European Journal of Neuroscience, Vol. 24, pp. 3213–3222, 2006 doi:10.1111/j.1460-9568.2006.05208.x

Gender-related differences in the human subthalamic area: a local field potential study

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Keywords: basal ganglia, electrophysiology, gender, pathophysiology, Parkinson's disease

Abstract

The objective of this study was to investigate the possible existence of gender-related neurophysiological differences in the oscillatory activity of the human subthalamic area. To this end, we recorded local field potentials (LFPs) after neurosurgical procedures for deep brain stimulation (DBS) in 24 patients (12 males and 12 females) with Parkinson's disease. LFP recordings at rest before levodopa medication (19 nuclei from 11 female patients and 16 nuclei from ten male patients) showed significantly higher power in the alpha/low-beta band (8–12 Hz, $P < 0.01$; 13–20 Hz, $P = 0.03$) in females than in males. After levodopa medication (ten nuclei from six female patients and 11 nuclei from seven male patients), the power in the high-gamma band (60–90 Hz) and of the 300 Hz rhythm was significantly higher in females than in males (high-gamma, $P = 0.007$; 300 Hz, $P = 0.002$). These findings show that functional gender-related differences in the central nervous system involve the human subthalamic area (STN) and its response to levodopa in Parkinson's disease. Gender-related neurophysiological differences may be important for understanding gender-specific features of neurodegenerative disorders and should be considered when interpreting LFP data from the human basal ganglia.

Introduction

Despite the common assumption that the effect of gender on brain function is negligible, there is evidence that research into gender influences could help in understanding brain function and disorders (Cahill, 2006). Yet, besides differing in size and weight (Khosla & Lowe, 1968; Miller & Corsellis, 1977; Lindboe, 2003), the human brain substantially differs between males and females (Federman, 2006). Neuroanatomical, electrophysiological and neuroendocrinological data clearly suggest the existence of sexual dismorphisms. How these differences originate, what they imply and the neurobiological and neurophysiological mechanisms through which they arise remain debatable (Cahill, 2006; Federman, 2006).

The electrical activity of the human central nervous system differs between males and females (Allison *et al*., 1983; Shearer *et al*., 1984; Erwin *et al*., 1991). Quantitative EEG studies in healthy subjects show that women have greater EEG power than men especially in the beta band (13–30 Hz) (Wada *et al*., 1994; Brenner *et al*., 1995; Briere *et al*., 2003; Nikulin & Brismar, 2006).

Among gender-related differences in the human brain are those related to sex hormones. Sex hormones shape the human brain inducing morphological, neurochemical and functional differences (Segovia *et al*., 1999; Federman, 2006). Gonadal hormones were also suggested to have a protective effect against neurodegeneration, determining gender-related differences in the risk factors, progression and recovery of several neurological and neuropsychiatric disorders (Dluzen, 1996, 2000; Dluzen & McDermott, 2000b, 2000a; Shulman, 2002; Dluzen & Horstink, 2003; Sawada & Shimohama, 2003; Craig *et al*., 2004; Czlonkowska *et al*., 2005).

Deep brain stimulation (DBS) is an established therapy for advanced Parkinson's disease (Bergman *et al*., 1990; Benazzouz *et al*., 1993; Limousin *et al*., 1998; Moro *et al*., 1999). DBS also offers a unique opportunity to record the electrical activity from the human basal ganglia. Compound neuronal activity recordings (local field potentials, LFPs) disclosed multiple rhythms operating in the subthalamo-pallidal loop, specifically modulated by drugs and behavioural cues (Brown *et al*., 2001; Cassidy *et al*., 2002; Levy *et al*., 2002; Brown, 2003; Foffani *et al*., 2003; Silberstein *et al*., 2003; Williams *et al*., 2003; Foffani *et al*., 2004; Kuhn *et al*., 2004; Priori *et al*., 2004; Brown & Williams, 2005; Doyle *et al*., 2005; Foffani *et al*., 2005a, b, c; Williams *et al*., 2005; Fogelson *et al*., 2006; Marceglia *et al*., 2006).

Despite the foregoing gender-related brain differences and the known gender-related phenomenological differences in Parkinson's disease (Hertrich & Ackermann, 1995; Lyons *et al*., 1998; Carey *et al*., 2002; Hariz *et al*., 2003; Homann *et al*., 2003; Martinelli *et al*., 2003; Zappia *et al*., 2005), no studies have yet assessed whether the electrical activity recorded from the basal ganglia differs in males and females.

In this study we sought possible gender-related differences in the LFP activity recorded after surgery from the human subthalamic (STN) area in Parkinson's disease.

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Received 13 July 2006, revised 14 September 2006, accepted 2 October 2006

Materials and methods

Patients

Twenty-four patients (12 females, 12 males) with Parkinson's disease were studied after their informed consent and local ethical committee approval (according to Helsinki declaration). Clinical and anamnestic data are detailed in Table 1. All the women included in this study, except one, were in physiological menopause.

All patients were bilaterally implanted in the STN with macroelectrodes for DBS (model 3389 Medtronic, Minneapolis, USA). Long-acting dopamine agonists were withdrawn approximately 72 h before DBS, whereas levodopa was withdrawn approximately 24 h before surgery. The STN was targeted by direct visualization through a CT-MRI fusion-based technique before surgery, as detailed elsewhere (Egidi *et al*., 2002; Rampini *et al*., 2003). The site of electrode implantation was then adjusted during surgery with recordings from the explorative microelectrodes (Priori *et al*., 2003), and by clinically assessing changes induced by stimulation through probe microelectrodes and through the implanted macroelectrodes. The intraoperative neurophysiological procedures also allowed us to estimate the length of the STN on the optimal track. Postoperative imaging CT scans were fused with preoperative T_2-weighted MRI to assess the final position of the DBS electrode and to verify the consistent placement of contact 1 within the STN (Fig. 1).

LFP recordings and analysis

LFPs were recorded from the implanted electrodes two or three days after surgery, before the subcutaneous high-frequency stimulator was

TABLE 1. Details of patients analysed (12 males, 12 females)

Patient	Gender	Age (years)	Recorded side	Recording condition	L-Dopa equivalent dose before surgery (mg)	Dopamine agonist equivalent dose before surgery (mg)*	NMDA antagonist dose before surgery (mg)	Other neuroactive medications
CO	F	54	DX	Off, on	1500	4	0	Antipsychotic, hypnotic/sedative
BE	F	69	DX	Off, on	1377	3	0	Antidepressant
			SX	Off, on				
PA	F	59	DX	Off, on	1400	0	200	None
			SX	Off, on				
SO**	F	39	SX	Off, on	800	3	0	None
TO	F	70	DX	Off, on	1200	1.8	200	Antidepressant, hypnotic/sedative
			SX	Off, on				
FI	F	55	DX	On	1250	3	0	None
			SX	On				
DG	F	64	DX	Off	1995	0	0	None
			SX	Off				
CE	F	55	DX	Off	1040	2	0	Hypnotic/sedative
			SX	Off				
NI	F	59	DX	Off	1671	2.34	0	COMT inhibitor
			SX	Off				
MA	F	61	DX	Off	925	3	100	None
			SX	Off				
VA	F	70	DX	Off	1010	3	200	COMT inhibitor
			SX	Off				
GI	F	53	DX	Off	900	0	0	
MA	M	59	DX	Off, on	1800	3	0	
			SX	Off, on				
CR	M	48	DX	Off, on	1140	2.4	0	
			SX	On				
CM	M	44	SX	Off, on	1500	0	150	None
ZE	M	56	SX	Off, on	2800	14	300	Antipsychotic, hypnotic/sedative
LG	M	66	DX	Off	975	0.36	200	None
			SX	Off				
DL	M	52	DX	Off	2400	0	0	None
			SX	Off				
DM	M	38	DX	Off	3230	5.6	0	None
			SX	Off				
PU	M	67	DX	Off	825	2.4	200	Hypnotic/sedative
			SX	Off				
MT	M	63	DX	Off	1260	1.56	200	None
			SX	Off				
PZ	M	67	SX	Off, on	1000	3.12	200	None
PI	M	63	DX	On	1292	0	0	COMT inhibitor
			SX	On				
CN	M	66	DX	On	900	0.7	0	None
			SX	On				

The neurophysiological results obtained in the patient in physiological menopause (**) were similar to the rest of the female population (< 1.8 SD) and were therefore not excluded from the study. Dopamine agonist equivalent doses (*) are given referred to pergolide with the following equivalences: 1 mg pergolide = 1.4 mg cabergoline = 1.5 mg pramipexole = 10 mg bromocriptine = 5 mg ropinirole, as reported in (Baas & Schueler, 2001; O'Suilleabhain & Dewey, 2002). NMDA antagonist therapy is the amentadine dose (expressed in mg/day). The levodopa equivalent dose was calculated with the conversion factor of 80 mg of immediate-release levodopa equal 100 mg of controlled-release levodopa.

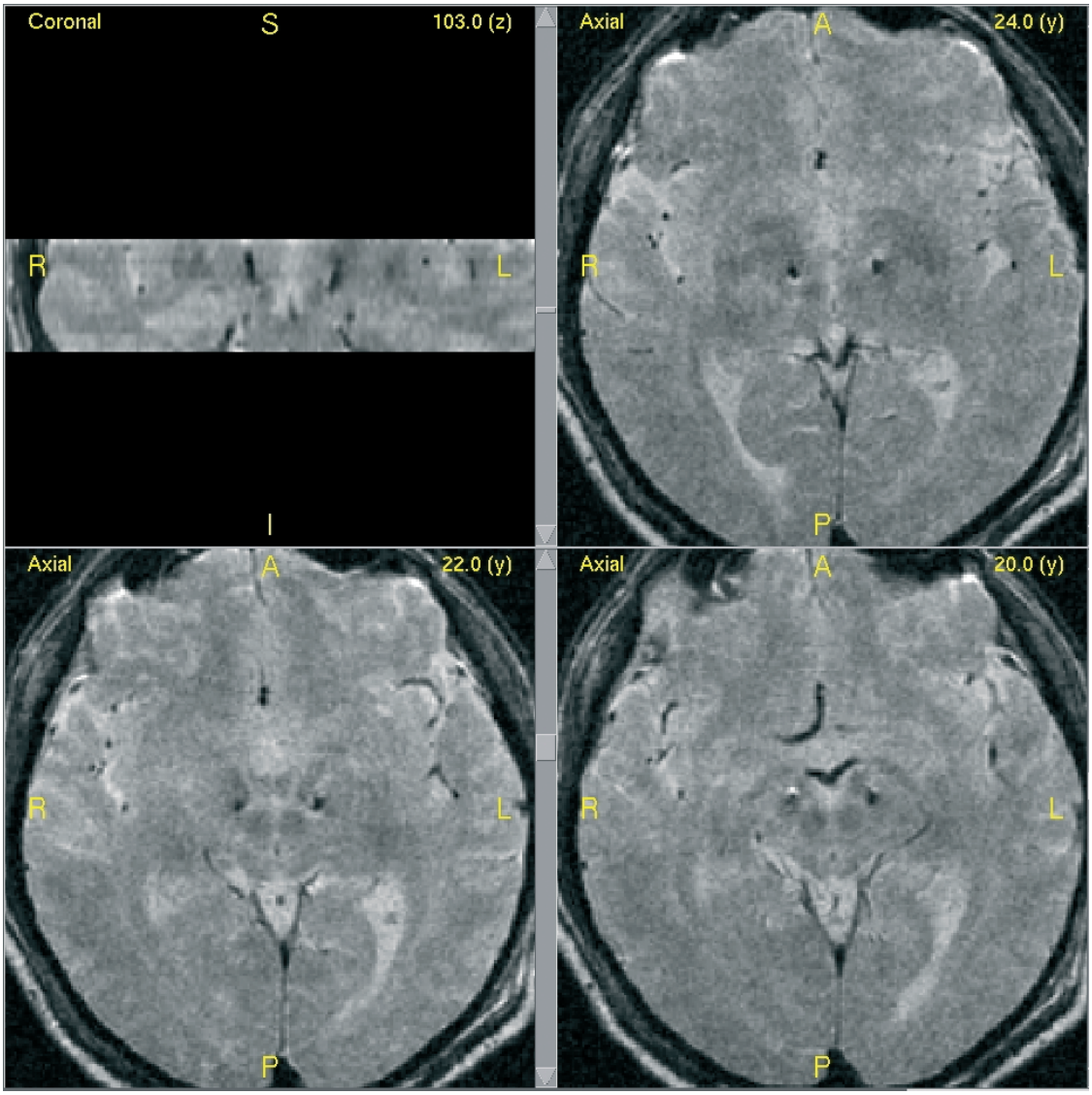

FIG. 1. The subthalamic DBS electrode location. Postoperative imaging showing electrode location in one representative male patient. CT postoperative scans were fused with preoperative T_2 weighted MRI scans. (Top) Coronal section (left panel) and axial section 24 mm (right panel); (bottom) axial sections ($y = 22$ mm, left panel; $y = 20$ mm, right panel). Note that the electrode locations correspond to the STN area. Images were obtained by the software 'Radionics, image fusion 2.11'.

connected, while macroelectrodes were still externalized and accessible. The 3389 Medtronic electrode has four cylindrical contacts (1.27 mm in diameter, 1.5 mm in length, spaced 2 mm centre to centre) denominated 0–1−2–3, beginning from the more caudal electrode. According to intraoperative and postoperative tests, contact 1 was consistent with placement within the STN. The recording procedure has been reported in detail elsewhere (Foffani *et al*., 2003). In brief, LFPs were recorded at rest (60–80 s), 12 h after withdrawal of levodopa treatment both before (off medication, 35 nuclei recorded, 16 nuclei from ten male patients and 19 nuclei from 11 female patients, see Table 1) and after (on medication, 21 nuclei recorded, 11 nuclei from seven male patients and ten nuclei from six female patients, see Table 1) patients received dopaminergic medication (50–200 mg of oral fast-acting levodopa – Madopar Dispersibile – Roche, Monza, MI, Italy). Individual levodopa doses given during the experiment were adapted to the habitual dose of fast-acting levodopa preparation patients were taking before surgery, to ensure full clinical efficacy. On medication, recordings were obtained after an experienced neurologist had scored changes in the patient's clinical conditions, at least 30 min after medication. LFPs were bipolarly captured from the 3389 electrode using the central closely spaced pair of contacts (contacts 1–2). Signals were preamplified, filtered (band pass 2–1000 Hz) and differentially amplified (100 000×) with an analogical amplifier (Signal Conditioner Cambridge 1902, Cambridge Electronic Design, Cambridge, England). In order to remove line noise (50 Hz) a notch filter was activated. The output signal was digitized (Cambridge Micro 1401, Cambridge Electronic Design, Cambridge, England), with a sampling rate of 2500 Hz and 12 bit quantization with 5 V range. All further analysis was conducted off-line with the Matlab software (version 6.5, The Mathworks, Natik, MA, USA). LFPs were normalized by subtracting the mean and dividing the result by the standard deviation of the 600–1000 Hz band-pass filtered signals. This procedure ensures matching background noise in all recordings, thus reducing signal variability (Foffani *et al*., 2003; Priori *et al*., 2004).

STN oscillations at rest were quantified by standard LFP power spectral analysis. Spectra were calculated using Welch's averaged, modified periodogram method; signals were divided into segments of 2048 samples, with no overlap; in each segment, the mean was subtracted; each segment was windowed by a Hanning window; the squared magnitude of the discrete Fourier transform of each segment was calculated; and the squared magnitudes of each segment were averaged, to obtain the estimated power spectral density (PSD). The resolution of the calculated spectrum was 1.22 Hz. From the estimated PSD we evaluated several variables to compare data from males and females. In particular, in accordance with the literature (Brown, 2003; Foffani *et al*., 2003; Priori *et al*., 2004; Foffani *et al*., 2006; Marceglia *et al*., 2006), we considered the frequency bands that are known to characterize the STN oscillatory pattern, i.e. the low frequencies (2 − 7 Hz), the alpha (8 − 12 Hz), the low-beta (13 − 20 Hz), the high-beta (20 − 35 Hz), the high-gamma (60 − 90 Hz) and the 300 Hz (260 − 340 Hz) frequency bands. The spectral power of each band was calculated on all individual nuclei, in patients off and on medication, as follows:

$$P_{(f1-f2)} = \frac{1}{f_2 - f_1} \int_{f_1}^{f_2} \mathrm{PSD}(f)\mathrm{d}f \qquad (1)$$

where f_1 and f_2 represent the boundary frequencies of the considered band ($f_1 - f_2$), $P_{(f1-f2)}$ is the spectral power in the band ($f_1 - f_2$) and PSD(f) is the PSD at the frequency f.

Statistical analysis

Clinical and anamnestic data were compared between males and females through the Wilcoxon signed-rank test (NCSS Software, Number Cruncher Statistical Systems, Kayseville-Utah, USA, $P < 0.05$). As the nuclei contributing to the analyses performed before and after levodopa were not the same, clinical and anamnestic data were separately analysed for the patients actually studied in each condition (patients recorded before levodopa – ten males, 11 females; patients recorded after levodopa – seven males, six females). To detect possible differences in the electrode location, two-tailed *t*-tests (NCSS Software, Number Cruncher Statistical Systems, Kayseville-Utah, USA, $P < 0.05$) were used to compare STN length and stereotactic coordinates (anterior posterior; lateral; vertical and ring; slide) between males and females. Data were separately considered for the nuclei actually analysed in each pharmacological condition (nuclei recorded before levodopa – 16 males, 19 females; nuclei recorded after levodopa – 11 males, ten females).

Significant gender-related differences in LFP recordings were tested with a three-way analysis of variance, considering nuclei as individual samples (ANOVA, NCSS Software, Number Cruncher Statistical Systems, Kayseville-Utah, USA). The first main factor was the gender (male and female; independent measures); the second was the dopaminergic condition (off and on medication; independent measures); and the third was the frequency band (low-frequencies, alpha, low-beta, high-beta, high-gamma, 300 Hz; repeated measures). Tukey–Kramer *posthoc* test was used to identify significant gender-related dopamine-dependent differences, estimating the error variance for independent measures in individual bands ($P < 0.05$). Logarithmic transformation was applied to reduce the variability between samples. Normal distribution of data was verified through the Kolomogorov–Smirnov normality test with a 5% decision level.

We also performed four control analyses (linear regression, NCSS Software, Number Cruncher Statistical Systems, Kayseville-Utah, USA) to exclude possible effects of the levodopa dose given chronically before surgery, of the disease duration, of the disease severity before surgery, and of the dopamine receptor agonists therapy before surgery on the electrophysiological differences. First, we calculated the linear correlation between power in the bands that showed significant gender-related differences before levodopa medication and the levodopa dose before surgery, in males, in females, and across all subjects. Second, we calculated the linear correlation between spectral power in the bands analysed and the years of disease before surgery, in males, in females, and across all subjects. Third, we calculated the linear correlation between power in the bands that showed significant gender-related differences before levodopa medication and the UPDRS III score off medication before surgery, in males, in females, and across all subjects and between power in the bands that showed significant gender-related differences after levodopa medication and the UPDRS III score on medication before surgery, in males, in females, and across all subjects. Fourth, we tested whether treatments with dopamine receptor agonists were related to the expression of LFP activities of various frequencies. To this end, we calculated the linear correlation between power in the bands of interest (both before and after levodopa administration) and the dopamine agonist equivalent dose before surgery across all subjects. For these analyses, in patients recorded bilaterally, power values were averaged between the left and the right STN.

Results

We compared clinical and anamnestic data between males and females, separately considering the patients recorded in the off and in the on condition. Results are detailed in Table 2. Males and females, recorded both in the off and in the on condition, were matched for age, years of levodopa therapy before surgery, levodopa equivalent therapy before surgery, dopamine-agonist equivalent therapy before surgery, NMDA antagonist therapy before surgery, motor scores assessed with the UPDRS III before surgery (off medication, for patients recorded in 'off' and on medication for patients recorded in 'on'), and complication scores (UPDRS IV) before surgery. We only found a significant difference in the years of disease history in the group of patients recorded off medication.

We also compared DBS target stereotactic coordinates and estimated STN length between males and females, separately considering the nuclei recorded in the off and in the on condition. Results are detailed in Table 3. We found no significant differences.

In LFP recordings obtained at rest after the final electrode was implanted for DBS, when patients were off medication the power spectra for both groups contained activity in four main frequency bands (Fig. 2A): very-low frequencies (2–7 Hz), alpha band (8–12 Hz), low-beta band (13–20 Hz) and high-beta band (20–35 Hz). After patients received dopaminergic therapy, spectral power for males and females showed the expected rhythm-specific changes (Brown, 2003; Foffani *et al*., 2003; Priori *et al*., 2004). Whereas low-frequency (2–7 Hz) and 300 Hz (260–340 Hz) power increased, the low-beta rhythm (13–20 Hz) decreased (Fig. 2B). The effects of levodopa administration on LFP rhythms in a subset of patients that were recorded both in off and in on levodopa condition (eight nuclei from five female patients and six nuclei from five male patients) (see Table 4). Figure 3 shows power spectra in the off and in the on pharmacological condition in two representative cases (one female and one male).

TABLE 2. Average clinical details of the patients considered in the study

	Off levodopa			On levodopa		
	Males ($n = 10$)	Females ($n = 11$)	P-value	Males ($n = 7$)	Females ($n = 6$)	P-value
Age (years)	55 ± 9.6	59.1 ± 9.3	0.323	57.5 ± 8.8	57.1 ± 11.4	0.942
Years of disease (years)	9.4 ± 2.9	13.1 ± 3.1	0.013	12.1 ± 2.6	13.6 ± 3.4	0.429
Years of therapy (years)	7.9 ± 2.6	9 ± 3.8	0.271	9.7 ± 3.5	8.1 ± 3.7	0.715
L-Dopa equivalent dose before surgery (mg/day)	1693.0 ± 841.9	1256.2 ± 369.8	0.307	1490.3 ± 653.5	1254.5 ± 247.4	0.721
Dopamine agonist equivalent dose before surgery (mg/day)	3.2 ± 4.1	2.0 ± 1.4	0.668	3.3 ± 4.9	2.5 ± 1.4	0.715
NMDA antagonist dose before surgery (mg/day)	125.0 ± 146.5	63.6 ± 103.0	0.213	92.8 ± 123.9	66.6 ± 103.3	0.742
UPDRS III before surgery	44.9 ± 14.6	45.3 ± 16.6	0.971	5.8 ± 4.4	4.9 ± 7.0	0.383
UPRDS IV before surgery	9.5 ± 2.6	11.2 ± 3.0	0.203	9.9 ± 3.5	12 ± 2.7	0.312

Data are presented as means ± SD. Values reported in the off levodopa column are the averaged values on the patients considered for the analysis in without dopaminergic stimulation (males ten patients; females 11 patients); Values reported in the on levodopa column are the averaged values on the patients considered for the analysis in with dopaminergic stimulation (males seven patients; females six patients).

TABLE 3. Details of actual stereotactic coordinates and STN estimated length

	Off levodopa			On levodopa		
	Males ($n = 16$)	Females ($n = 19$)	P-value	Males ($n = 11$)	Females ($n = 10$)	P-value
Stereotactic coordinates						
AP (mm)	7.06 ± 7	6.05 ± 3.9	0.910	10.7 ± 7.7	8.8 ± 4.6	0.775
LAT (mm)	12.1 ± 2.9	12.5 ± 3.1	0.748	11.6 ± 2.7	12.5 ± 1.9	0.528
VERT (mm)	−17.7 ± 5.3	−21.5 ± 6.2	0.235	−19.3 ± 4.7	−20.5 ± 4.9	0.863
RING (degree)	51.9 ± 4.2	55.5 ± 3.8	0.057	52.2 ± 3.4	57.2 ± 5	0.059
SLIDE (degree)	14.5 ± 1.7	13.6 ± 2.4	0.374	13.8 ± 1.3	12.2 ± 2.1	0.345
STN estimated length (mm)	5.2 ± 1.1	4.3 ± 1.4	0.058	4.2 ± 0.8	3.7 ± 1.2	0.350

Data are presented as means ± SD. Values reported in the off levodopa column are the averaged values on the nuclei considered for the analysis in without dopaminergic stimulation (males ten patients; females, 11 patients); Values reported in the on levodopa column are the averaged values on the nuclei considered for the analysis in with dopaminergic stimulation (males seven patients; females six patients).

The three-way ANOVA on the spectral power in the bands of interest [low frequencies (2–7 Hz), alpha (8–12 Hz), low-beta (13–20 Hz), high-beta (20–35 Hz), high-gamma (60–90 Hz) and 300 Hz (260–340 Hz)] disclosed an overall significant difference between males and females (main factor GENDER $P = 0.002$) and the expected difference between LFP rhythms (main factor BAND $P < 0.000\,001$). Also as expected, the various LFP rhythms were differently affected by levodopa (interaction factor BAND × L-DOPA $P < 0.000\,001$). More important, the differences between males and females in the various LFP rhythms significantly depended on the patients' dopaminergic condition (interaction factor GENDER × BAND × L-DOPA $P = 0.03$ Fig. 2C and D). In particular, *posthoc* analysis disclosed that before levodopa medication the power in the alpha and low-beta bands was significantly higher in females than in males (alpha −1.11 ± 0.36 log AU vs. −1.54 ± 0.29 log AU, $P = 0.0026$; −1.12 ± 0.58 log AU vs. −1.55 ± 0.29 log AU, $P = 0.03$, Fig. 2C). Interestingly, the low-beta and the alpha band were strongly correlated ($R^2 = 0.37$; $P = 0.0001$). After levodopa medication the power in the high-gamma band and in the 300 Hz rhythm was significantly higher in females than in males (high-gamma −2.73 ± 0.28 log AU vs. −2.98 ± 0.13, $P = 0.007$; 300 Hz −2.65 ± 0.26 log AU vs. −2.87 ± 0.15 log AU, $P = 0.002$, Fig. 2D).

In the control analyses, no correlation was found between the levodopa doses before surgery and the power in LFP bands was significantly different between males and females before levodopa medication (alpha, all subjects $R^2 = 0.10$, $P = 0.07$; females $R^2 = 0.12$, $P = 0.13$; males $R^2 = 0.007$, $P = 0.9$; low-beta, all subjects $R^2 = 0.001$, $P = 0.6$; females $R^2 = 0.01$, $P = 0.7$; males $R^2 = 0.004$, $P = 0.94$). Also, we did not find any significant correlation between the years of disease before surgery (which differed in the group of patients recorded in off) and the spectral power in LFPs band in off (alpha, all subjects $R^2 = 0.03$, $P = 0.42$; females $R^2 = 0.35$, $P = 0.06$; males $R^2 = 0.17$, $P = 0.23$; low-beta, all subjects $R^2 = 0.01$, $P = 0.59$; females $R^2 = 0.08$, $P = 0.39$; males $R^2 = 0.1$, $P = 0.37$). Furthermore, we found no correlations between the disease severity, assessed with the UPDRS III score, and the LFP bands displaying significant gender-related differences (off levodopa – alpha, all subjects $R^2 = 0.04$, $P = 0.36$; females $R^2 = 0.02$, $P = 0.69$; males $R^2 = 0.12$, $P = 0.31$; low-beta, all subjects $R^2 = 0.10$, $P = 0.14$; females $R^2 = 0.09$, $P = 0.35$; males $R^2 = 0.2$, $P = 0.19$; on levodopa – high-gamma, all subjects $R^2 = 0.01$, $P = 0.64$; females $R^2 = 0.002$, $P = 0.93$; males $R^2 = 0.24$, $P = 0.26$; 300 Hz: all subjects $R^2 = 0.10$, $P = 0.28$; females $R^2 = 0.10$, $P = 0.55$; males $R^2 = 0.26$, $P = 0.24$). Finally, the dopamine agonist therapy did not correlate with any of the LFP bands, either before, or after levodopa administration (off levodopa – low frequencies, $R^2 = 0.003$, $P = 0.79$; alpha, $R^2 = 0.03$, $P = 0.45$; low-beta, $R^2 = 0.03$, $P = 0.48$; high-beta, $R^2 = 0.01$, $P = 0.65$; high-gamma, $R^2 = 0.07$, $P = 0.26$; 300 Hz, $R^2 = 0.02$, $P = 0.61$; on levodopa – low

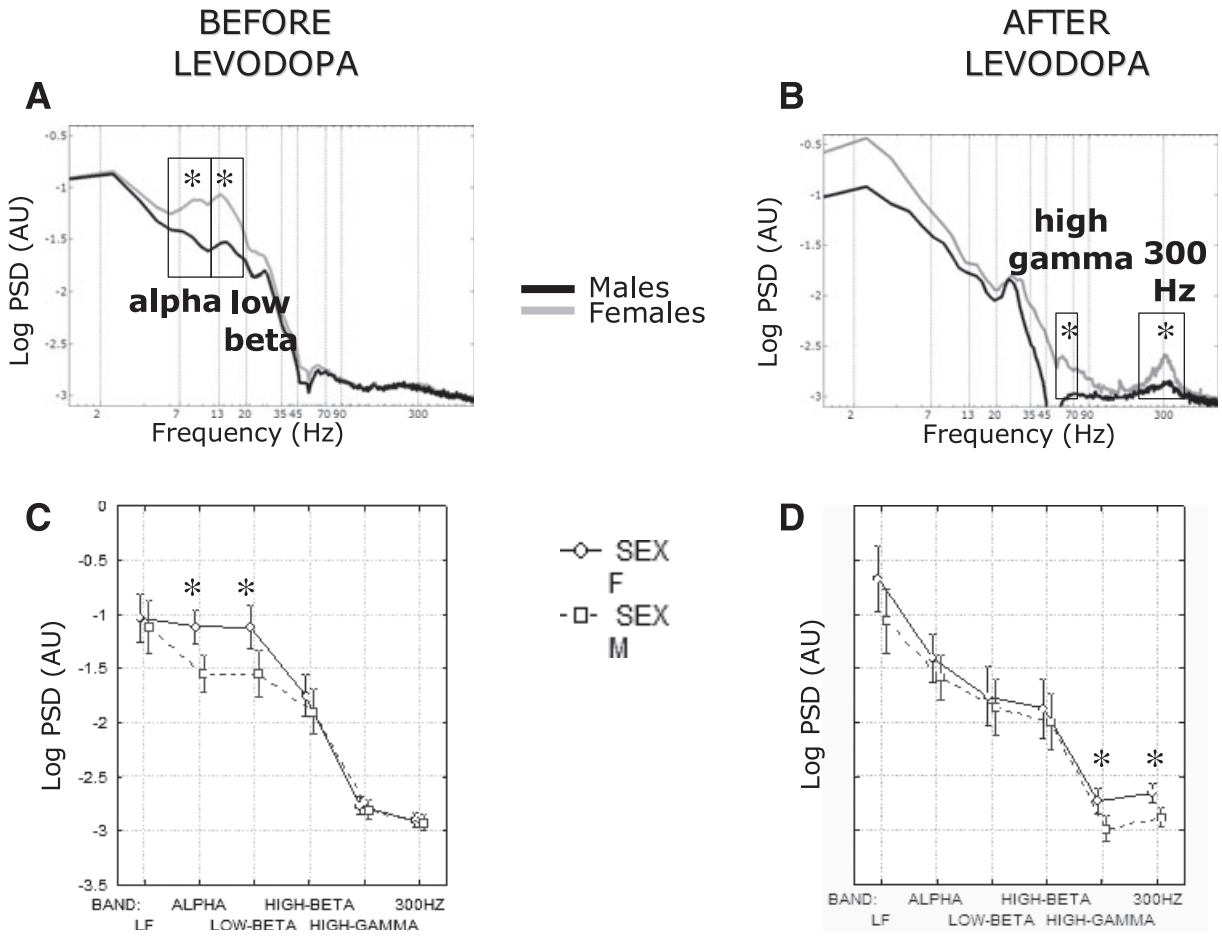

FIG. 2. Gender differences in local field potentials. The upper part of the figure shows the LFP power spectra before (A) and after (B) levodopa administration. The black line represents male power spectra (A, average of 16 nuclei from ten patients; B, average of 11 nuclei from seven patients) and the grey line female power spectra (A, average of 19 nuclei from 11 patients; B, average of ten nuclei from six patients). The *x*-axis reports frequencies (Hz), plotted on a logarithmic scale between 0 and 600 Hz; the *y*-axis shows power spectral density (PSD) values, expressed in logarithmic arbitrary units (AU). The lower part of the figure shows the three-way analysis of variance (ANOVA) results for the interaction of the factors gender (male, SEX M; female, SEX F), treatment [before levodopa, left side (C); after levodopa, right side (D)] and band (low frequencies (LF); ALPHA; LOW-BETA; HIGH-BETA; HIGH-GAMMA; 300 (Hz). On the *x*-axis are reported the bands; on the *y*-axis is reported the band spectral power. Note the significantly higher alpha and low-beta spectral power before levodopa (A and C) and the significantly higher high-gamma and 300 Hz spectral power after levodopa medication (B and D) in females than in males, as shown by *.

frequencies, $R^2 = 0.07$, $P = 0.39$; alpha, $R^2 = 0.2$, $P = 0.12$; low-beta: $R^2 = 0.16$, $P = 0.18$; high-beta, $R^2 = 0.15$, $P = 0.19$; high-gamma, $R^2 = 0.04$, $P = 0.54$; 300 Hz, $R^2 = 0.04$, $P = 0.51$).

Discussion

The analysis of LFP recordings after surgery in patients with Parkinson's disease undergoing DBS consistently disclosed significant gender-related differences in the electrical activity recorded from the human STN area. Our results showed that in the absence of dopaminergic stimulation females had higher spectral power in the alpha/low-beta (8–20 Hz) band than males; after dopaminergic therapy had restored more physiological dopamine levels, females had higher spectral power in the high-gamma (60–90 Hz) band and at 300 Hz than males.

Methodological considerations

These gender-related differences in electrical activity seem unlikely to arise for methodological or technical reasons. Our study sample both off and on levodopa was preoperatively matched for clinical features and medical history. Only the years of disease history were higher in females than in males in the patients analysed off dopaminergic stimulation. However, we found no correlation between years of disease history and LFP oscillations in any band. No differences in the motor scores were present, UPDRS motor scores did not correlate with oscillatory activities displaying gender-related differences, and surgical procedures were the same in both groups. When we compared the stereotactic coordinates we found no statistically significant gender-related differences. Postoperative imaging showed that the electrode localization corresponded with the predefined target, supporting the observation of a comparable electrode final position. Because we also used the same recording and signal processing procedures and statistical analyses for males and females, our findings do not depend on differences in analysis procedures. Patients studied in the on condition received a levodopa dose adapted to the habitual dose of fast-acting levodopa preparation they were taking before surgery. This patient-specific dosage prevented the LFP oscillations evaluated on levodopa to be biased from possible differences in body mass between males and females. We did not find any correlation between LFP oscillations and either levodopa-equivalent daily dosage, dopamine

TABLE 4. Details of levodopa-induced changes on LFP bands spectral power, in females, in males and in all subjects that were recorded both in the off and in the on levodopa condition (eight nuclei from five female subjects; six nuclei from five male subjects)

	LFP bands spectral log power (AU)			
	Before levodopa	After levodopa	Change	*P*-value
Females ($n = 8$)*				
Low frequencies (2–7 Hz)	−1.171 ± 0.29	−0.639 ± 0.58	↑	0.04
Alpha (8–12 Hz)	−1.121 ± 0.43	−1.492 ± 0.30	–	NS
Low-beta (13–20 Hz)	−1.061 ± 0.50	−1.892 ± 0.18	↓	0.003
High-beta (21–35 Hz)	−1.679 ± 0.36	−1.881 ± 0.27	–	NS
High-gamma (70–90 Hz)	−2.680 ± 0.27	−2.706 ± 0.30	–	NS
300 Hz (260–340 Hz)	−2.864 ± 0.08	−2.583 ± 0.25	↑	0.01
Males ($n = 6$)*				
Low frequencies (2–7 Hz)	−1.302 ± 0.23	−0.971 ± 0.52	(↑)	NS (0.07)
Alpha (8–12 Hz)	−1.498 ± 0.32	−1.521 ± 0.42	–	NS
Low-beta (13–20 Hz)	−1.445 ± 0.36	−1.891 ± 0.34	↓	0.03
High-beta (21–35 Hz)	−1.777 ± 0.46	−1.939 ± 0.63	–	NS
High-gamma (70–90 Hz)	−2.839 ± 0.09	−2.953 ± 0.12	–	NS
300 Hz (260–340 Hz)	−2.903 ± 0.03	−2.793 ± 0.11	↑	0.04
All nuclei ($n = 14$)*				
Low frequencies (2–7 Hz)	−1.227 ± 0.27	−0.781 ± 0.56	↑	0.02
Alpha (8–12 Hz)	−1.282 ± 0.42	−1.504 ± 0.34	–	NS
Low-beta (13–20 Hz)	−1.226 ± 0.47	−1.892 ± 0.25	↓	0.0004
High-beta (21–35 Hz)	−1.722 ± 0.39	−1.906 ± 0.44	–	NS
High-gamma (70–90 Hz)	−2.748 ± 0.22	−2.811 ± 0.27	–	NS
300 Hz (260–340 Hz)	−2.881 ± 0.07	−2.673 ± 0.22	↑	0.001

Data are presented as means ± SD. Significant changes ($P < 0.05$) are shown by an arrow in the corresponding direction, whereas nonsignificant changes (NS) are indicated by a dash. * The nuclei here considered were recorded both in off levodopa and in on levodopa.

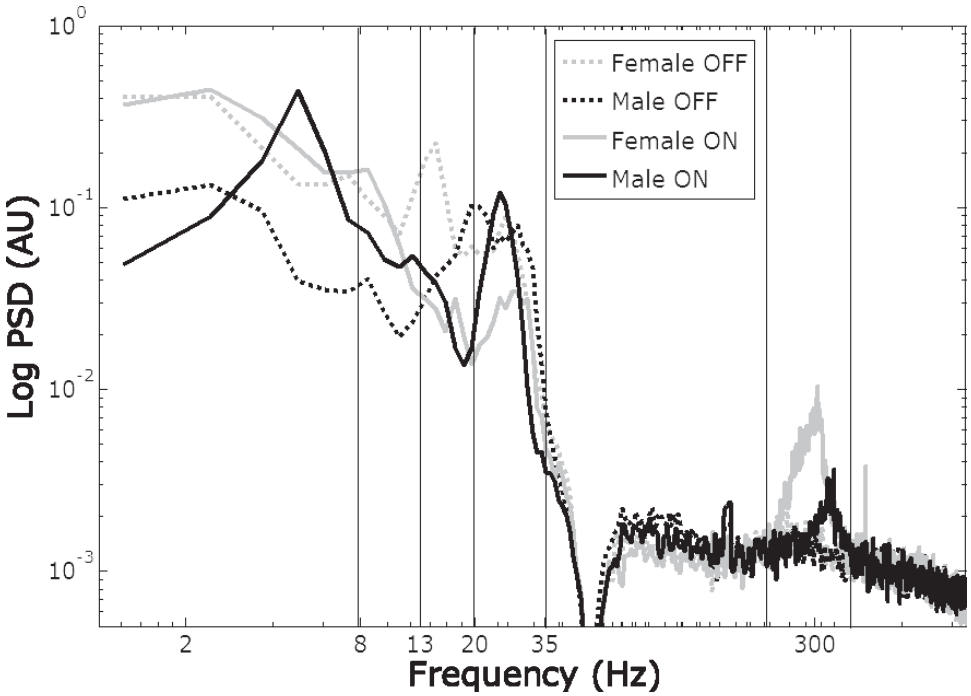

FIG. 3. LFPs recording and spectral analysis in one nucleus from a male patient (black lines) and one from a female patient (grey line). The *x*-axis reports frequencies (Hz), plotted on a logarithmic scale between 0 and 600 Hz; the *y*-axis shows power spectral density (PSD) values, expressed in logarithmic arbitrary units (AU). The two patients were studied both off (dotted line) and on (solid line) levodopa. Black vertical lines indicate the boundaries of the frequency bands.

agonists therapies or NMDA antagonist therapies before surgery. Differences in LFP oscillations off levodopa are unlikely to reflect differences in body and brain size or skull thickness nor does the literature report differences in the brain impedance between the genders. Indeed the estimated STN length did not differ between males and females in our patients.

In conclusion, no apparent methodological biases were introduced in our analysis and clinical differences were kept well apart from electrophysiological differences.

Gender-related differences in LFPs

LFPs represent network oscillations due to the synchronous activity of large populations of neurons (Creutzfeldt *et al*., 1966; Frost, 1968; Murthy & Fetz, 1992; Baker *et al*., 1997; Donoghue *et al*., 1998; Goldberg *et al*., 2004; Magill *et al*., 2004). Studies on LFPs demonstrated that dopamine intake specifically modulate multiple STN rhythms (Brown *et al*., 2001; Levy *et al*., 2002; Foffani *et al*., 2003; Priori *et al*., 2004; Brown & Williams, 2005; Alonso-Frech *et al*., 2006) and their reciprocal interactions (Marceglia *et al*., 2006). Our results add to this scenario a new element i.e. STN rhythms exhibit gender dimorphism, a factor that should in future be taken into account when data from this area are interpreted.

Current interpretation of LFP data points out the substantial antikinetic role played by the low-beta band and its interaction with the high-beta band (Priori *et al*., 2004; Brown & Williams, 2005; Foffani *et al*., 2005c; Marceglia *et al*., 2006). Conversely, the low-frequency band and fast rhythms (high-gamma and 300 Hz) are associated with the levodopa on state and increase during the execution of movements (Foffani *et al*., 2003; Priori *et al*., 2004; Brown & Williams, 2005). The low-frequency band also increases after DBS (Priori *et al*., 2006). The direct association between clinical features and LFP bands is nonetheless still controversial, for several reasons. Although the dopamine-dependent reduction of LFP power in the beta band correlates with the improvement of rigidity and bradykinesia (Kuhn *et al*., 2006) this correlation is lost after anticholinergic medication (Priori *et al*., 2004) or during clinical improvement elicited by DBS (Foffani *et al*., 2006). The low-frequency band has been recently connected to the amount of dyskinesias and hyperkinetic movement induced by levodopa intake (Foffani *et al*., 2005a; Alonso-Frech *et al*., 2006), but nondyskinetic oscillations can also be observed in this frequency range (Priori *et al*., 2004; Priori *et al*., 2006). Finally, the clinical correlate for higher frequency bands is still uncertain (Foffani *et al*., 2003).

Our results showed that in the absence of dopaminergic stimulation females had higher spectral power in the alpha/low-beta band (8–20 Hz) than males; after dopaminergic medication females had higher spectral power in the high-gamma (60–90 Hz) and 300 Hz rhythm than males. These differences arose in groups of patients matched for preoperative clinical features and undergoing the same surgical procedures. Our results are not in contradiction with the reported correlation between the dopamine-dependent reduction of beta LFP power and UPDRS III clinical improvement (Kuhn *et al*., 2006). In fact, this correlation does not imply that the absolute beta LFP power correlates with clinical state, which indeed is not the case (Priori *et al*., 2004; Foffani *et al*., 2006; Kuhn *et al*., 2006). EEG studies in normal subjects reported higher beta power in women than in men (Wada *et al*., 1994; Brenner *et al*., 1995; Briere *et al*., 2003; Nikulin & Brismar, 2006). The results of Yaar & Shapiro (1983) in patients with Parkinson's disease also imply that the beta band power in the scalp EEG was larger in females. Hence, our findings demonstrating higher beta power in female STN LFPs before levodopa agree with previous scalp EEG studies in healthy subjects and in patients with Parkinson's disease.

LFPs and sex hormones

Some current knowledge suggests that the gender-related differences we observed might reflect the known action of gonadal hormones on the nigrostriatal system. Even though immunoreactivity studies have localized intracellular androgen receptors in substantia nigra cells immunoreactive for tyrosine hydroxylase, testicular hormones appear to exert a relatively minor influence over striatal motor functions (Kritzer, 1997; Bialek *et al*., 2004) and do not prevent striatal dopamine depletion induced by neurotoxins (Dluzen, 1996; Becker, 1999). These findings argue against a role of the higher gonadal testosterone levels in men for explaining the gender-related differences we found. Conversely, oestrogens remarkably affect the development and function of the dopaminergic nigrostriatal system (Becker & Beer, 1986; Becker, 1990; Guivarc'h *et al*., 1995; Dluzen *et al*., 1996a, b; Becker & Rudick, 1999; Dluzen, 2000; Kuppers *et al*., 2000). The actions of oestrogens arise not only from their transient effect on adult brain (Becker, 1990; Thompson & Moss, 1994; Becker & Rudick, 1999; Kuppers *et al*., 2000), but also from their long-lasting influence in the development of the nigrostriatal system (Matsumoto & Arai, 1976; Toran-Allerand, 1976; Reisert *et al*., 1987; Arai *et al*., 1996; Sibug *et al*., 1996; Beyer & Karolczak, 2000; Kuppers *et al*., 2000). Our female patients were mostly in the menopause and, hence, without acute oestrogen stimulation but with the nigrostriatal system primed by the hormonal action during the early stage of life. The loss of acute oestrogen stimulation could further worsen the electrophysiological abnormalities resulting from reduced dopaminergic activity, leading to higher synchronization in electrical STN activity and higher power in the alpha/low-beta band in females. At the same time, the long-term effects of oestrogen on the nigrostriatal system, persisting even after the menopause (Becker & Rudick, 1999), could affect the dynamics of the response to dopaminergic stimulation, even if unable to produce significant differences in the UPDRS scores. The boosting action of oestrogen on the dopaminergic system is supported by the hyperkinetic movement disorders observed after oestrogen replacement therapy and oral contraceptive use in non-parkinsonian women (Steiger & Quinn, 1991; Miranda *et al*., 2004). An enhanced response to dopaminergic stimulation at least at the nigrostriatal level might therefore explain the higher high-gamma and 300 Hz power in females than in males after levodopa had restored more physiological dopaminergic levels. The long-term action of gonadal hormones could therefore lower the threshold of the 300-Hz rhythm, an electrical event pharmacologically driven by dopaminergic medication (Foffani *et al*., 2003).

Conclusions

Although the mechanisms responsible for the gender-related differences we observed are conjectural, the LFP gender-related differences strongly argue against methodological and aspecific factors and suggest that the functional organization of the STN area and levodopa pharmacodynamics differ in the two genders. Sexual-dimorphism in the central nervous system therefore involves the human STN and, possibly, other basal ganglia structures. Our findings imply that studies investigating LFPs in patients with Parkinson's disease should take into account gender-related differences.

Acknowledgements

The authors wish to thank Dr Ettore Accolla for his kind cooperation. The study was supported by Fondazione IRCCS Ospedale Maggiore, Policlinico, Mangiagalli and Regina Elena di Milano (Italy), Centro Dino Ferrari for Neurodegenerative Disorders (Italy), Ministero della Salute (Italy), Ministero dell'Istruzione, dell'Università e della Ricerca (Italy). G. Foffani was partly supported by a visiting professorship from Università di Milano. S. Marceglia is a PhD student supported by Fondazione IRCCS Ospedale Maggiore, Policlinico, Mangiagalli and Regina Elena di Milano (Italy) at the Dipartimento di Bioingegneria, Politecnico di Milano.

Abbreviations

DBS, deep brain stimulation; LFP, local field potentials; PSD, power spectral density; STN, subthalamic area.

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