraoperative neurophysiological recordings were favored by the robotized system (3P Maranello Stereotactic System, CLS – SRL, Forli', Italy) with remote infrared control on up to five independent tracks. Signals from neuronal recordings were amplified (WPI, DAM-8) and sampled (sampling rate 20 kHz) online by a computer connected to a CED 1401 interface. Data from either PPN or substantia nigra pars reticulata (SNr) were analyzed off-line using the spike 2 analysis program. During the STN-DBS, spikes were discriminated from noise and from stimulation artifacts on the basis of their amplitude using a digital double-threshold window discriminator. Action potential shape was matched with a template to distinguish somatic action potential from fiber activity. Electrical STN stimulation consisted of pulses of 60 μs width and 2–3 V delivered at 130 and 185 Hz. PPN or SNr neuronal activity was evaluated for 5 min before, during and after extended STN stimulation. The time during which spikes recording is occulted by saturation of amplifier after stimulation (~0.2 ms) was taken into account to calculate the firing rates during stimulation. Peri-stimulus time histograms were reconstructed by triggering at specific millisecond intervals (from 100 to 6/7 ms) in the before and after stimulation period and from the interstimulus period in the stimulation period.

Results

Figure 1 outlines the trajectory approach to the PPN, considering the final target at −11.8 (±1.6 mm) with respect to the anterior–posterior commissural plate (AC–PC line). Note that the whole trajectory (mean 9 mm, ranging from 7.1 to 9.7 mm) describes a 76–80° angle in the coronal plane (Fig. 1a and b), thus moving from lateral to medial. The beginning of the track (ending of dashed line in Fig. 1a and b) usually corresponds to −4 below AC–PC and is silent, but at 0.3–0.8 mm, neuronal firing activity becomes detectable (PPd in Fig. 1a and b and upper trace in Fig. 1c). The spike amplitude (mean=224 μV ±60) is rather small, yet easily distinguishable from the background noise (e.g. upper trace in Fig. 1c, with a rather prominent positive phase). Overall, the 27 multiunits collected in the dorsal portion of the PPN (out of four tracks in four hemispheres in two patients) defined an irregular firing activity, characterized by typical broad spikes (2.6 ms ±810 μs, n=27). The PPN firing rate ranged from 8 to 29 Hz (mean 14.6). The relative low impedance of the recording electrodes (0.5–1 MΩ) did not allow unequivocal segregation of single-unit firing activity. This sort of multiunits can hardly be considered suitable for mathematical analysis of discharge patterns or for pharmacological studies, but contributed to a better definition of this novel surgical target.

At 3 mm caudal with respect to the trajectory track start (and about 4–5 mm above the programmed target area), the firing pattern suddenly changes with the occurrence of a well defined pattern, that is an irregular high-frequency discharge around 70 Hz, attributable to SNr multiunits (Fig. 1a and b and middle trace in Fig. 1c). The mean firing activity of SNr units was 73.8 Hz (±38.6, n=33). Finally, the caudal border of the SNr was followed by a transient silent zone ending at −11/−12 with respect to the AC–PC line, in the target area; here, only a few scattered units were still collected (n=5 out of four trajectory tracks, exemplary recording is the bottom trace in Fig. 1c).

In most of the dorsal PPN units, we have investigated whether acoustic stimuli or passive movements had any impact on PPN firing frequency. Passive limb movements consisted in fast (<1 s) flexion or extension of the wrist or elbow contralateral to the recorded hemisphere. These passive movements were repeated in sequence, at intervals of 4–5 s or more. The majority of the PPN multiunits (21 out

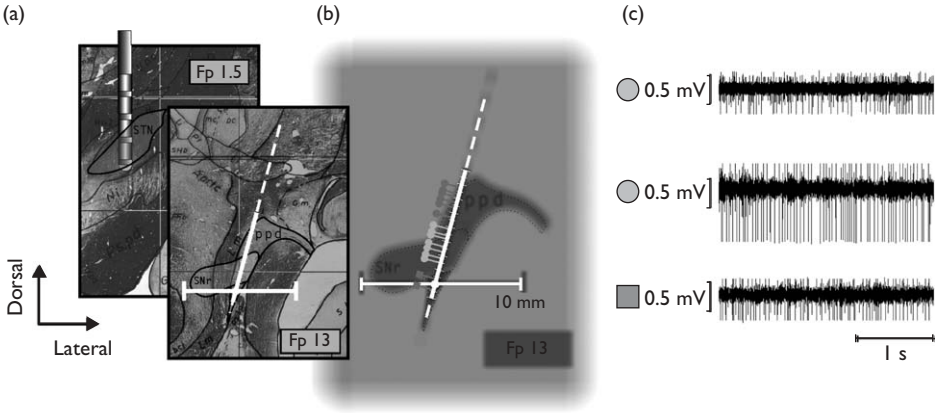

Fig. 1 Features of the trajectory track targeting peduncolopontine nucleus (PPN). (a) Two superimposed coronal sections of the Shaltenbrand atlas. On the bottom (1.5 mm posterior to the mid-commissural plane) are shown details of the region, which contain the subthalamic nucleus (STN) (yellow) with a representation of the Medtronic 3389; in front (13 mm posterior to the mid-commissural plane), schematic diagram of the region containing PPN (red) and substantia nigra pars reticulata (SNr) (blue). (b) Emphasizes the standard trajectory through PPN (80° angle on the coronal plane); each spherical symbol indicates a multiunit microrecording ($\geq$2 min). (c) Representative traces of dorsal PPN (ppd, upper one), SNr (middle one) and lower PPN (lower trace=target region).

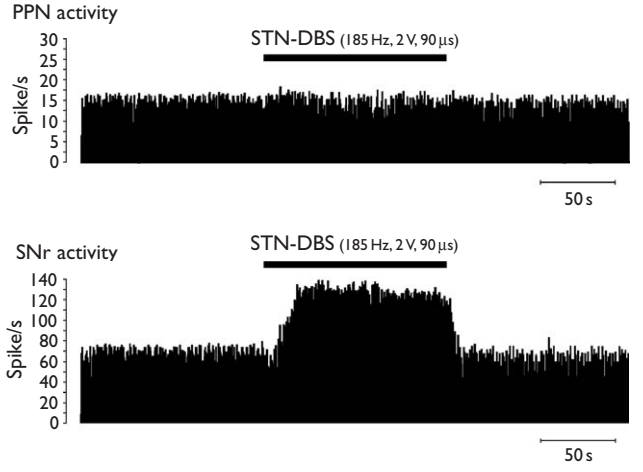

Fig. 2 Subthalamic nucleus (STN)-mediated effects on peduncolopontine nucleus (PPN) and substantia nigra pars reticulata (SNr). The histogram shows the firing activity in dorsal PPN (upper trace) and SNr (lower trace) before, during and after clinically efficacious STN-DBS (our standard parameters). Note the negligible changes in PPN and the large firing activity increase in SNr.

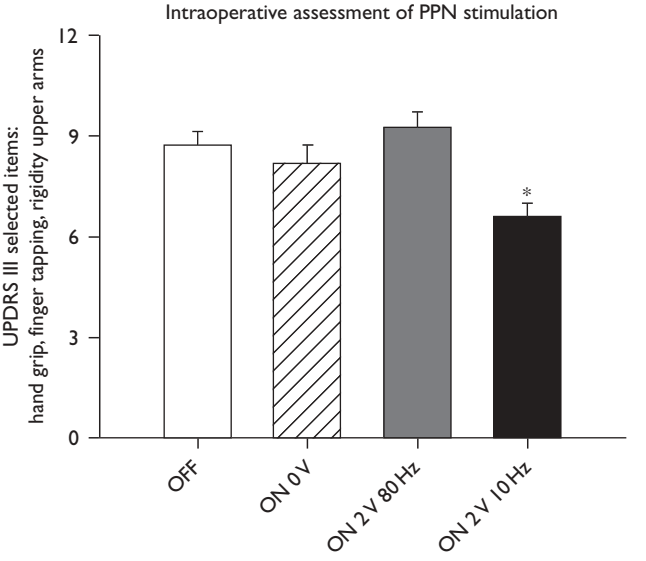

Fig. 3 Clinical intra-operatory score under peduncolopontine nucleus (PPN) activation. The histogram highlights the mean score in four PPN-implanted patients (*y*-axis represents the summation of two items for akinesia plus an average evaluation of upper arm rigidity). Each item scores from 4 (=worse) to 0 (=no impairment at all). Note the significant improvement during low-frequency stimulation (black column).

of 27) exhibited no well-defined pattern of response to passive or active single-joint activation; in the remaining six, either a slight inhibition or inhibition followed by excitation was observed (data not shown). Similarly, acoustic 'clicks' were without consistent effect.

The combined implantation of the STN and PPN during the same surgical session produced further electrophysiological tests (Fig. 2). As shown by representative histograms in Fig. 2, the macroelectrode placed in the STN was activated (2 min, 185 Hz, 2 V, 90 µs) during concomitant microrecordings in the dorsal PPN (Fig. 2a) or SNr (Fig. 2b). Aside from evaluating the clinical efficacy of the STN-DBS (at least, the absence of any adverse effects), microrecordings were critical to judge to what extent the STN played any clear effect on different subregions of the human brain stem. Only slight changes were detected in PPN firing activity during the STN stimulation (if any, a 5% inhibition, not reaching, however, a significant level). This may imply that the STN-PPN direct pathway might be robust in only rodents or cats while it is negligible in primates and humans. On the contrary, the STN-DBS promoted a large increase in SNr firing discharge (+94%, n=12; exemplary histogram in Fig. 2b).

Figure 3 illustrates our intraoperatory score. In all four cases that were treated with permanent implantation of Medtronic 3389 (Medtronic Inc., Minneapolis, Minnesota, USA) in the PPN, brief sequences of nucleus stimulation

were performed while the patients were unaware about stimulation parameters. We chose the following protocol: bipolar stimulation (distal contacts), slowly progressively increasing voltage up to 3 V and two distinct stimulation frequencies: low (10 Hz) and high (80 Hz). Figure 3 summarizes the mean results: a slight but consistent improvement ($P<0.05$) of the finger tapping (see Participants and methods) is detectable during the 3-min stimulation at 2 V and at 10 Hz. Conversly, a modest worsening characterized the 'high frequency' test (80 Hz columns). A subjective feeling of 'well-being' was experienced in all four stimulations, suggesting the possible occurrence of placebo-like effects. The significance of the beneficial effect was, however, reinforced by the lack of response under the 0 V stimulation.

Discussion

This paper represents the first evidence that PPN, in PD patients, may be identified and targeted safely. Owing to the investigational nature of this study, only a single trajectory through the PPN was performed. We could not map all the specific subregions hypothetically composing the mammalian PPN area, as detailed, for instance, by Takakusaki and co-authors [17] in experimental animals.

We have made, however, a number of observations. First, we did not detect any clear change of PPN firing activity following acoustic stimuli. Despite the well-known involvement of PPN in the neuronal pathway mediating acoustic startle response [18] (and the high percentage of neurons – about 40% – responsive to auditory click stimuli – single units), we did not document any change of firing frequency or patterning. In addition, as revealed by the lack of consistent response to passive movements, PPN neurons did not manifest peculiar single-joint receptive fields. This is likely related to the surgery conditions *per se*, for instance the inopportunity to execute complex motor tasks [19] and also the simultaneous presence of the STN macroelectrode, whose 'acute' effects are not fully predictable.

The absence of any reliable burst-like firing activity was a surprising result. 'Bursty' PPN neurons were described in rodents [19], cats [17,20] and primates [21] as a consistent, although, small subpopulation while the vast majority of neurons have been reported to fire in an irregular tonic manner, and eventually transiently at the beginning or the end of desired movement in primates [21].

The discrepancy may arise from the following considerations: our sample ($n=27$) of multiunits is still inadequate to gather a wide panorama of PPN patterns. In addition, 'bursty' mode is enhanced by postural changes or is clearly related to specific frequency of locomotion [20,21]. The latter is not reproducible in the restrained conditions of the surgical environment. Finally, it is possible, that in a chronic disease such as PD, the biophysical properties of the voltage-gated conductance that underlie the bursting discharge (low-threshold calcium spikes and/or inward rectifiers governing rebound excitation) are not preserved as in healthy mammals.

Another striking finding of our report concerns the lack of electrophysiological change in PPN in response to clinically efficacious STN-DBS. The small sample size and the possibility that the PPN area recorded was not in the terminal field of the STN region stimulated may provide an explanation. It is possible that macrorecordings (i.e. local field potentials as utilized by Brown and co-authors [22]) in the short-term follow-up after operation will address these questions better. On the other hand, in the same surgery session and track, SNr units manifested a peculiar response to activation of the STN-DBS (Fig. 2b). Hence, despite the procedural and experimental difference, we are led to believe that the role of the STN-PPN pathway, central in rats or cats, might have become clearly less marked with evolution.

The key finding of our work is that we have demonstrated a good and reliable trajectory founded on the identification of a random PPN firing dominated by small broad spikes and an irregular higher frequency firing discharge in the more caudal and distal tiers of SNr. In addition, evidence emerged on undoubtable intraoperatory clinical response to PPN activation at low frequency, characterized by a sort of subjective arousal and an objective relief of akinesia.

Future lines of research will elucidate whether PPN-DBS would definitively acquire the status of target structure for advanced PD. From now on, it is worth revisiting a more extensive definition of electrophysiological features in the MPTP-treated primates. Concomitantly, we will optimize, given the ethical limitations for intraoperatory assessments, the analysis of LFP acquired from PPN, in combination with electroechocardiogram recordings from the scalp during PPN chronic stimulation.

Conclusions

Our findings so far highlight the fact that PPN territory is a feasible reliable target without major surgery risks and sufficient electrophysiological hallmarks. Further, PPN low-frequency stimulation may have a role in the therapy for parkinsonism (supporting previous experience by Aziz and co-authors), although a more extensive validation is necessary.

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