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The subthalamic nucleus is involved in successful inhibition in the stop-signal task: A local field potential study in Parkinson's disease

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ABSTRACT

Normal actions and behaviors often require inhibition of unwanted and inadequate movements. Motor inhibition has been studied using the stop signal task, in which participants are instructed to respond to a go signal. Sporadically, a stop signal is also delivered after a short interval following the go signal, prompting participants to inhibit their already started response to the go signal. Functional MRI studies using this paradigm have implicated the activation of the subthalamic nucleus in motor inhibition. We directly recorded subthalamic nucleus activity from bilaterally implanted deep brain stimulation electrodes in a group of 10 patients with Parkinson's disease, during performance of the stop signal task. Response inhibition was associated with specific changes in subthalamic activity in three different frequency bands. Response preparation was associated with a decrease in power and cortico-subthalamic coherence in the beta band (12–30 Hz), which was smaller and shorter when the response was successfully inhibited. In the theta band, we observed an increase in frontal cortico-subthalamic coherence related to the presence of the stop signal, which was highest when response inhibition was unsuccessful. Finally, a specific differential pattern of gamma activity was observed in the "on" motor state. Performance of the response was associated with a significant increase in power and cortico-subthalamic coherence, while successful inhibition of the response was associated with a bilateral decrease in subthalamic power and cortico-subthalamic coherence. Importantly, this inhibition-related decrease in gamma activity was absent in the four patients with dopamine-agonist related impulse-control disorders. Our results provide direct support for the involvement of the subthalamic nucleus in response inhibition and suggest that this function may be mediated by a specific reduction in gamma oscillations in the cortico-subthalamic connection.

Introduction

The capacity to inhibit movement, behavior and emotions is a fundamental component of adaptive human behavior. Stopping a decision or an action to which the individual is already committed has important biological significance and may mean the difference between success and failure, or survival and death. Reactive inhibition, that is stopping a prepared or an initiated action when this is indicated by an external signal, appears to rely on the activation of a fast-operating network between the inferior frontal gyrus, pre-supplementary motor area (pre-SMA) and the subthalamic nucleus (STN) (Aron and Poldrack, 2006; Chambers et al., 2009). In such a network, the STN is considered to act as a final relay station for the "last minute" inhibition of an action (Aron and Poldrack, 2006; Eagle et al., 2008; Frank, 2006). This hypothesis was formulated on the basis of evidence from three main sources. First, functional studies with magnetic resonance imaging (fMRI) in healthy participants have demonstrated an increase in the BOLD signal in the subthalamic region during stop signal tasks (Aron and Poldrack, 2006; Li et al., 2008). Second, deep brain stimulation (DBS) of the STN induces abnormal impulsivity in some patients, *i.e.*, poor inhibition in conflict-associated decision processes (Frank et al., 2007; Jahanshahi et al., 2000) or when withholding prepotent movements (Ray et al., 2009).

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DBS may also induce abnormal behaviors such as gambling or hypersexuality, especially following stimulation through contacts located within the ventral STN (Kulisevsky et al., 2002; Mallet et al., 2007; Mandat et al., 2006; Raucher-Chene et al., 2008). Finally, experiments in rodents have demonstrated an increased number of premature responses in reaction time tasks (Baunez et al., 1995) and errors in a modified version of the stop signal task after an excitotoxic subthalamic lesion (Eagle and Baunez, 2010; Eagle et al., 2008). Despite these findings, there is no *direct* evidence for the involvement of the STN in response inhibition in humans.

The implantation of electrodes for DBS in PD patients has allowed the recording of local field potential (LFP) activity in the STN. A well-defined pattern of activity has now been recognized in this structure. Beta band activity predominates in the "off" medication state but is significantly attenuated during the "on" medication state along with the appearance of higher frequencies (gamma activity and 300 Hz activity) (Alonso-Frech et al., 2006; Brown et al., 2001; Foffani et al., 2003; Levy et al., 2002; Priori et al., 2004). Levodopa-induced dyskinesias exhibit a peak of activity around 8 Hz in the dorsal (motor) STN, while those with drug-induced impulsivity show increased activity at a slightly lower frequency (6 Hz) in the ventral STN (Rodriguez-Oroz et al., 2011). Dopaminergic medication also affects cortico-subthalamic coherence similarly, whereby beta coherence predominates in the "off" state and gamma coherence appears in the "on" state (Williams et al., 2002). Thus, recording STN LFPs may provide a clearer picture of the putative role of STN in response inhibition.

We therefore recorded LFPs in the STN and assessed cortico-subthalamic coherence during a stop signal task similar to that used in fMRI studies, and we observed distinct patterns of STN activity associated with successful and unsuccessful response inhibition. Accordingly, we provide here direct evidence of STN involvement in response inhibition in humans.

Methods

Patients

Eleven PD patients in whom electrodes for chronic stimulation had been implanted bilaterally in the STN over the last 3 years were initially included in the study. All patients fulfilled the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (Hughes et al., 1992). One patient was subsequently excluded from the study, as the responses obtained during the recording session were unreliable due to reduced attention, leaving a total of 10 participants for the time–frequency analysis. One further patient was excluded from the event-related coherence analysis due to a poor quality EEG signal. All patients were right-handed according to the Oldfield handedness inventory (Oldfield, 1971). The study conformed to the standards set by the latest revision of the Declaration of Helsinki and was approved by the institutional ethical committee (Comité de ética de investigación clínica de la Universidad de Navarra). All patients provided written informed consent. The neurophysiological recordings from patients 1, 2 and 3 at rest have been included in previous publications (Lopez-Azcarate et al., 2010; Rodriguez-Oroz et al., 2011).

Surgical procedure

An image fusion procedure was used to obtain the stereotactic co-ordinates for surgery. The day before surgery, 1.5-Tesla Magnetic Resonance Imaging (MRI) of the brain was performed on each patient. On the day of surgery, once the CRW frame (Cosman-Robert-Wells, Radionics, Burlington, MA) was positioned under local anesthesia, computerized tomography scans of the brain were obtained and the image data fused with the MRI using BrainLab software. Coordinates for the STN were determined from T2-weighted MRI images in axial planes with the target placed 4 mm below and 12–13 mm lateral to the inter-commissural line, and 3 mm posterior to the mid-intercommissural point. The motor region of the STN was defined intra-operatively by microrecording (200–600 KΩ platinum/iridium FHC microelectrodes [Bowdoinham, ME]) and micro-stimulation. Our group has carried out this procedure routinely for many years (Guridi et al., 2000; Rodriguez-Oroz et al., 2001).

A Medtronic 3389 electrode with 4 active contacts (designated 0, 1, 2 and 3 in the right side and 4, 5, 6 and 7 in the left side from ventral to dorsal, where each contact is 1.5 mm high and placed at 0.5 mm intervals: total length 7.5 mm) was placed at the selected coordinates of the STN, with the ventral-most contact (contact 0 in the right side, contact 4 in the left side) placed in the ventral part of the nucleus. Clinical assessment of the efficacy and adverse effects of DBS was performed intra-operatively before securing the electrode in the chosen position. Subsequently, the electrode was fixed with a burr hole ring and cap, and it was connected to percutaneous connectors with extension wires that exit through a small incision in the skin. Correct placement of the electrodes was confirmed in all subjects by postoperative MRIs. The mean coordinates of the different contacts are shown in Supplementary Table 1.

Recording procedure and data acquisition

Signals were recorded 4–5 days after implantation of the electrodes in the STN and before internalizing the connection cables and the implantable pulse generator. STN field potentials were recorded by connecting the different leads of the wire corresponding to each contact on the electrode to differential amplifiers using a custom-made cable and a sequential bipolar montage, which resulted in a total of three channels per side (0–1, 1–2 and 2–3). The signal was filtered at 0.3–1000 Hz, amplified 50,000 fold and sampled at 2000 Hz. Accordingly, five EEG channels (FC3, C3, Cz, FC4 and C4) were simultaneously recorded with the same filters and sampling frequency, but with a lower amplification (×20,000). EEG and STN signals were stored in a PC using Spike2 software and a CED 1401 plus A/D converter (Cambridge Electronic Design, Cambridge, UK). The stimuli delivered and the resulting responses were recorded through the same converter and software by means of synchronized digital outputs through the parallel port of the computer executing the stimulation program.

All patients were first studied in the "off" motor state after overnight withdrawal of all anti-parkinsonian medication (minimum 12 h). Subsequently, patients received their usual morning dose of L-dopa + dopa decarboxylase inhibitor (150–250/50 mg) and they were again studied after reaching the "on" motor state. The patients were seated in a comfortable chair in an electrically shielded and partially sound isolated room while performing the task.

Stop signal paradigm

The stop signal task (Logan et al., 1984) was used to assess motor inhibition in PD patients. A series of interleaved Go and Stop trials was presented to the patients. On the Go trials, participants were presented with a green arrow that pointed to the left or right, and they were asked to respond as fast as possible using their index and middle fingers of their dominant hand to press the left or right response keys respectively ('F' and 'G' keys on a computer keyboard). On Stop trials (50% of the trials), participants had to avoid responding when a stop signal (red cross) appeared after a variable stop-signal delay (SSD) following the green arrow. We used a 50/50 ratio of Go and Stop trials, to ensure sufficient number of stop trials for capturing changes in power in subthalamic activity associated with successful and unsuccessful inhibition. This ratio of Go/Stop trials also ensured maximal uncertainty across trials. Each participant performed 4 blocks of 98 trials (49 Go and 49 Stop trials per block). The number