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Low and high-frequency somatosensory evoked potentials recorded from the human pedunculopontine nucleus

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HIGHLIGHTS

- SEPs can be recorded in humans from DBS electrode located in the Pedunculopontine Tegmental nucleus (PPTg) area.
- PPTg SEPs can origin from either the medial lemniscus or the cuneate nucleus.
- 1000 Hz and 1600 Hz HFOs may be identified in the PPTg traces.

ABSTRACT

Objective: To investigate the generators of the somatosensory evoked potential (SEP) components recorded from the Pedunculopontine Tegmental nucleus (PPTg).
Methods: Twenty-two patients, suffering from Parkinson's disease (PD), underwent electrode implantation in the PPTg area for deep brain stimulation (DBS). SEPs were recorded from the DBS electrode contacts to median nerve stimulation.
Results: SEPs recorded from the PPTg electrode contacts could be classified in 3 types, according to their waveforms. (1) The biphasic potential showed a positive peak (P16) whose latency (16.05 ± 0.61 ms) shifted of 0.18 ± 0.07 ms from the lower to the upper contact of the electrode. (2) The triphasic potential showed an initial positive peak (P15) whose latency (15.4 ± 0.2 ms) did not change across the DBS electrode contacts. (3) In the last SEP configuration (mixed biphasic and triphasic waveform), the positive peak was bifid including both the P15 and P16 potentials.
Conclusion: While the P16 potential is probably generated by the somatosensory volley travelling along the medial lemniscus, the P15 response represents a far-field potential probably generated at the cuneate nucleus level.
Significance: Our results show the physiological meaning of the somatosensory responses recorded from the PPTg nucleus area.

1. Introduction

Pedunculopontine Tegmental nucleus (PPTg) is a pontomesencephalic structure involved in the pathophysiology of Parkinson's disease (PD) and other neurodegenerative disorders (Jellinger, 1988; Garcia-Rill, 1991; Manaye et al., 1999; Pahapill and Lozano, 2000). Recently, it has been introduced as a novel target for deep brain stimulation (DBS) in movement disorders (Mazzone et al., 2005b, 2008, 2009a, 2011, 2013; Jenkinson et al., 2005; Plaha and Gill, 2005; Stefani et al., 2007; Lozano and Snyder, 2008; Zrinzo et al., 2008). Although the therapeutic benefits of PPTg DBS are not yet definitely elucidated, motor symptoms, in particular freezing of gait and axial disturbances, can be improved (Ferraye et al., 2010; Follett and Torres-Russotto, 2012; Hazrati et al., 2012; Moro et al., 2010; Ostrem et al., 2010; Peppe et al., 2010; Mazzone et al., 2011, 2012, 2013; Thevathasan et al., 2011a,b; Wilcox et al., 2011).

Implanted lead in the PPTg area may be used to record the somatosensory evoked potentials (SEPs), possibly generated within deep cerebral structures difficult to be investigated by using

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surface electrodes, such as the medial lemniscus (Hanajima et al., 2006; Insola et al., 2008). Although SEPs from PPTg area to upper limb stimulation have been recently described (Mazzone et al., 2007, 2011; Yeh et al., 2010; Insola et al., 2011, 2012), there has not been a systematic study of the PPTg SEP waveforms. In particular, the generating sources of these responses are still unknown.

The present study aimed to investigate the PPTg waveforms, in terms of spatial and temporal distribution, and their relationship with the SEP components recorded from the scalp surface. Moreover, the high frequency oscillations (HFOs) subtending the low frequency PPTg SEPs were analyzed.

2. Materials and methods

2.1. Patients

SEPs were recorded to median nerve stimulation in 22 patients (21 men, 1 woman; mean age 63.7 ± 9.9 years) with PD. None of them had sensory problems. Patients especially suffered from gait disturbances and postural instability resistant to pharmacological treatment. The study was approved by the local ethics committee and all patients gave their informed consent to participate to it.

In 15 patients, the DBS electrodes were placed in the right PPTg, while in one patient the bilateral PPTg nucleus was implanted. In 2 patients, the PPTg and the subthalamic nucleus (STN) were implanted bilaterally, while in other 2 patients both the right PPTg and STN were implanted. In one patient, the DBS electrodes were placed in the bilateral PPTg and Globus Pallidum pars interna (GPi), while the remaining patient had the bilateral PPTg and the left GPi implanted. In summary, SEPs were recorded from 27 PPTg, 6 STN, and 3 GPi.

Table 1
Coordinates of the PPTg electrode contact 0 in all patients.

Patients	Z		X	Y
	PMJ	AC–PC	DfM	VFLd
Type I SEPs – biphasic				
1	5.00	15	7.00	6.09
2	3.03	11.3	10	4.01
3	0	11	7.00	6.00
4	5.00	13	7.00	7.00
5	3.03	14.3	6.00	8.00
6	0	12	6.00	7.00
7	0	11	5.00	7.00
8	5.00	17	8.00	4.00
9	3.00	23	7.00	7.00
10	5.00	25	8.00	6.00
11	9.00	21	7.00	8.07
Mean ± SD	3.4 ± 2.4	15.7 ± 5.0	7.0 ± 1.3	6.5 ± 1.4
Type II SEPs – triphasic				
1	7.00	19	7.00	5.01
2	7.00	16	6.00	6.09
3	7.00	11	5.07	7.00
4	7.00	19	7.00	6.09
5	9.00	19	0*	2.2*
6	7.0	20	5.00	4.08
Mean ± SD	7.3 ± 0.8	17.3 ± 3.3	5.1 ± 2.6	5.4 ± 1.8
Type III SEPs – mixed				
1	0	12	6.00	7.01
2	6.00	15	8.00	7.00
3	6.00	17	5.00	6.09
4	6.00	18	8.00	7.00
5	7.0	13.05	6.00	4.01
Mean ± SD	5.0 ± 2.8	15.1 ± 2.4	6.6 ± 1.3	6.4 ± 1.3

PMJ = ponto-mesencephalic junction; AC–PC = anterior commissura–posterior commissura line; DfM = deviation from midline; VFLd = anterior distance from the ventricular floor line.

2.2. Surgical procedure

We used the same procedure described in detail in previous papers (Mazzone et al., 2005a,b, 2008, 2009a, 2011, 2013). DBS multipolar electrodes (Medtronic® Minneapolis, USA, Neurological Division) were implanted: 3389 for PPTg and STN, 3387 for GPi. The stereotactic electrode implantation in the targeted nucleus was performed with our Maranello double emiarch system (Mazzone et al., 2009a, 2011, 2013). Briefly, the target planning was based on stereotactic angio-CT scans, using the ponto-mesencephalic junction line (PMJ) and the Obex as reference points for the PPTg, while the stereotactic classic standardized coordinates respect to the anterior commissura–posterior commissura (AC–PC) line were used for STN and GPi. The 3D reconstruction of the cerebral vascular system, made by means of the navigation Maranello Stereotactic System® (CLS Titanium, Forlì, Italy), allowed us to exclude the possibility that any conflict could occur between the chosen lead trajectory and the vessels. Once the PPTg target was reached, intraoperative SEPs were performed to calculate the macroelectrode position (Insola et al., 2012). In Table 1, we report the *x*, *y*, and *z* coordinates (in millimeters) representing the distance of the deepest contact from reference points: ponto-mesencephalic junction (PMJ) and AC–PC line for the *z* coordinate, deviation from midline (DfM) for the *x* coordinate, and anterior distance from the ventricular floor line (VFLd) for the *y* coordinate.

In order to select the best target for the deep brain stimulation (DBS) of STN or GPi nuclei, extracellular electrophysiological recordings were performed during the surgery, under local analgesia, using semi-microelectrodes (FHC, USA). Upon completing the procedure, an X-ray of the cranium in stereotactic conditions in antero-posterior and latero-lateral was made to verify any discrepancy between the targeted coordinates and the ones actually carried out (by means of recalculation system software, 3P Maranello). In all patients, the definitive electrode position was verified after surgery by brain magnetic resonance imaging (MRI – Philips Gyroscan 0.1 T) or computerized tomography (CT) (Fig. 1). The electrode implantation surgery was followed by a 15 days test period. During this phase, clinical evaluation was performed during DBS-off and DBS-on. Different configurations of the DBS were tested, i.e., monopolar vs. bipolar, high frequency vs. low frequency (for PPTg), continuous vs. cyclic stimulation.

2.3. SEP recording technique

Immediately after the implant, the stimulator is kept switched off and the intracranial lead is still accessible, so that the 4 contacts can be connected to the neurophysiological equipment and used to record SEPs. In all patients, the neurophysiological study was performed 3 days after the lead implant, before the DBS started. All patients were in drug wash-out condition. In patients with bilateral PPTg implant both median nerves were stimulated, while in patients with unilateral PPTg implant the median nerve contralateral to the implanted PPTg was stimulated. Stimuli (0.2 ms duration) were delivered by skin electrodes at the wrist, with an intensity slightly above the motor threshold. The stimulation rate was 1.5 Hz. SEPs were recorded from the 4 macroelectrode contacts and from disk recording electrodes (impedance below 5 KΩ) placed at 2 scalp locations: (i) the parietal region contralateral to stimulation (P3/P4) and (ii) the frontal region (Fz). The scalp surface electrodes and the intracranial leads were referred to an electrode placed on the auricular lobe ipsilateral to the stimulation. The ground electrode was at the stimulated arm. The analysis time was 50 ms, with a sampling rate of 10,000 Hz. The amplifier bandpass was 3–3000 Hz (12 dB roll-off). Two averages of 1000 trials each were obtained.