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Theta-phase closed-loop stimulation induces motor paradoxical responses in the rat model of Parkinson disease

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ABSTRACT

Background: High-frequency deep brain stimulation (DBS) has become a widespread therapy used in the treatment of Parkinson's Disease (PD) and other diseases. Although it has proved beneficial, much recent attention has been centered around the potential of new closed-loop DBS implementations.
Objective: Here we present a new closed-loop DBS scheme based on the phase of the theta activity recorded from the motor cortex. By testing the implementation on freely moving 6-OHDA lesioned and control rats, we assessed the behavioral and neurophysiologic effects of this implementation and compared it against the classical high-frequency DBS.
Results: Results show that both stimulation modalities produce significant and opposite changes on the movement and neurophysiological activity. Close-loop stimulation, far from improving the animals' behavior, exert contrary effects to those of high-frequency DBS which reverts the parkinsonian symptoms. Motor improvement during open-loop, high-frequency DBS was accompanied by a reduction in the amount of cortical beta oscillations while akinetic and disturbed behavior during close-loop stimulation coincided with an increase in the amplitude of beta activity.
Conclusion: Cortical-phase-dependent close-loop stimulation of the STN exerts significant behavioral and oscillatory changes in the rat model of PD. Open-loop and close-loop stimulation outcomes differed dramatically, thus suggesting that the scheme of stimulation determines the output of the modulation even if the target structure is maintained. The current framework could be extended in future studies to identify the correct parameters that would provide a suitable control signal to the system. It may well be that with other stimulation parameters, this sort of DBS could be beneficial.

Introduction

Since Benabid reported the first successful case of thalamic stimulation as a chronic treatment of Parkinson's disease (PD) tremor [1], deep brain stimulation (DBS) has become a standard clinical routine to alleviate the motor symptoms of PD [2,3] and dystonia [4,5]. During the last years the use of DBS has been extended to treat other psychiatric and neurologic disorders such as obsessive compulsive disorder [6,7], resistant depression [7,8] or Alzheimer's disease [9]. The DBS therapy consists in the implantation of multi-contact electrodes in subcortical regions that deliver electrical impulses at a constant rate [10,11]. For the treatment of PD the electrodes are typically placed in the subthalamic nucleus (STN) [3,12,13] or internal globus pallidus (GPi) [3,14,15] and the stimulation frequency is set around 130 Hz.

Despite of its efficacy, the high-frequency stimulation (HFS) presents numerous shortcomings. Disruptive effects can go beyond the treatment of the disease symptoms producing cognitive, postural and behavioral side-effects [16–19], effectiveness may be reduced by the evolution of the disease and the battery discharge compels the patient to visit the hospital for adjustment [20].

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To cope with this issues, alternative DBS approaches such as the closed-loop DBS have emerged during the last years [21]. By using a feedback signal, closed-loop stimulation delivers electrical impulses in an adaptive manner considering at every moment the patient's state. Although there are different options for their implementation, in all cases a control signal is required to decide when the electrical impulses should be released. In this context, physiological signals represent a good candidate to serve as feedback signal to control the DBS [22,23] and first experimental works show promising results [24–27]. Here, we introduce and test a new closed-loop approximation. Previous studies carried out by our laboratory have emphasized the importance of the phase of low-frequency oscillations such as delta and theta in the modulation of brain activity [28,29]. The phase/amplitude coupling in physiological [29] and pathological conditions [30] supports the idea of the low frequencies relevance as a coordinator of high frequency activity. In this way, the phase of theta activity has been demonstrated to mediate in cognitive processes and the communication between distant brain structures [31,32]. Following this, we designed an adaptive closed-loop system using a specific phase of the theta cortical activity to control the stimulation. We set out to test the effects of this closed-loop paradigm in a rat model of PD and demonstrate that theta phase-locked DBS has significant neurophysiological and behavioral effects.

Materials and methods

Animals

Two groups of adult male Wistar rats were used (250–300 gr), including 15 hemi-Parkisonian and 18 control rats. In addition group of four control rats (same strain, sex and weight) were used to assess the specificity of the changes induced by close-loop vs. open-loop theta stimulation schemes. Animal care and surgery procedures were approved by the animal ethics committee; Comité de Ética para la Experimentación Animal, Universidad de Navarra, approval CEEA132-12.

Hemi-Parkinsonian rat model

The hemi-Parkinsonian rat model was induced by unilateral injection of 6-hydroxydopamine (6-OHDA) into the left medial forebrain bundle (MFB). The stereotaxic coordinates were calculated using Paxinos atlas [33]: AP: −4.5 mm, L: 1.2 mm and V: −7.9 mm from bregma. Before the surgery, rats were pretreated with pargyline (50 mg/kg, Sigma-Aldrich) to inhibit monoamine oxidase and desipramine (25 mg/kg Sigma-Aldrich) to protect noradrenergic neurons. Surgeries were carried out under inhalatory anaesthesia (oxigen flow 0.7 l/min, 2% isoflurane). Once the animals were anesthesized, an injection of 6-OHDA together with acid ascorbic was performed using a microliter syringe (Hamilton, Switzerland). A total of 6 μl were injected at the speed of 1 μl/min. After the surgery, animals were returned to the animal facilities. Control rats underwent the same surgery but instead of 6-OHDA, saline was injected.

Surgical electrode implantation

Before the electrode implantation surgery hemi-parkisonian rats were left eight weeks of lesion evolution. Oscillatory activity was recorded using a stainless-steel screw placed in the skull (1.6 mm diameter, Plastics One, USA, ref 363). The screw was implanted in the left primary motor cortex (CxM1). Reference and ground screws were placed over the cerebellum. Unilateral electrical stimulation was delivered through a bipolar electrode (SNEx100 Kopf Instruments, California) implanted in the left STN [34,35]. All coordinates were selected according to previous studies [34,36].

Experiment protocol

The experiment started five days after the electrode implantation. First, the threshold for direct motor activation was calculated by following the procedure described in Ref. [34]. Specifically, biphasic square pulse trains (130 Hz, 60μs-width) were delivered and amplitude of train stimuli successively increased from 20 μA in 20 μA steps until observing a motor response from the animals (characterized by a stereotypic rotational response). At this point, the amplitude value determines the motor threshold for DBS stimulation on each animal and defines the amplitude of the DBS stimulation for the forthcoming experiments, that is fixed at 80% of the threshold. Animals showing contralateral muscle contraction elicited by the electrical stimulation (4 control and 2 lesioned) were rejected to discard the possibility of having electrodes placed near or into the internal capsule.

The day after, animals were connected to the recording/stimulation cables and a grid test with no stimulation was carried out. Animals were then moved to a custom-made arena (60 cm × 60 cm) and let free to move for 20 min. After the habituation period, animals were recorded continuously during 15 min; 5 min of pre-stimulation, 5 min under electrical stimulation and 5 min after stimulation (post-stimulation). Animals undertook two different sessions that were delivered separately; one under a classic DBS scheme, and another following the proposed closed-loop implementation. After each session, a grid test under DBS stimulation was performed. Sessions were separated at least 6 h to let animals to recover from the previous session. To avoid any time effects, the order of the sessions was randomized between animals.

Electrophysiological recordings

Brain signals were recorded using a multichannel cable (Ref:363/441/6W/Spring, Plastics One, USA) connecting a headstage (unity gain, Plexon Inc., USA) with a differential amplifier (PBX system, filters:0.3–8000 Hz and gain1000, Plexon Inc., USA). Signals were digitalized at 25000 Hz and stored for offline analysis using a CEDpower1401 A/D together with Spike2 software (CED, UK).

Electrical stimulation

We coined the term *classic* stimulation to the traditional way DBS is performed in PD patients. The stimulation consists on delivering biphasic pulses, 60μs-width, at 130 Hz. These parameters have been widely used by previous studies [34,36,37] and are similar to the ones used for clinical routine [10,30]. In this study, electrical stimulation was delivered using a square pulse S88K stimulator together with two PSIU6 constant current units (GRASS, USA) to achieve the generation of biphasic pulses.

Closed-loop stimulation

Our closed-loop system was designed to stimulate the STN during the peaks of the theta oscillatory activity (4–8 Hz) recorded from the CxM1. To do that, the activity recorded from the CxM1was filtered *online* in the delta/theta band range and depending on the phase of the signal, an activation pulse was sent to the SK88 stimulator that released a short train of three pulses (130 Hz, 60 μs, biphasic). The activation pulse was only sent when two criteria were met: (1) the phase moment of the theta activity was the peak,

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