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Pedunculopontine nucleus stimulation induces monocular oscillopsia

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ABSTRACT

two patients with Parkinson’s disease with pedunculopontine nucleus (PPN) stimulation for gait impairments reported “trembling vision” during the setting of the electrical parameters, although there was no clinically observable abnormal eye movement. Oculomotor recordings revealed frequency locked voltage dependent vertical or oblique movements of the eye ipsilateral to the active contact, suggesting current spreading to the mesencephalic oculomotor fibres. These results emphasise the difficulty of stimulating this mesencephalic region.

Stimulation of the pedunculopontine nucleus (PPN) in the 25 Hz frequency region appeared promising for treating levodopa unresponsive gait impairment in patients with Parkinson’s disease (PD).1,2 We started studying the effects of PPN stimulation on such symptoms after obtaining approval from the local ethics committee and written informed consent from patients. During setting of the electrical parameters, the first two patients reported “trembling vision” although there was no clinically observable eye movement. We performed ocular motor recordings under different stimulation settings to understand this effect.

RESULTS

Electrical parameters setting

The PPN was implanted as previously described for the STN except that, because of the size of the brainstem, two or three microelectrodes instead of five were used during surgery to map the PPN area. During surgery and for the three microelectrodes, patient No 1 reported trembling vision during 25 Hz acute stimulation at intensities above 2 mA. Patient No 2 did not report any such effect. Quadripolar electrodes (model 3389; Medtronic Minneapolis, Minnesota, USA; with contacts numbered 0–3 for the right electrode and 4–7 for the left one, 0 and 4 being the most distal) were bilaterally implanted. The x (lateral to midline), y (anterior to the posterior commissure) and z (dorsosventral, below the bicommissural line) coordinates of the electrode tip were 4.04, −13.26 mm and 7.24, −13.26 mm in patient No 1, and 6.10, −0.42, −13.26 mm and 7.24, −0.42, −13.26 mm in patient No 2. During single contact monopolar stimulation at amplitudes above 1 V, patients complained of monocular trembling vision ipsilateral to the active contact at stimulation frequencies below 35 Hz only (table 1). Clinical examination failed to detect any abnormal eye movement or change in pupil size. For chronic stimulation, the voltage was set just below the threshold of the visual effect. At stimulation frequencies above 35 Hz, especially 130 Hz, patients complained of paresthesias mainly located in the face and upper limb contralateral to the stimulation at 0.1–1.0 V. These paresthesias prevented any prolongation of examination or oculomotor recording. At these frequencies, we observed eyelid elevation in the two patients, and diplopia in patient No 2, who agreed to tolerate paresthesias for a few seconds.

PATIENTS AND METHODS

Patients

Patient Nos 1 and 2 were 68 years of age and suffered from advanced PD. Both had benefited from bilateral subthalamic nucleus (STN) stimulation for the past 4 years. Severe levodopa and stimulation unresponsive freezing of gait, associated with frequent falls, had however appeared 1–2 years after STN surgery. The patients therefore underwent implantation of the PPN.

Oculographic recording was performed during monopolar stimulation of the contacts used therapeutically (patient No 1, contacts 0 and 4; patient No 2, contacts 1 and 5). Three frequencies (5, 15 and 25 Hz) were tested, with a stimulation amplitude of 0.5 V above the threshold for perception of oscillopsia. In patient No 1, the amplitude was further increased (up to 3 V) to investigate the voltage dependence of the effect.

Eye movement recording, data acquisition and offline analysis have already been described.4 The sampling frequency was 500 Hz and the spatial resolution was better than 0.05°. During the recording session, patients had to fixate on a central target presented on the screen.

Patient No 1

The eye position data recorded with different electrical parameters are shown in fig 1. The 25 Hz/2.5 V stimulation induced regular ipsilateral 25 Hz eye movement, upward for right-sided stimulation, oblique up and in for left-sided stimulation.
Similarly, the 5 Hz/2 V left-sided stimulation induced oblique in and upward 5 Hz left eye movement. Increased stimulation voltages (to 3 V) induced eye movement of the same frequency, but increased amplitude (0.45° horizontal, 0.6° vertical).

**Patient No 2**

Regular ipsilateral 25 Hz oblique in and upward eye movements were induced by right-sided 25 Hz/1.5 V and left-sided 25 Hz/2.5 V stimulation. The 5 Hz/2.5 V, right-sided stimulation induced a similar eye movement of 5 Hz frequency.

Thus unilateral stimulation of the PPN region induced abnormal movements of the ipsilateral eye, synchronous with stimulation frequency and of voltage dependent amplitude. The direction of the induced eye deviation was either pure elevation or mixed elevation and adduction.

**DISCUSSION**

The aim of this study was to understand the pathophysiology of monocular oscillopsia reported by patients during low frequency stimulation of the PPN. The results clearly demonstrate that this perception is related to mild abnormal eye movements of the ipsilateral eye that are imperceptible to the examiner. These up and in eye movements can be best explained by electrical current spread to the nearby fibres of the oculomotor nerve (third cranial nerve) passing just above and medial to the PPN within and between the red nucleus and the substantia nigra (fig 2).5 6 Specifically, the activated fibres innervate the elevator (superior rectus and/or inferior oblique) and medial rectus muscles. The direction of the eye deviation is likely related to the lateral position of the contacts with respect to the oculomotor nerve, and correlates with the partially known somatotopy of the oculomotor fascicule in the midbrain.7 However, MRI data do not enable precise localisation of the active contact with respect to the oculomotor fibres.

Since eye movement only occurred ipsilateral to the stimulation, an infranuclear origin is very likely. Indeed, fibres to both the ipsilateral and contralateral superior rectus muscles exit from the oculomotor nucleus8 9 and its stimulation would have induced bilateral eye elevation. Furthermore, the oculomotor nucleus is located far more posterior of the electrodes than its fibres. Stimulation of the trochlear nerve is also very unlikely. The trochlear nucleus is located too far posterior of the electrode position and the nerve exits from the dorsal surface of the brainstem to innervate the contralateral superior oblique muscle.

Stimulation spreading to the fibres of the oculomotor nerve and imprecise diplopia has already been reported in patients implanted in the STN, but as an adverse effect caused by misplaced electrodes.10 11 Interestingly, both hyperactivity of the oculomotor nerve and “midbrain tremor” of the contralateral limb related to red nucleus dysfunction were reported.10 This is consistent with the hypothesis that high frequency stimulation has opposite effects (ie, excitation on white (oculomotor nerve) and inhibition on grey (red nucleus) matter).10 12 Therefore, our data are consistent with the idea that some of the oculomotor fibres are excited.

This is further supported by the fact that the eye movements were synchronous with the stimulation frequency. The eyelid elevation observed at higher frequencies likely results from activation of the levator palpebrae muscle, also dependent on the oculomotor nerve, and suggests an evolution from phasic to tonic extraocular muscle contraction as frequency increases. Similarly, the eye deviation and diplopia observed in patient No 2 at 150 Hz are coherent with a tonic activity. This is consistent with the notion that spreading of current to the pyramidal tract in patients with STN stimulation results in synchronous rhythmic myoclonus at low frequency, shifting to tonic motor

### Table 1

Voltage thresholds (V) for perception of oscillopsia at 5 and 25 Hz (pulse width 60 μs) for the four contacts of the two electrodes tested under monopolar cathodal stimulation, –O and 4 being the most distal contacts.

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Electrode</th>
<th>Contact</th>
<th>Threshold (V)</th>
<th>Patient No 1</th>
<th>Patient No 2</th>
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<tr>
<td>25</td>
<td>Right</td>
<td>0</td>
<td>2.0</td>
<td>1 2 3 0 1</td>
<td>2 3</td>
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<td></td>
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<td>1</td>
<td>2.0</td>
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<td>6</td>
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<td>7</td>
<td>0.30</td>
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<tr>
<td></td>
<td>Left</td>
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Characteristics of the monocular eye movements recorded for each tested electrode using a voltage 0.5 V above threshold. –, no eye movement as the initial adverse effect.
contractions at high frequency. Therefore, it is likely that oscillopsia disappears at higher frequencies when the frequency of the movements reaches the flicker fusion threshold.

Because of the functional anatomy of this region, it is not surprising that stimulation induces adverse effects, even if the electrodes are correctly placed in the PPN area. Indeed, the PPN is located in the mesencephalic reticular formation between the fibres of the oculomotor nerve medially, and the medial lemniscus, whose stimulation would induce paresthesias, laterally. The occurrence of oscillopsia under PPN stimulation may limit the use of high voltages or require bipolar stimulation, thus restricting the volume of tissue neuromodulation around the active contacts. Oscillopsia has already been reported during low frequency stimulation of the periaqueductal grey matter for the treatment of pain and was a seriously limiting factor. These results emphasise the difficulty of deep brain stimulation in this mesencephalic region, and the need for designing thinner electrodes with directional electrical fields.

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Competing interests: None.

Ethics approval: The study was approved by the local ethics committee.
REFERENCES