Electroencephalographic responses to intraoperative subthalamic stimulation

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This study reports the effects of intraoperative stimulation of the subthalamic nucleus on brain electrical activity in advanced Parkinson’s patients. To our knowledge, this is the first study about electroencephalographic responses in the very early phase of deep brain stimulation, during the implantation of the electrodes. We found an increase of γ band bilaterally over the sensorimotor cortex in the range 45–55 Hz, which was associated with clinical improvement as assessed by means of muscle rigidity decrease. These results indicate that the electroencephalographic γ responses to deep brain stimulation are present at the very beginning of the treatment process, and may help better understand the short and long-term effects of deep brain stimulation. NeuroReport 17:1465–1468 © 2006 Lippincott Williams & Wilkins.

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Introduction

Deep brain stimulation of the subthalamic nucleus induces motor improvement in patients with advanced Parkinson’s disease [1]. The effects of high-frequency stimulation on electrical cortical activity have been investigated with functional imaging, transcranial magnetic stimulation and the electroencephalogram (EEG), although the details of how high-frequency stimulation works are not yet fully understood.

Positron emission tomography and functional magnetic resonance imaging have shown a decrease of regional cerebral blood flow in the primary motor cortex when patients undergo subthalamic nucleus stimulation [2,3] and transcranial magnetic stimulation studies have shown a change in intracortical inhibition after subthalamic nucleus stimulation [4,5]. A fundamental contribution to the understanding of deep brain stimulation mechanisms comes from EEG recording [6,7]. For example, Silberstein et al. [6] found a reduction of EEG coherence over 10–35 Hz after chronic high frequency subthalamic nucleus stimulation, as well as after a treatment with levodopa, and there is general agreement that subthalamic nucleus stimulation might restore the normal activity of the sensorimotor cortex in Parkinson’s disease [8–12]. Importantly, all these findings derive from studies performed in Parkinson’s disease patients who had undergone electrode implantation weeks, months or years before. By contrast, the present study investigates the brain electrical responses to high frequency subthalamic nucleus stimulation during the surgical implantation of the electrodes, that is, at the very early stage of deep brain stimulation.

Methods

Study participants

Twelve patients (six men, six women; age 60.4 ± 4.7 years) participated in the study after giving written informed consent for surgery, mapping procedures and EEG recording. All the experimental procedures were carried out in accordance with the Declaration of Helsinki and after the approval of the local ethics committee. Clinical evaluation was performed by means of the Unified Parkinson’s Disease Rating Scale (UPDRS) [13] by experienced neurologists. These patients presented a 12 ± 2.4 year history of Parkinson’s disease, and a presurgical UPDRS III total score mean of 50 ± 6.5 after a 12-h dopaminergic treatment-free period. The levodopa equivalent daily dosage was 1160 ± 290.7 mg. Any pharmacological therapy was interrupted the day before surgery.

Localization of subthalamic nucleus

All the patients underwent a brain three-dimensional magnetic resonance imaging scan before surgery. At surgery, after positioning of a Cosman–Roberts–Wells stereotactic frame (CRW Radionics, Burlington, Massachusetts, USA), a stereotactic computed tomography scan was performed. Then, the magnetic resonance imaging and computed tomography slices were fused by the Stereoplan...
system (Radionics) and the anterior and posterior commissural coordinates and the length of the intercommissural line were calculated. The subthalamic nucleus was anatomically localized 2.5 mm posterior and 4 mm inferior with respect to the mid-commissural point and 12 mm from the midline. The electrode track was planned using a 58°–63° anterior–posterior angle and 14°–20° lateral angle. Neurophysiologically identification of the subthalamic nucleus was carried out by microrecording (Microtargeting Electrodes Type BP, FHC, Bowdoinham, Maine, USA). Microelectrode impedances were acquired from 0.5 to 1.5 MΩ and the electrical signals were acquired by means of the Microguide system (Microguide, Alpha Omega, Nazareth, Israel). After microrecording of the subthalamic nucleus electrical activity, the intraoperative microstimulation was performed to assess clinical and side effects before the positioning of the definitive macroelectrode. The intraoperative microstimulation was performed at three rostrocaudal levels inside the recording subthalamic area. The intensity of microstimulation ranged from 1 to 4 V with a width of 60 μs and a frequency of 130 Hz, using a monopolar cathodic stimulation.

Electroencephalogram recording and data analysis
Before the beginning of the operation, eight Ag–AgCl electrodes were applied to the scalp, so that the EEG was recorded from eight scalp loci of the 10–20 International System. The electrodes were positioned on F7, F8, C3, C4, T5, T6, O1 and O2, with a linked common ear reference. The exact positioning of the electrodes was obtained by applying C3 and C4 on the central sulcus, which was identified by means of a sagittal computed tomography scan. Impedance was less than 2 kΩ in each active lead, and each channel was acquired at 256 Hz. A frequency filter cutting the frequencies above 55 Hz and below 6.5 Hz was applied in order to eliminate artifacts due to Parkinsonian tremor (4–6 Hz). A notch filter was also used (50 Hz). No harmonic frequencies due to microstimulation were expressed between 6.5 and 55 Hz. The EEG recordings were performed in the awake patient during the intraoperative microstimulation. Local anesthesia with 2% carbocaine was induced immediately before positioning the stereotactic framing and cutting the skin. Acquired signals were stored on a computer for subsequent analysis (Galileo Mizar NT, EBNeuro, Florence, Italy). Ocular artifacts were discarded by visual inspection when their amplitude was larger than 100 μV. In each patient, EEG epochs of 20 s (10 s before and 10 s after stimulation onset) were selected for the analysis. In order to avoid peristimulus artifacts, however, we discarded 100 ms before and 100 ms after stimulation onset from the analysis (Fig. 1a). Seventy-six epochs (42 on the right and 34 on the left) were analyzed.

Electroencephalogram analysis
Power spectrum analysis was performed by means of the Welch algorithm (Hanning windowing function). The frequency bands were subdivided into δ-2 (6.5–8 Hz), α-1 (8–10 Hz), α-2 (10–12 Hz), β-1 (12–18 Hz), β-2 (18–24 Hz), β-3 (24–32 Hz), γ-1 (32–45 Hz) and γ-2 (45–55 Hz). The δ and θ-1 bands (0–4 and 4–6.5 Hz) were discarded to avoid inclusion of Parkinsonian tremor activity at 4–6 Hz. Although relative powers show lower interindividual variability [14], we also considered absolute powers, as our analysis was basically a within-subjects comparison (prestimulus versus poststimulus onset). The EEG data were normalized by means of the Gasser logarithmic transformation [15]. Two-dimensional statistical maps of frequency distribution for both absolute (b) and relative powers (c). Note the effects of deep brain stimulation of the left and the right subthalamic nucleus (STN) on brain electrical activity. The level of significance, shown on the colour scale bar, ranges from low (P < 0.05) to high (P < 0.01) statistical significance.

Statistical analysis
Analysis of EEG frequency bands was performed by means of two-tailed Student’s t tests for populations of unequal variance (Galileo Statistics Package for EEG data, EBNeuro). Statistical maps were reconstructed comparing prestimulus and poststimulus EEG epochs for both absolute and relative powers. Each map of the present work shows a scale with the different values of P, ranging from low (P < 0.05) to high (P < 0.01) significance.

Results
Six patients showed an exordium of the disease in the left hemisoma and six in the right hemisoma. One patient was
ambidextrous, as measured by the Edinburgh Handedness Inventory. Those EEG segments in which the stimulation reduced muscle rigidity at the wrist by more than 90% on item 22 of the UPDRS III were used for the present analysis.

The effects of high frequency subthalamic nucleus stimulation on brain electrical activity were analyzed in both hemispheres and in each frequency band. Figure 1b shows the significant changes, according to the statistical scale, of the absolute powers after both left and right subthalamic nucleus stimulation. During the stimulation of the left subthalamic nucleus, we found a significant increase of the $\gamma$-2 band in the sensorimotor regions at the level of C3 $[(f(33) = -3.089, P < 0.0041)]$ and C4 $[(f(33) = -2.91, P < 0.0064)]$ as well as in O1 $[(f(33) = -3.0622, P < 0.0044)]$ and T6 $[(f(33) = -2.7133, P < 0.0105)]$. By contrast, when the right subthalamic nucleus was stimulated, no significant change in absolute power was observed. Figure 1c shows the statistical maps for the relative powers, which showed significant changes ranging from low to high. Overall, we found an increase of $\gamma$-1 in C3 $[(f(41) = -2.491, P < 0.018)]$ and C4 $[(f(33) = -2.222, P < 0.033)]$ and $\gamma$-2 in C3 $[(f(33) = -2.358, P < 0.025)]$ and C4 $[(f(33) = -2.246, P < 0.032)]$ when the left subthalamic nucleus was stimulated. The stimulation of the right subthalamic nucleus produced an increase of $\gamma$-1 in C3 $[(f(41) = -2.093, P < 0.043)]$ and in F8 $[(f(41) = -2.219, P < 0.032)]$, a significant increase of $\gamma$-2 in C3 $[(f(41) = -2.990, P < 0.005)]$, and an increase of $\gamma$-2 in C4 $[(f(41) = -2.187, P < 0.035)]$. $\gamma$-2 also increased in other loci during right subthalamic nucleus stimulation, including F8 $[(f(41) = -2.389, P < 0.022)]$, O2 $[(f(41) = -2.587, P < 0.013)]$, T5 $[(f(41) = -2.268, P < 0.029)]$ and T6 $[(f(41) = -2.188, P < 0.034)]$. The stimulation of the right subthalamic nucleus also induced an increase of relative power of $\beta$-2 in F8 $[(f(41) = -2.688, P < 0.011)]$ and of $\beta$-3 in C3 $[(f(41) = -2.369, P < 0.023)]$, T5 $[(f(41) = -2.408, P < 0.021)]$ and F8 $[(f(41) = -2.034, P < 0.049)]$.

**Discussion**

The novel aspect of the present study is that brain electrical activity, as assessed by means of surface EEG, was recorded intraoperatively, when the subthalamic nucleus was stimulated for the first time. This condition gives us the opportunity to describe the stimulation-induced effects on EEG patterns before the possible occurrence of adaptive cortical–subcortical compensatory phenomena related to high frequency subthalamic nucleus stimulation. For example, neuronal plasticity of the direct neostriatal outflow pathway in early Parkinson’s disease has been reported [16], and this might compensate for the degeneration of nigrostriatal dopamine neurons and the maintenance of normal communication between the basal ganglia and the cortex in early Parkinson’s disease.

Stimulation of the subthalamic nucleus is accompanied by an increase in the power of the $\gamma$ frequencies recorded from the sensorimotor cortical areas. These $\gamma$ changes are in agreement with the model first proposed by Brown and Marsden [17]. In particular, this model attributed to the human basal ganglia, with a key function of the subthalamic nucleus, the major role in facilitating the synchronization of cortical activities in the $\gamma$ band (30–50 Hz). The basis of Parkinson’s disease might lie in the absence of the dynamic organization of oscillatory activities into frequency bands between basal ganglia and motor cortex [18]. The increase in power of the $\gamma$ pattern is also in line with Garcia et al. [19], who have recently suggested that high frequency subthalamic nucleus stimulation reduces the pathological 11–30 Hz pattern [20,21] and induces activity in the $\gamma$ range. We did not find a decrease in this $\beta$ pattern, and this might represent a difference between short and long-term effects of high frequency stimulation. Thus, short and long-term stimulation might result in the predominance of one of the suggested possible mechanisms of deep brain stimulation, silencing or restorative effects. Or otherwise, the sensory motor cortex would undergo reorganization by changing activity in response to short and long-term stimulation. Further studies should be designed to answer these questions. Therefore, in line with the hypothesis about deep brain stimulation suggested by Garcia et al. [19], the present study shows that $\gamma$ activation over the sensorimotor regions is already present at the very early stage of deep brain stimulation, that is, when high frequency subthalamic nucleus stimulation is performed for the first time. It should be noted, however, that additional regions showed changes in the $\gamma$ range as well as in the $\beta$ range and this also depended on whether the analysis was performed using absolute or relative power. In this regard, some methodological considerations are in order. In fact, it has long been known that absolute and relative power analysis may produce different outcomes, and this depends on many factors, like the high interindividual variability of the absolute powers. Therefore, as relative powers show lower interindividual variability [14], they should be considered more reliable. Indeed, the effects of the stimulation of the left and right subthalamic nucleus were more consistent when the relative powers were considered, although laterization effects cannot be ruled out [22]. It should also be emphasized that some degree of variability of EEG responses to subthalamic nucleus stimulation could be due to the intraoperative setting, which is somewhat different from deep brain stimulation several weeks after surgery.

If on the one hand the intraoperative setting represents a good opportunity to analyze the effects of acute high frequency subthalamic nucleus stimulation, on the other hand this approach presents some limitations. First, we recorded the surface EEG signals using only eight channels because the patient’s scalp coincided with the operative field. Thus, the spatial resolution of the brain mapping is certainly limited. Second, we analyzed the high-frequency stimulation-induced effects after the stimulation of only one side. The conventional steps of electrode implantation do not allow the study of the EEG during the acute simultaneous stimulation of both subthalamic nuclei. Third, we did not compare acute versus chronic stimulation because the former was performed with microelectrodes while the latter was carried out with macroelectrodes. Fourth, we only monitored clinical improvement related to wrist rigidity, thus limiting the extension of our findings to other symptoms, such as tremor and bradykinesia. We decided to assess rigidity because of its short latency following subthalamic nucleus stimulation [23]. In addition, rigidity does not depend on attention and other cognitive factors, while tremor and bradykinesia are more dependent on cognition-related factors. Lastly, owing to the interruption of the pharmacological therapy the day before surgery, we cannot rule out additional long-lasting pharmacological effects on the EEG.
Conclusion
This study provides the first evidence of γ activation over sensorimotor regions when high frequency subthalamic nucleus stimulation is performed for the first time, and extends previous observations of the long-term effects of deep brain stimulation on EEG.

References