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Research report

Response inhibition rapidly increases single-neuron responses in the subthalamic nucleus of patients with Parkinson's disease

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ABSTRACT

The subthalamic nucleus (STN) plays a critical role during action inhibition, perhaps by acting like a fast brake on the motor system when inappropriate responses have to be rapidly suppressed. However, the mechanisms involving the STN during motor inhibition are still unclear, particularly because of a relative lack of single-cell responses reported in this structure in humans. In this study, we used extracellular microelectrode recordings during deep brain stimulation surgery in patients with Parkinson's disease (PD) to study STN neurophysiological correlates of inhibitory control during a stop signal task. We found two neuronal subpopulations responding either during motor execution (GO units) or during motor inhibition (STOP units). GO units fired selectively before patients' motor responses whereas STOP units fired selectively when patients successfully withheld their move at a latency preceding the duration of the inhibition process. These results provide electrophysiological evidence for the hypothesized role of the STN in current models of response inhibition.

1. Introduction

Neuroimaging studies have shown that response-stopping processes activate a frontal-subcortical network (Aron, 2006; Chikazoe et al., 2009; Li, Yan, Sinha, & Lee, 2008). The dynamics of this network has been conceptualized in several computational models of response inhibition (Frank, 2006; Ratcliff & Frank, 2012; Wiecki & Frank, 2013) in which rapid

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suppression of a prepared move involves a fast stopping signal neurally implemented via a putative hyperdirect pathway (Monakow, Akert, & Künzle, 1978; Nambu, Takada, Inase, & Tokuno, 1996). This hyperdirect pathway assumes projections of the frontal cortex (pre-SMA, inferior frontal gyrus and anterior cingular cortices) onto the subthalamic nucleus (Haynes & Haber, 2013). This hypothesis is attractive, but it is currently only supported by a few intracerebral electrophysiological recordings in humans-during the stop signal task (SST)-showing that beta (15–35 Hz) oscillations of local field potentials (LFP) increased during stopping in the inferior frontal gyrus (Jha et al., 2015; Swann et al., 2009; Wessel, Conner, Aron, & Tandon, 2013) and in the STN (Benis et al., 2014) at latencies that precede the time needed to cancel movements (stop signal reaction time, SSRT). Indirect evidence also comes from reports that showed that STN lesions cause ballistic and involuntary movement in non-human primates and humans (Crossman, Sambrook, & Jackson, 1984; Nishioka, Taguchi, Nanri, & Ikeda, 2008) as well as inaccurate and premature responding in reaction time tasks performed by rats (Baunez, Nieoullon, & Amalric, 1995; Eagle et al., 2008) and humans (Obeso et al., 2014). Finally, effects of bilateral high frequency stimulation of the STN in patients with Parkinson's disease (PD) remain to be firmly established, as both improvement (Mirabella et al., 2012; Swann et al., 2011; van den Wildenberg et al., 2006) or worsening of inhibitory performance (Obeso, Wilkinson, Rodríguez-Oroz, Obeso, & Jahanshahi, 2013; Ray et al., 2009) have been reported.

The STN is thus modeled as an important region within the response inhibition brain-network, but the functional mechanisms involved at the cellular level during response inhibition remain unclear despite recent advances in monkeys and rats (Isoda & Hikosaka, 2008; Schmidt, Leventhal, Mallet, Chen, & Berke, 2013). Thus, even if a consensus seems to emerge from many models that hypothesize that a neuronal population within the STN should increase its firing rate during successful stopping at a latency that should precede the SSRT (Boucher, Palmeri, Logan, & Schall, 2007; Frank, 2006; Logan & Cowan, 1984; Ratcliff & Frank, 2012; Schall, Stuphorn, & Brown, 2002; Wiecki & Frank, 2013), the electrophysiological evidence supporting this idea remains weak. We recently identified such neurons in the putative associative-limbic area of the STN of patients suffering from obsessive-compulsive disorders (OCD) (Bastin et al., 2014). But whether such cells can be observed in the putative sensorimotor territory of the STN remains unclear. To test this hypothesis, we used STN micro-recordings during deep brain stimulation (DBS) surgery in patients with PD and analyzed single unit responses during a stop signal paradigm. We found that STN neurons responded selectively during successful response inhibition, at latencies that preceded the SSRT.

2. Materials and methods

2.1. Patients

Intraoperative recordings were obtained from 21 PD patients (13 male and 8 female; mean ± SEM age: 58.4 ± 1.5 y.o.; 19 right-handed; no psychiatric comorbidity; additional details in Table 1). They were selected for their ability and readiness of collaborating in a demanding cognitive task while undergoing therapeutic bilateral STN implantation of DBS electrodes (Benabid, Chabardès, Mitrofanis, & Pollak, 2009). They had been suffering from idiopathic PD for 10.6 ± .8 years. They responded well to Levodopa (Unified Parkinson Disease Rating Scale, UPDRS ON Levodopa: 15.9 ± 2.1; OFF Levodopa: 42.17 ± 2.5) and had disabling motor fluctuations and/or Levodopa-induced dyskinesia refractory to the adjustment of anti-parkinsonian medication. They presented no relevant deterioration in overall cognitive evaluation (Table 1, average Mattis Dementia Score was 138.6 ± 1, on a scale from 0 to 144, with higher scores indicating preserved cognition, Mattis, 1976) and only relatively mild dysexecutive syndrome (frontal score: 41.29 ± 1.4, on a scale from 0 to 50, with a higher score indicating preserved executive functions, Pillon, Dubois, Lhermitte, & Agid, 1986). The electrophysiological signals were recorded while patients were in an OFF state since medication was stopped on the night before surgery (12 h preoperatively). All patients gave their written informed consent to participate to this study that was approved by our local ethics committee (Grenoble University Hospital, Comité de Protection des Personnes Sud-Est I, protocol number: 2011-A00083-38).

2.2. Electrode implantation and neuronal recordings

As in routine DBS procedure of Grenoble University Hospital (Benabid et al., 2009; Thobois et al., 2010), electrophysiological signals recorded from five tungsten microelectrodes (2 mm apart, tip diameter <10 μm; impedance of .2–6 MΩ at 1 KHz, FHC microelectrodes, Bowdoinham, USA) were used to optimize STN targeting based on the spiking properties of STN cells. Raw neuronal activity was amplified (×10), band-pass filtered between 300 and 6000 Hz and sampled at 48 kHz. The STN was preoperatively targeted using stereotactic magnetic resonance imaging (MRI). In patients with PD, the following coordinates are used to target the putative sensorimotor STN: 6/12 of the anterior-posterior commissural (AC-PC) length posterior to the AC, 12 mm lateral to the midline, and 3 mm below the AC-PC line. This targeting was further refined by the pattern of electrophysiological activity typically observed in the STN area (Benabid et al., 2009), i.e., the presence of asymmetrical spikes at high frequency with bursting patters and/or proprioceptive responses to passive movements. Importantly, we previously reported task-related electrophysiological modulations from the putative non-motor part of the STN recorded in OCD patients. Note that in patients with OCD, the non-motor part of STN is targeted 2 mm anterior and 1 mm medial to the PD target (Chabardès et al., 2012). When STN cells were detected the behavioral task was proposed to patients. Patients were laying horizontally, their head maintained in the stereotaxic frame. Correct vision of the monitor by the patient was ensured before starting the task.

2.3. Behavioral task

Patients performed 0–4 intra-operative SST sessions of 100–200 trials per STN side, depending on clinical constraints