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Subthalamic local field potentials after seven-year deep brain stimulation in Parkinson's disease

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ABSTRACT

Studies describing subthalamic (STN) local field potentials (LFPs) recorded during deep brain stimulation (DBS) in patients with Parkinson's disease (PD), within the first month after DBS electrode implant, show that DBS modulates specific STN oscillations: whereas low-frequency (LF) oscillations (2–7 Hz) increase, beta oscillations (8–30 Hz) variably decrease. No data show whether LFPs remain stable for longer than one month after DBS surgery. Having long-term information is essential especially for use as a long-term feedback control signal for adaptive DBS systems. To evaluate how STN activity behaves years after prolonged chronic stimulation in PD we studied STN LFPs at rest without DBS and during ongoing DBS, in 11 parkinsonian patients 7 years (7.54±1.04) after STN electrode implantation for DBS (hyperchronic group) and in 16 patients 3 days after STN electrode implantation (acute group). STN LF and beta-band LFPs recorded at rest at 7 years contained almost the same information as those recorded at 3 days. STN recordings showed similar LFP responses to DBS in the acute and hyperchronic stages: whereas during ongoing DBS the LF power band increased for the whole population, beta activity decreased only in nuclei with significant beta activity at baseline. The LF/beta power ratio in all nuclei changed in both study groups, suggesting that this variable might be an even more informative marker of PD than the single LF and beta bands. Because STN LFP activity patterns and STN LFP responses to DBS stay almost unchanged for years after DBS electrode implantation they should provide a consistent feedback control signal for adaptive DBS.

Introduction

In patients with Parkinson's disease (PD) undergoing deep brain stimulation (DBS), neural activity recorded from large neuronal ensembles (local field potentials, LFPs) through DBS electrodes, provides valuable neurophysiological information. In PD patients LFPs can be recorded from the first choice target for DBS, the subthalamic nucleus (STN) (Benabid et al., 2009; Yu and Neimat, 2008). Pathological LFP rhythms recorded from the STN in parkinsonian patients oscillate in the low-frequency (LF) band (2–7 Hz) (Foffani et al., 2006; Giannicola et al., in press), beta band (8–30 Hz) (Kuhn et al., 2004, 2008; Zaidel et al., 2009), gamma band (60–90 Hz) (Brown and Williams, 2005) and high-frequency band (>200 Hz) (Foffani and Priori, 2006; Foffani et al., 2003; Ozkurt et al., 2011). Studies describing STN LFPs recorded during DBS, within the first month after DBS electrode implantation, show that DBS modulates specific STN oscillations; whereas LF oscillations increase (Giannicola et al., in press; Rossi et al., 2008), beta oscillations variably decrease (Eusebio et al., 2010; Giannicola et al., in press; Rosa et al., 2011). Because these DBS signal changes correlate with patients' clinical improvement (Foffani et al., 2006; Giannicola et al., 2010; Kuhn et al., 2008) intensive research now focuses on how to adapt STN DBS online to the patient's clinical state through LFP signal feedback (Burgess et al., 2010; Chang et al., 2008; Limousin and Martinez-Torres, 2008; Marceglia et al., 2007; Rosin et al., 2011; Schwalb and Hamani, 2008). An important need for developing closed-loop adaptive DBS is to ensure that these changes persist over time after DBS electrode implantation.

An earlier study from our laboratory described DBS-induced changes in STN LFPs recorded one month after DBS surgery in

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patients with PD (Rosa et al., 2011). Comparing STN LFPs recorded in PD patients immediately after and 30 days after DBS surgery we found that weeks after DBS electrode implant STN LFPs remain stable. In a subgroup of patients LFP beta activity recorded during DBS decreased immediately after and 30 days after DBS surgery. No studies have yet shown how STN LFPs behave years after DBS surgery and chronic stimulation. Knowing more about DBS signal changes over time could be useful in developing a feedback control signal to improve overall DBS system performance.

In this study, seeking previously unavailable information to show how STN activity behaves, years after prolonged chronic stimulation for PD, we recorded STN LFPs at baseline without DBS and during ongoing DBS in two groups of patients: in one group 3 days after STN electrodes were implanted for DBS (acute group, 16 patients) and in the other group at subcutaneous pulse generator replacement (hyperchronic group, 11 patients) after chronic DBS for 7 years (7.54 ± 1.04). As independent variables, we studied the STN LFP LF and beta bands before and during DBS at the two time-points. Because both rhythms play key roles in the PD, we also studied their interaction by analyzing the LF/beta power ratio.

Methods

Patients

We studied 16 patients (10 men) with idiopathic PD treated with DBS who underwent surgery for DBS electrode implantation (acute group) and 11 patients (6 men) who underwent surgery to replace the subcutaneous pulse generator about four days after the battery had run out (hyperchronic group). All patients were studied after their informed consent and local institutional review board approval (LIMPE, 2003). Of 16 patients belonging to the acute group 12 patients are those whose data reported in Giannicola et al. (in press). The study conformed with the Declaration of Helsinki. All patients were bilaterally implanted with DBS macroelectrodes (model 3389 Medtronic, Minneapolis, MN, USA) in the STN. DBS surgery and pulse generator replacement surgery took place at the Functional Neurosurgery Unit of the IRCCS Istituto Galeazzi of Milan, Italy and at the Neurosurgery Unit at the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. Patients' details are reported in Tables 1 and 2.

Surgical procedures

All patients underwent DBS surgery as described elsewhere (Marceglia et al., 2010). Surgery needed to change the pulse generator, because the battery had run out, entailed removing the pulse generator from the subcutaneus pocket, extracting the extension connector pins from the pulse generator sockets, reinserting the pins into the new pulse generator sockets, and inserting the new pulse generator into the subcutaneous pocket.

Before the pins were reinserted into the sockets and the new pulse generator was placed in the subcutaneus pocket, the pins for the implanted electrodes were accessible for STN LFP recordings. The implanted 3389 Medtronic electrode had four cylindrical contacts (diameter 1.27 mm, length 1.5 mm, placed 2 mm apart center-to-center) denominated 0–1–2–3 for the left and 4–5–6–7 for the right side beginning from the more caudal contact. Surgery for generator exchange was done under local anesthesia and LFPs were recorded in awake patients. All patients were studied at least 8 h after withdrawal from antiparkinsonian medication (off levodopa).

Table 1
Patients' clinical details — acute group.

Patient	Age (years)	Gender	Stimulated and recording side	Voltage (V)	Impedance recording contact (kΩ)
1	70	M	Left	4.0	3.3
2	51	M	Left	3.0	2.7
3	70	F	Right	4.0	2.7
4	60	F	Right	3.5	2.9
5	48	F	Right	3.5	11.0
6	61	F	Right	3.0	10.0
7	48	M	Right	3.0	10.0
8	63	F	Left	2.5	11.0
9	62	M	Left	3.2	3.2
10	67	M	Right	5.0	5.0
11	64	M	Right	3.5	5.0
12	44	M	Right	3.5	3.5
13	52	M	Left	4.0	4.0
14	54	M	Right	3.5	3.5
15	78	F	Left	3.0	3.0
16	62	M	Left	3.5	3.5

Experimental protocol and local field potential recordings

For patients belonging to the acute group, each experimental session lasted about 1 h, and patients sat comfortably in an armchair whereas for patients belonging to the hyperchronic group, each session lasted approximately 30 min and sessions took place in the operating room. Experimental sessions for the hyperchronic group took place four days after DBS was off because the battery had run out. The clinical off condition was evaluated by the same neurologist before each recording session. Clinical improvement during DBS was evaluated during each recording session.

Electrical impedance was evaluated in electrode contact pair used for recordings. LFPs were recorded at rest (baseline, 3 min) and after DBS was turned ON (DBS on, 3 min). Monopolar STN-DBS was delivered at 130 Hz and a pulse width of 60 μs through the electrode contact positioned in the optimal functional target, contact 1, and differential LFP recordings were acquired between contacts 0 and 2 in the stimulated side for the acute group (Giannicola et al., in press). DBS was delivered through the electrode contacts used for chronic stimulation and patients received DBS at the settings (frequency, pulse width and voltage) used during chronic stimulation. Differential LFP signals were acquired between contacts free for recordings in the hyperchronic group (Table 2).

Macroelectrode impedance was evaluated with an impedance meter at 30 Hz (Model EZM 4, Grass, USA). LFPs were recorded through the FilterDBS device for artifact-free LFP recordings during ongoing DBS (Rossi et al., 2007). Two standard electrodes (RedDot, 3M, USA) were used, one placed on the left was used as the recording reference and the other on the right supraclavicular area was used as the stimulation reference. For electrical stimulation we used a constant voltage stimulator (Dual Screen, Medtronic, Minneapolis, USA). The recorded signals were amplified (50,000×) and filtered (0.5–45 Hz) through the FilterDBS, then digitized through a USB-6251 multifunctional device with 8 inputs (National Instruments Corporation, Austin, TX, USA) at 500 sample/s and 16 bit resolution with 10 V range.

Data analysis

Spectral analysis was run off-line with Matlab software (version 7.10, The MathWorks, Natick, MA, USA). Signals were preliminarily band-passed (2–45 Hz) with a finite impulse response (FIR) filter and resampled at 125 Hz. Signals containing noise, throughout the recording, were discarded after visual inspection. The oscillatory activity recorded from the STN was quantified in the frequency domain by analyzing power spectral density (PSD) for the recorded LFPs using a non-parametric approach based on the discrete Fourier transform (DFT). Spectra were calculated using Welch's averaged, modified periodogram (Welch, 1967). To test whether DBS influenced LFP activity we considered 60 s long signal segments in the two states