

Signal features of surface electromyography in advanced Parkinson's disease during different settings of deep brain stimulation



Saara M. Rissanen ^{a,*}, Verneru Ruonala ^a, Eero Pekkonen ^{b,c}, Markku Kankaanpää ^d, Olavi Airaksinen ^e, Pasi A. Karjalainen ^a

^a Department of Applied Physics, University of Eastern Finland, Finland

^b Department of Neurology, Helsinki University Central Hospital, Finland

^c BioMag Laboratory, Helsinki University Central Hospital, Finland

^d Department of Physical and Rehabilitation Medicine, Tampere University Hospital, Finland

^e Department of Physical and Rehabilitation Medicine, Kuopio University Hospital, Finland

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HIGHLIGHTS

- Efficacy of deep brain stimulation (DBS) treatment was quantified here by using surface EMG and acceleration measurements.
- EMG signal features differed between different DBS settings for biceps brachii muscles.
- EMG features pointed to previously defined optimal settings in most of patients.

ABSTRACT

Objective: Electromyography (EMG) and acceleration (ACC) measurements are potential methods for quantifying efficacy of deep brain stimulation (DBS) treatment in Parkinson's disease (PD). The treatment efficacy depends on the settings of DBS parameters (pulse amplitude, frequency and width). This study quantified, if EMG and ACC signal features differ between different DBS settings and if DBS effect is unequal between different muscles.

Methods: EMGs were measured from biceps brachii (BB) and tibialis anterior (TA) muscles of 13 PD patients. ACCs were measured from wrists. Measurements were performed during seven different settings of DBS and analyzed using methods based on spectral analysis, signal morphology and nonlinear dynamics.

Results: The results showed significant within-subject differences in the EMG signal kurtosis, correlation dimension, recurrence rate and EMG–ACC coherence between different DBS settings for BB but not for TA muscles. Correlations between EMG feature values and clinical rest tremor and rigidity scores were weak but significant.

Conclusions: Surface EMG features differed between different DBS settings and DBS effect was unequal between upper and lower limb muscles.

Significance: EMG changes pointed to previously defined optimal settings in most of patients, which should be quantified even more deeply in the upcoming studies.

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1. Introduction

Several parts of the brain participate in controlling the posture, force and movements in humans. These parts include the premotor

and primary motor cortex, cerebellum and basal ganglia (Moritani et al., 2004). In Parkinson's disease (PD), there is a progressive degeneration of dopaminergic neurons in the substantia nigra in the basal ganglia. This leads to abnormalities in the basal ganglia function and finally to the primary symptoms of PD: resting tremor, rigidity (increased muscle tone) and bradykinesia (slowness of movements) (Wichmann et al., 2008). PD cannot be cured but the symptoms can be relieved with medication that aims either

* Corresponding author at: Department of Applied Physics, University of Eastern Finland, P.O. Box 1627, FI-70211 Kuopio, Finland. Tel.: +358 40 355 2370.

E-mail address: saara.rissanen@uef.fi (S.M. Rissanen).

to increase the amount or to inhibit the breakdown of dopamine in the brain (Gárdián and Vécsei, 2010). Deep brain stimulation (DBS) can be used to treat advanced PD, when optimal oral medication fails to sufficiently control motor symptoms. The most common target is subthalamic nucleus (STN), although Globus Pallidus Interna (GPi) stimulation has also been used as treatment option in advanced PD (Malhado-Chang et al., 2008). DBS delivers high frequency current to stimulate the STN in the basal ganglia resulting in a complex pattern of excitatory and inhibitory effects that modulate the entire network between basal ganglia, thalamus and cortex. It is thought that DBS regularizes neuronal patterns preventing the transmission of pathologic bursting and oscillatory activity in the brain. This results in improved processing of the sensorimotor information and alleviation of motor symptoms (Miocinovic et al., 2013). Often there is a significant reduction in the daily levodopa dose, when STN is stimulated (Benabid et al., 2009; Malhado-Chang et al., 2008).

Efficacy of DBS treatment depends significantly on the correct placement of stimulation electrodes, and on the optimal settings of stimulation parameters. In constant-voltage mode (which is the most common mode used), the controllable stimulation parameters are the amplitude, frequency and width of the stimulation pulse. By choosing active electrode contacts and their polarity, the electrical current can be targeted to correct neural elements (Volkman et al., 2006; Montgomery, 2010). In some cases, the optimization of DBS treatment is not straightforward because the stimulation parameters are set by subjective evaluation of symptoms and the symptoms may respond to DBS with a variable delay (Levin et al., 2009; Groiss et al., 2009). Rigidity and tremor respond usually within a few minutes and they require only little co-operation from the patient. The tremor may, however, be influenced by the emotional state in some patients. Bradykinesia may respond to DBS in several hours or even days. Therefore, the changes in bradykinesia may not be observed during the DBS adjustment session in all patients (Malhado-Chang et al., 2008; Volkman et al., 2006). With a careful adjustment of stimulation parameters also the unpleasant adverse effects such as dyskinesia, dystonia (involuntary muscle contractions), dysarthria (speech problems) and abnormal eye function (e.g. diplopia), may be eliminated (Malhado-Chang et al., 2008; Miocinovic et al., 2013).

The DBS parameters have a therapeutic range, inside which the clinical efficacy is maximal while the current consumption stays reasonable. It has been observed that an increase in the stimulation amplitude leads to increase in the distance of the stimulated neural elements and usually to a reduction in motor symptoms (Volkman et al., 2006). On the other hand, amplitude increase may give rise to unwanted side-effects by stimulating adjacent elements besides STN (Groiss et al., 2009). Therapeutic amplitudes range between 1 and 3.5 V, above which the electrical current consumption may rise abruptly (Volkman et al., 2006). The adjustment of pulse amplitude is usually done in 0.3–0.5 V steps (Montgomery, 2010). If needed, the pulse width (60–90 μ s) can be increased in order to compensate reduction in the stimulation amplitude (Malhado-Chang et al., 2008). It is known that low DBS frequencies (<10 Hz) may increase parkinsonian symptoms and high frequencies reduce them. The therapeutic pulse frequencies are thought to be above 100 Hz and usually maximal benefit of DBS is around 130 Hz (Volkman et al., 2006). However, it has been noticed that high-frequency DBS (130 Hz) may worsen gait and speech while low-frequency DBS (60 Hz) may improve them in some patients (Xie et al., 2012; Montgomery, 2010; Moreau et al., 2008). System Oscillations theory (Montgomery, 2010) has been suggested as one explanation for that.

Surface electromyography (EMG) enables the objective quantification of neuromuscular function. Therefore, it may be useful in quantifying treatment efficacy in PD. Previous EMG-based

studies have shown that DBS may change the EMG signal characteristics by increasing the dominant tremor frequency in the EMG spectrum (Blahak et al., 2007; Sturman et al., 2004) and by reducing the EMG–acceleration coherence during a resting condition and with backward counting (Sturman et al., 2004, 2007). DBS may also increase the size of the first agonist burst and the number of agonist bursts during rapid point-to-point movements of the elbow and ankle (Vaillancourt et al., 2004, 2006). Rissanen et al. (2011) have presented previously a principal component (PC)-based tracking method for quantifying the effects of DBS in PD by using EMG and kinematic measurements and analysis. The presented method was capable of detecting differences in the surface EMG and acceleration (ACC) signal features between the DBS on- and DBS off-states. However, it stays unclear, if muscle activation and surface EMG are unequal between different settings of the DBS parameters. If surface EMG was unequal between different settings of DBS treatment, it could work in helping the optimal adjustment of DBS treatment. It is also unclear, if surface EMG is changed similarly in upper and lower extremity muscles during the adjustment of DBS settings.

This study aims answer to three questions: What happens to the surface EMG signal characteristics of arms and legs:

- when the stimulation amplitude is increased or decreased with 0.3 V?
- when the stimulation frequency is increased or decreased with 30 Hz?
- when the stimulation pulse width is increased with 30 μ s?

In this study, surface EMGs were measured from the biceps brachii (BB) and tibialis anterior (TA) muscles of 13 PD patients with previously implanted DBS during seven different settings (varying stimulation amplitude, frequency or pulse width) of the DBS treatment. The selected DBS settings were supposed to be safe for the patients and causing minimal side-effects. The measured signals were analyzed using different EMG signal parameters.

2. Methods

2.1. Subjects

Thirteen patients with advanced PD participated in this study after giving their informed consent. All patients had been treated with bilateral STN-DBS (Kinetra or Activa PC Neurostimulators, Medtronic Inc., Minneapolis, MN, USA) for 2–34 months. The details of patients, clinical scores (total scores of UPDRS III Motor Examination), STN-DBS details and medications are given in Table 1. The study was approved by the local human ethics committee of the Kuopio University Hospital. The EMG measurements were performed during seven different stimulation settings which are detailed in Table 2. The setting state *S0* refers to the previously (less than 6 months ago) defined optimal parameter values that each patient had used for DBS treatment. Because of severe symptoms, the patients were on-medication during the measurements. If the patient suffered from difficult adverse effects with some stimulation settings, the measurement was canceled and the analysis was not performed with those settings. One patient could not be measured with *A+* and one patient with DBS OFF. Four patients could not be measured with *W+*. The order of setting states *A+*, *A-*, *F+*, *F-* and *W+* was randomized between patients in the measurements. However, the first setting state was *S0* in all patients, which corresponds to typical adjustment session of previously implanted DBS. From that state we got the reference values for clinical scores. The last setting state studied was OFF in all patients, because the symptoms were quite severe in many patients when

Table 1
Patients, clinical scores, STN-DBS details and medications.

Patient	Age	Sex	UPDRS III on (off) ^a	DBS months ^b	Optimal settings of STN-DBS	Medications and levodopa equivalent doses (LEDs) calculated according to Tomlinson et al. (2010)
1	46	M	21 (36)	5	Right: A0 = 3.5 V, F0 = 130 Hz, W0 = 60 μs; Left: A0 = 3.7 V, F0 = 130 Hz, W0 = 60 μs	Levodopa/carbidopa/entacapone 150 mg/37.5 mg/200 mg×5, rasagiline 1 mg×1 and pramipexole 1.57 mg×1 (total LED 1257 mg)
2	59	F	26 (≥ 37)	34	Right: A0 = 3.4 V, F0 = 130 Hz, W0 = 60 μs; Left: A0 = 3.2 V, F0 = 130 Hz, W0 = 60 μs	Levodopa/carbidopa/entacapone 150 mg/37.5 mg/200 mg×4, levodopa/carbidopa/entacapone 125 mg/31.25 mg/200 mg×2, carbidopa/levodopa 50 mg/200 mg×1, rotigotine 6 mg/24 h and if needed levodopa/benserazide 100 mg/25 mg×1–2 (total LED 1516–1716 mg)
3	64	M	22 (29)	23	Right: A0 = 3.1 V, F0 = 130 Hz, W0 = 60 μs; Left: A0 = 3.3 V, F0 = 130 Hz, W0 = 60 μs	Levodopa/carbidopa/entacapone 75 mg/18.75 mg/200 mg×5, rotigotine 10 mg/24 h and if needed levodopa/benserazide 50 mg/12.5 mg (total LED 803–853 mg)
4	58	F	10 (18)	5	Right: A0 = 2.6 V, F0 = 130 Hz, W0 = 60 μs; Left: A0 = 2.5 V, F0 = 130 Hz, W0 = 60 μs	Levodopa/carbidopa/entacapone 50 mg/12.5 mg/200 mg×1, ropinirole 12 mg×1 and rasagiline 1 mg×1 (total LED 407 mg)
5	64	M	16 (36)	2	Right: A0 = 2.8 V, F0 = 130 Hz, W0 = 60 μs; Left: A0 = 3.4 V, F0 = 130 Hz, W0 = 90 μs	Pramipexole 1.05 mg×1 and levodopa/benserazide 100 mg/25 mg×2 (total LED 205 mg)
6	66	M	21 (28)	8	Right: A0 = 2.5 V, F0 = 130 Hz, W0 = 60 μs; Left: A0 = 2.5 V, F0 = 130 Hz, W0 = 60 μs	Carbidopa/levodopa 25 mg/100 mg×3, pramipexole 2.1 mg×1 and rasagiline 1 mg×1 (total LED 610 mg)
7	66	M	34 (45)	21	Right: A0 = 2.3 V, F0 = 130 Hz, W0 = 60 μs; Left: A0 = 3.3 V, F0 = 130 Hz, W0 = 60 μs	Ropinirole 8 mg×1, carbidopa/levodopa 12.5 mg/50 mg×3 and selegiline 10 mg×1 (total LED 410 mg)
8	38	M	27 (50)	22	Right: A0 = 3.4 V, F0 = 130 Hz, W0 = 60 μs; Left: A0 = 3.4 V, F0 = 130 Hz, W0 = 60 μs	Levodopa/carbidopa/entacapone 50 mg/12.5 mg/200 mg×2 and pramipexole 2.1 mg×1 (total LED 344 mg)
9	71	M	22 (36)	4	Right: A0 = 3.1 V, F0 = 130 Hz, W0 = 60 μs; Left: A0 = 3.4 V, F0 = 130 Hz, W0 = 60 μs	Carbidopa/levodopa 25 mg/100 mg×5 (total LED 500 mg)
10	47	M	31 (38)	4	Right: A0 = 2.3 V, F0 = 180 Hz, W0 = 60 μs; Left: A0 = 2.5 V, F0 = 180 Hz, W0 = 60 μs	Levodopa/carbidopa 100 mg/25 mg×3–4, rotigotine 4 mg/24 h and selegiline 10 mg×1 (total LED 521–621 mg)
11	58	F	12 (23)	6	Right: A0 = 2.4 V, F0 = 130 Hz, W0 = 60 μs; Left: A0 = 2.4 V, F0 = 130 Hz, W0 = 60 μs	Levodopa/carbidopa/entacapone 50 mg/12.5 mg/200 mg×6, pramipexole 1.05 mg×1, levodopa/carbidopa 200 mg/50 mg×1 and rasagiline 1 mg×1 (total LED 807 mg)
12	70	M	31 (62)	30	Right: A0 = 2.7 V, F0 = 130 Hz, W0 = 60 μs; Left: A0 = 3.3 V, F0 = 130 Hz, W0 = 60 μs	Levodopa/carbidopa/entacapone 50 mg/12.5 mg/200 mg×4, levodopa/benserazide 100 mg/25 mg×1 and carbidopa/levodopa 50 mg/200 mg×1 (total LED 568 mg)
13	45	M	31 (≥ 36)	29	Right: A0 = 3.1 V, F0 = 120 Hz, W0 = 60 μs; Left: A0 = 3.1 V, F0 = 120 Hz, W0 = 60 μs	Levodopa/carbidopa/entacapone 75 mg/18.75 mg/200 mg×10, rasagiline 1 mg×1 and ropinirole 2 mg×1 (total LED 1140 mg)

^a UPDRS III on was evaluated with the optimal DBS settings (S0) at the beginning of measurement session. UPDRS III off was evaluated with DBS off and medication on. For Patient 2 and Patient 13, UPDRS III off could not be completely estimated because of difficult symptoms. Therefore, the ≥-notion is used.

^b DBS months means the number of months after DBS implantation.

Table 2
Settings of DBS.

DBS settings code	Pulse amplitude	Stimulation frequency	Pulse width
S0	A0	F0	W0
A–	A0 – 0.3 V	F0	W0
A+	A0 + 0.3 V	F0	W0
F–	A0	F0 – 30 Hz	W0
F+	A0	F0 + 30 Hz	W0
W+	A0	F0	W0 + 30 μs
OFF	OFF	OFF	OFF

A0, F0 and W0 are the individual previously defined optimal values for each patient.

the stimulator was switched off and we did not want the patients to stop the study before trying all setting states.

During each setting state, a DBS-experienced neurologist evaluated the severity of resting tremor and rigidity in the upper and lower limbs. The neurologist and the patient were not blind to the DBS settings. EMG measurement was started five minutes after the adjustment of parameters and new settings were adjusted soon after the measurement. In that way, we could minimize the effects of medication on results while the total time needed for measurements was minimized. Five minutes was chosen based on our clinical experience that the response to resting tremor

and rigidity appears quite soon (in optimal cases within few minutes and usually well below five minutes) while programming DBS in advanced PD. This finding is supported by the DBS-study of Moro et al. (2002) that demonstrated clear response to DBS after five minutes of DBS-reprogramming. Also a study of Airaksinen et al. (2012) with magnetoencephalography (MEG) showed that the brain activity of advanced PD patients was changed within five minutes after switching the DBS on or off. In that study, a negative correlation of occipital alpha was found with UPDRS motor scores and rigidity subscores (Airaksinen et al., 2012). Response to motor fluctuations may appear more slowly, but in this study the tremor and rigidity were the focus of interest.

In the clinical evaluation, ten patients showed changes in the severity of tremor or rigidity of arms or legs between different DBS settings and three other patients did not have any tremor or rigidity during the measurements. These three patients had received DBS treatment mainly due to difficult on–off fluctuation in symptoms.

2.2. Measurements

In this study, isometric contractions of BB and TA muscles were studied. During the measurement from BB, subjects were asked to hold their elbows at a 90° angle with their palms up for 20 s.

During the measurement from TA, subjects were asked to keep their toes up while keeping the heel on the floor for 10 s. During both tasks, subjects were sitting on a chair and their arms and legs were not loaded with additional weights. Loading was not used because the PD-related EMG signal features are most visible in the unloaded condition (Meigal et al., 2009).

Surface EMGs were measured from both BB and TA muscles by using disposable Ag/AgCl electrodes (Medicotest, model M-00-S, Ølstykke, Denmark) in bipolar connection (center-to-center inter-electrode spacing 3 cm) as by Rissanen et al. (2011). The reference electrodes were placed 6–7 cm laterally from the recording electrodes. ME6000 -biosignal monitor (Mega Electronics Ltd., Kuopio, Finland) was used for signal registration with a sampling frequency of 1000 Hz. The raw EMG signals were analogically band-pass filtered with an anti-aliasing filter (Butterworth, band-pass 8–500 Hz) and amplified (differential amplifier, CMRR > 130 dB, total gain 1000, noise <1 μ V). The signal analysis was done with a PC after 14-bit analogue-to-digital conversion. One isometric contraction of BBs and one isometric contraction of TAs were measured for each patient during each setting state of DBS parameters.

The accelerations of forearms were measured by using tri-axial accelerometers (Meac-x, Mega Electronics Ltd., range ± 10 g) on the palmar side of wrists. ACC signals can describe of possible tremor and other involuntary movements during the isometric muscle contraction. The accelerations were not measured from the legs.

2.3. Signal analysis

2.3.1. Pre-processing of signals

The middle 18-s long segment of the BB task and the middle 6-s long segment of the TA task were analyzed by using Matlab (The MathWorks, Inc.). EMG signals were high-pass filtered (cut-off 10 Hz) with smoothness priors method as by Rissanen et al. (2007).

The DBS artifact (at stimulation frequency F_{stim} between 100 and 210 Hz) and its harmonics were removed from the EMG signals of BB in two stages. First, the EMGs were low-pass filtered with a 9th-order Butterworth filter (cut-off frequency 150 Hz). Then, the DBS artifacts below 150 Hz were removed by interpolating the Fourier transform of EMG signal around the stimulation artifact (between $F_{stim} - 2.5$ Hz and $F_{stim} + 2.5$ Hz) and taking the inverse Fourier transform in order to get the filtered signal (see the method theory by Mewett et al. (2004)). The EMG signals of TA did not contain DBS artifacts. This is likely because the distance between the pulse generator and legs is longer than the distance between the pulse generator and the arms. Therefore, the EMG signals of TA were not low-pass-filtered before analysis. However, it was checked that the results would had been the same if the filtering had been done similarly for EMG signals from both muscles.

2.3.2. EMG features

Following PD-characteristic signal parameters were extracted from the EMG signals of BB and TA:

- sample kurtosis of EMG
- recurrence rate of EMG
- correlation dimension of EMG
- coherence parameter between EMG and ACC (only for arms)

The parameters were calculated from the measurements of both sides of the body.

The calculation methods of the parameters have been presented previously by Rissanen et al. (2012) and they can be interpreted as follows. Sample kurtosis is the fourth centered moment of EMG sample values, and therefore it measures the impulsiveness of EMG signal. Sample kurtosis is generally higher in PD patients than in healthy subjects. Correlation dimension and recurrence rate are

methods of nonlinear dynamics. The parameters are calculated from embedding vector distances. The embedding vectors are formed from EMG signal by taking time shifted samples. Correlation dimension quantifies the complexity of EMG signal and it is usually lower in PD patients than in healthy subjects. Recurrence rate measures the percentage of recurring structures in the EMG and it is usually higher in PD patients than in healthy subjects. Coherence parameter measures similarities in the EMG and ACC spectra. The power spectral densities of EMG and ACC and their cross-spectral density were estimated here by using Welch's averaged periodogram method. The coherence parameter is the area of the magnitude squared coherence spectrum in the frequency range [0–50] Hz (Rissanen et al., 2008, 2009).

We examined within-subject differences in the signal parameters with respect to previously defined optimal DBS settings S_0 by using paired samples *t*-test for normally distributed variables and Wilcoxon signed rank test for other variables. The normality of parameter distribution was checked with the Lilliefors test.

3. Results

3.1. Clinical UPDRS-scores of patients

UPDRS-subscores (III. Motor Examination) of resting tremor and rigidity were clinically evaluated by a neurologist with each setting state. In UPDRS, each subscore gets a value between 0 and 4 and higher scores mean more severe symptoms. The evaluated tremor and rigidity score differences with respect to state S_0 are presented as a histogram for each DBS setting state in Fig. 1. In the figure, a negative score difference means reduction and a positive score difference an increase in symptom severity. The total number of score differences (i.e. cases) per each setting state was between 18 and 26, because the scores were evaluated for both (right and left side) arms and legs. Because of severe adverse effects the scores could not be evaluated for all 13 patients in all setting states.

One can observe in Fig. 1, that the arm tremor scores were the same or higher with $A-$ and $F-$ than with the state S_0 in all patients. With the state OFF , they were the same or higher than with the state S_0 in 91% of cases. The rigidity scores of arms were the same or lower with the state $A+$ than with the state S_0 in all cases. With the state OFF , they were the same or higher than with the state S_0 in 95% of cases. The leg tremor and rigidity scores were the same or higher with the state OFF than with the state S_0 in all patients. The rigidity scores of legs were the same or lower with the states $A+$ and $F+$ than with the state S_0 in all patients. The reductions in the scores with respect to increase in the stimulation amplitude or frequency are in concordance with previous findings (Volkman et al., 2006). However, it must be noted that higher parameter values may cause adverse effects in some patients.

3.2. Visual inspection of EMG signals

EMG signals of PD patients were visually inspected. EMG recordings from the BB of one PD patient (Patient 2) during seven different settings of DBS are presented in Fig. 2. One can observe that the EMGs of the patient contain recurring EMG bursts with the state OFF and with $F-$. Some clustering of motor unit action potentials can be observed also with $W+$. With other settings ($S_0, A-, A+$ and $F+$) the EMG signals look similar to the EMG signals of healthy subjects as presented by Rissanen et al. (2011). According to clinical evaluation, the arm tremor of the patient was highest with the state OFF and with $F-$, and with other settings ($S_0, A-, A+, F+$ and $W+$) no tremor was observed. Upper arm rigidity score was highest with the state OFF , and with $F-$ and $W+$ the rigidity score was low. With other settings

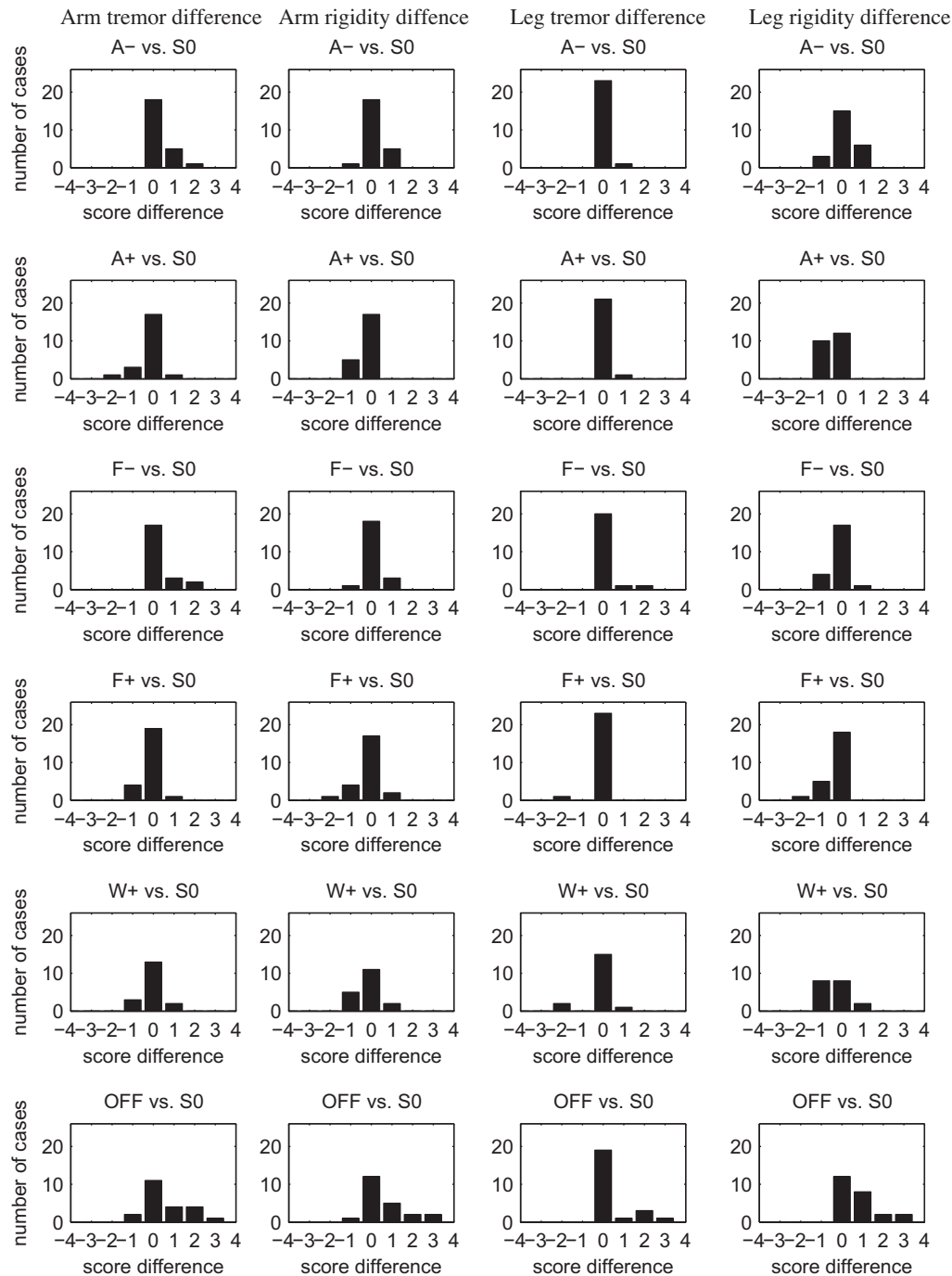


Fig. 1. Histogram of differences in the clinical scores of rest tremor and rigidity with respect to state S0 for 13 PD patients (for each patient there is one right and one left side value) during each setting state of DBS treatment.

(S0, A-, A+ and F+), no rigidity was observed. In this patient, the clinical scores are consistent with the visual inspection of EMG signal morphology. Similar differences between the DBS settings were observed in the BB EMGs of other patients as well. However, the differences were not as clear in all patients.

EMG recordings from the TA of one PD patient (Patient 7) are presented in Fig. 3. One can observe that the EMG signals contain PD-characteristic spikes or bursts during all settings. However, during F+ and W+ there seems to be fewer spikes than during other settings. During OFF-state, the spikes are clustered into recurring bursts with the frequency of 4 Hz. In clinical evaluation, the tremor score of legs was highest with the state OFF and with F-, and no tremor was observed during F+ and W+.

The rigidity was lowest during A+ and W+, and equal during S0, A-, F-, F+ and OFF. According to the visual inspection of signals, during states F+ and W+ the EMG signals look closest to the signals of healthy subjects although PD-characteristic spikes are present also during those states. According to the clinical evaluation, the tremor and rigidity scores would be lowest during W+, F+ and A+.

3.3. EMG features

The calculated EMG feature differences with respect to state S0 are presented for each DBS setting state in Fig. 4. Each dot in the

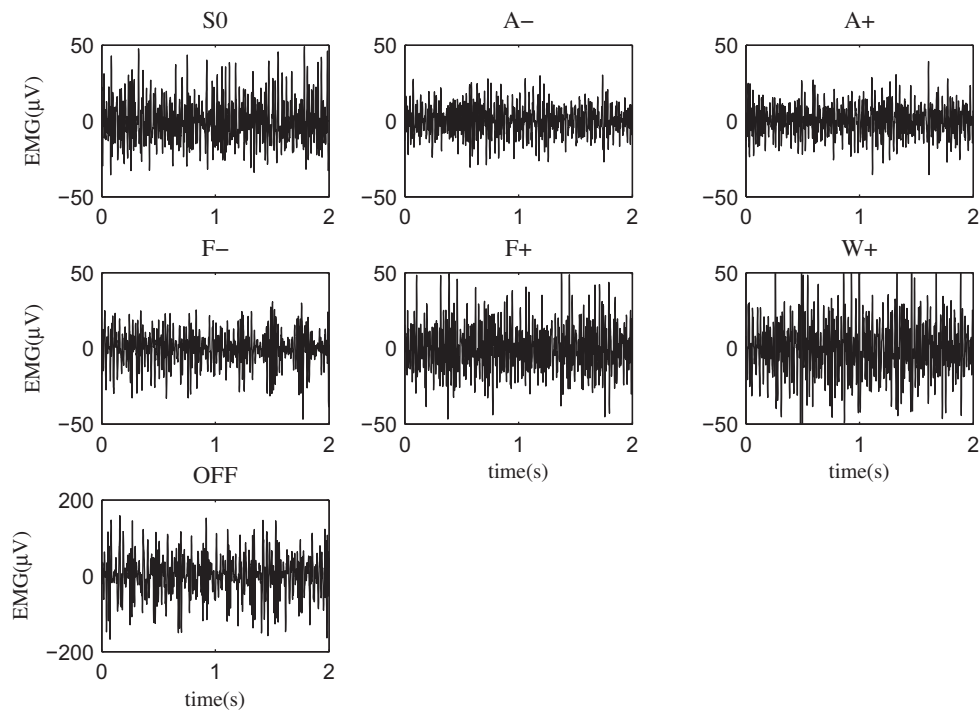


Fig. 2. EMG recordings from left BB of Patient 2 during seven different settings of the DBS treatment.

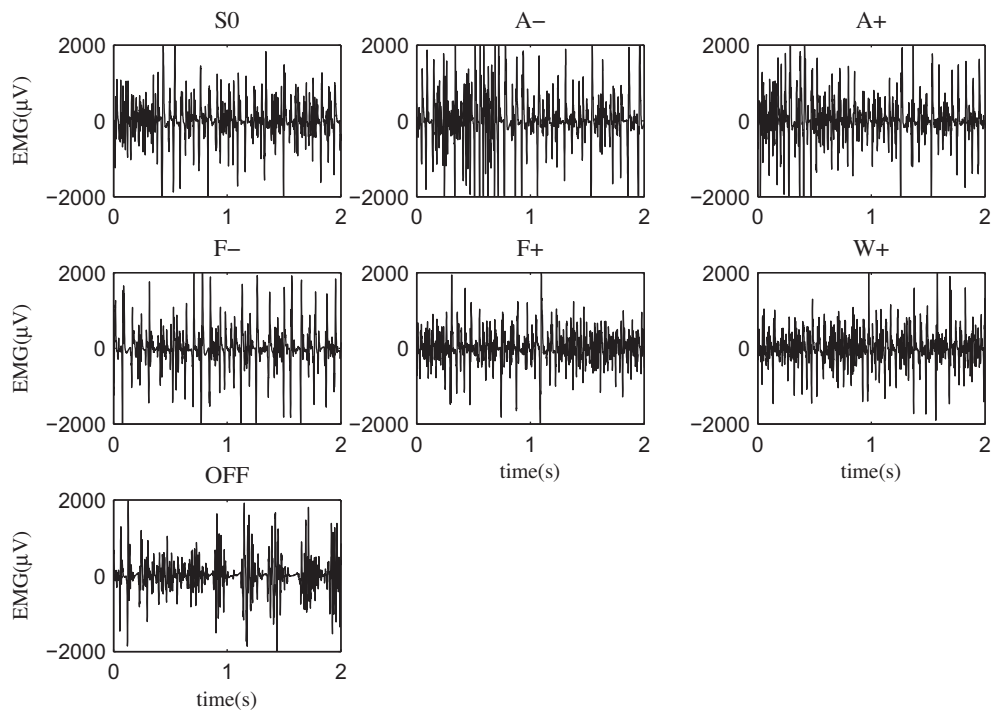


Fig. 3. EMG recordings from right TA of Patient 7 during seven different settings of the DBS treatment.

figure presents the feature difference in the specified setting state for each subject. In each setting state, there are two dots per each subject: one for the left side muscle and one for the right side muscle of the subject. Because of severe adverse effects the scores could not be evaluated for all 13 patients in all setting states. Significant within-subject differences (paired samples *t*-test for normally distributed variables and Wilcoxon signed rank test for other variables, $p < 0.05$) were found in the following EMG

parameter values. The sample kurtosis of BB EMG was significantly different (higher in most of cases) with the states A-, A+, W+ and OFF than with the state S0. Higher kurtosis indicates more impulsive (i.e. more PD-like) EMG signals (Rissanen et al., 2012). The correlation dimension of BB EMG was significantly different (lower in most of cases) with the states A-, A+, F-, W+ and OFF than with the state S0. Lower correlation dimension indicates more regular (i.e. more PD-like) EMG signals (Rissanen et al., 2012). The

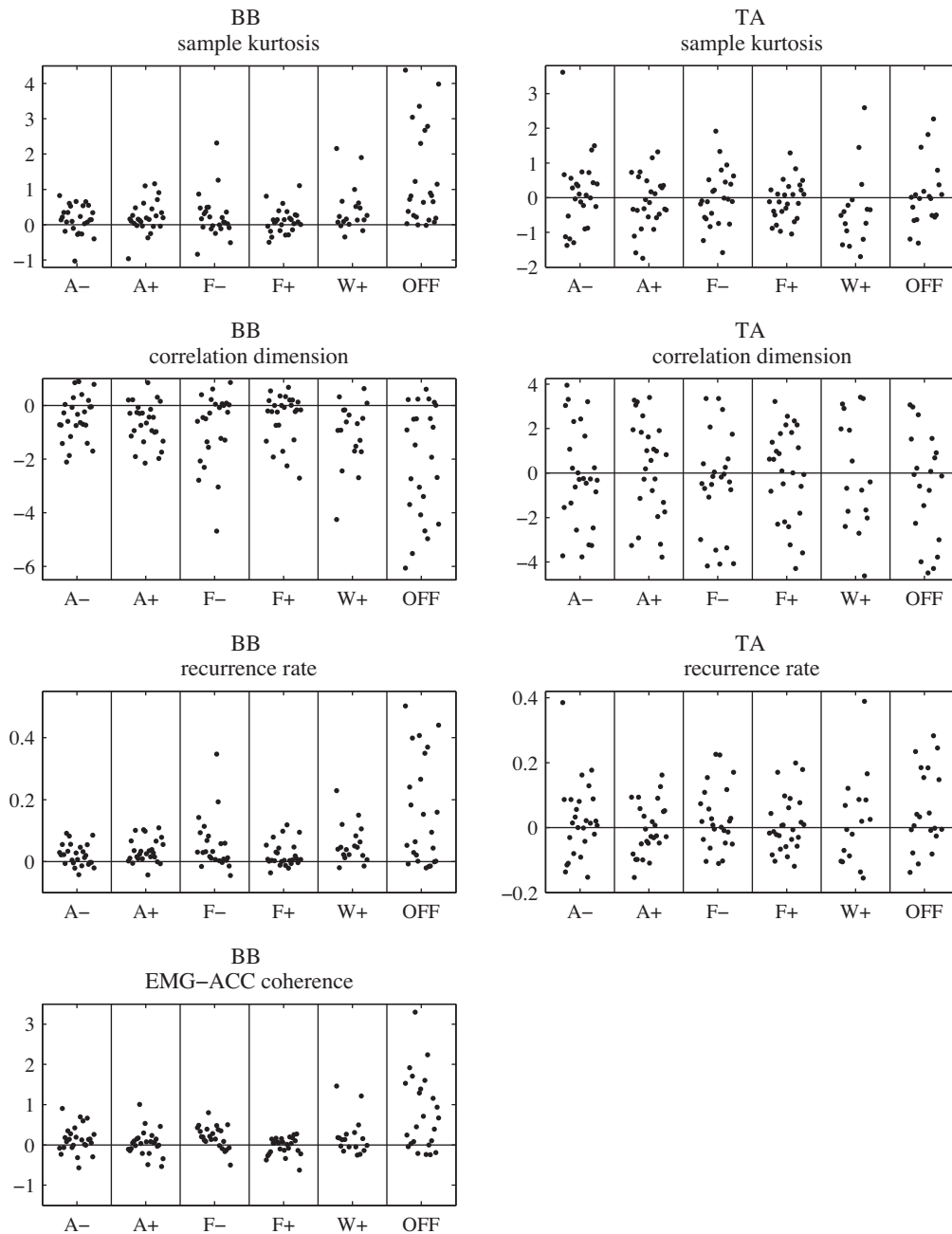


Fig. 4. Differences in the EMG parameter values with respect to state S0 for 13 PD patients (for each patient there is one right and one left side value) during each setting state of DBS treatment.

recurrence rate of BB EMG was significantly different (higher in most of cases) with the states A-, A+, F-, F+, W+ and OFF than with the state S0. Higher recurrence rate indicates higher number of recurring EMG structures, which is typical for PD (Rissanen et al., 2012). EMG-ACC coherence parameter was significantly different (higher in most of cases) with the states A-, F- and OFF than with the state S0. Higher coherence parameter is typical for PD (Rissanen et al., 2012). In the EMG features of TA, there were no significant differences with respect to state S0, which can be observed as spreading of variable value differences in the Fig. 4.

The correlations between EMG feature values and clinical scores (absolute values of rest tremor and rigidity) were quantified by using the Spearman's ρ -test. In the correlation analysis, all DBS conditions were analyzed together. The number of values for each

EMG feature and clinical score was $N = 160$ (because all patients could not be measured in all setting states). The correlation between the arm tremor score and EMG variables was weak but significant for kurtosis ($R = 0.241$, $p = 0.002$), for correlation dimension ($R = -0.336$, $p = 1.62 \times 10^{-5}$) and for recurrence rate ($R = 0.304$, $p = 1.03 \times 10^{-4}$). This implies that when the arm tremor increases, the BB EMGs tend to get more impulsive and regular and they tend to contain more recurrent structures. The correlation between the arm rigidity score and EMG variables was weak but significant for kurtosis ($R = 0.202$, $p = 0.011$) and for coherence parameter ($R = 0.334$, $p = 1.78 \times 10^{-5}$). This implies that when the arm rigidity increases, the BB EMGs tend to get more impulsive and coherent with the involuntary arm movement. The increase in

EMG impulsiveness, regularity, recurrence and coherence imply an increase in the level of motor unit synchronization in muscles. It has been suggested that during STN DBS and medication therapy, the motor units are fired more independently than without the therapy (Sturman et al., 2004). Between the leg tremor score and EMG variables, the correlation was weak but significant for kurtosis ($R = 0.368$, $p = 2.69 \times 10^{-6}$), for correlation dimension ($R = -0.311$, $p = 8.66 \times 10^{-5}$) and for recurrence rate ($R = 0.300$, $p = 1.59 \times 10^{-4}$). The correlation was not significant between the leg rigidity score and any of the EMG variables.

There was a group of three patients (Patients 4, 9 and 11) that did not have clinically observable tremor or rigidity with any of the DBS settings. These patients had received DBS treatment mainly because of difficult on–off-fluctuation in symptoms. In this subgroup of patients, there were differences between patients in the BB EMG kurtosis and coherence response to different DBS settings. The standard deviation of kurtosis between different DBS settings was $\sigma_k \leq 0.21$ for Patients 4 and 11 (right and left side arms), while it was twice as high $\sigma_k = 0.42$ for Patient 9 (right arm). The standard deviation of coherence variable was $\sigma_c = 1.20$ for Patient 9 (left arm), while it was only $\sigma_c \leq 0.15$ for Patients 4 and 11 (left and right side arms).

4. Discussion

Muscle activation of PD patients was studied here during different settings of DBS treatment by using several EMG signal features. The results showed that there are significant within-subject differences in the analyzed EMG signal features between different DBS settings for BB but not for TA muscles. The inter-subject variability of DBS effect was high in this study, which has been observed previously also by Kelly et al. (2010) and Rissanen et al. (2011).

DBS is effective in reducing motor symptoms in advanced PD although the action mechanisms of the treatment method still stay partly unclear. It is known that the efficacy of DBS depends on: the optimal electrode placement, selecting of best electrode contacts, and programming of stimulation pulse amplitude, frequency and width. It is possible that surface EMG could help in quantifying efficacy of DBS in PD and in adjusting the DBS-settings in some patients. However, it is not known, how different DBS parameters affect the muscle activation in PD. This study aimed to answer to that question. There have been few previous studies that have analyzed differences in the motor symptoms of PD between different settings of DBS by using kinematic measurements (O'Suilleabhain et al., 2003; Mera et al., 2011; Patel et al., 2009; Zwartjes et al., 2010). The number of patients in those studies has been quite low ($N \leq 6$) and surface EMG has not been analyzed. Because the movements are caused by muscle activation, it is possible that EMG could detect signs of PD although the motor symptoms could not be detected using kinematic measurements or subjective clinical evaluation.

The response of DBS treatment is thought to be U-shaped. That is, symptoms are usually improved when the electrical current or voltage is increased. However, occasionally symptoms may get worse if electrical current is further increased (Montgomery, 2010). The amplitude of electrical current is thought to be the most significant factor in reducing parkinsonian symptoms. When the stimulation amplitude is increased, the tremor and rigidity are usually relieved (Volkmann et al., 2002). In this study, the measurements were started with previously defined optimal parameter values. Stimulation amplitude was modified with small steps (± 0.3 V) responding to the typical adjustment session used in PD patients with previously implanted DBS. The stimulation frequency was kept inside the therapeutic frequency range (in most patients 130 ± 30 Hz). It was noticed that the impulsiveness and recurrent structure of EMG increased, and the complexity of EMG

decreased in most patients when the stimulation amplitude was increased or decreased and the stimulation frequency was decreased from previously defined optimal settings. It suggests that the surface EMG features could point to the optimal settings in most of patients, which could help the clinicians in arriving at the optimal DBS settings more quantitatively.

In this study, different results were obtained for BB than for TA muscles. In fact, it has been noticed recently that high-frequency DBS may affect differently the upper than the lower extremity muscle function. Systems Oscillations theory by Montgomery (2010) provides one explanation for that. The theory suggests that the basal ganglia-thalamo-cortical system consists of sets of nested neural oscillators that each have a fundamental frequency. Therapeutic DBS may resonate with specific oscillators leading to improvement of physiological information processing. This theory proposes that different motor functions have different carrier frequencies that are determined by human anatomy. For example, longer neural loops for lower limb motor control may operate at lower frequencies than shorter neural loops for upper limb motor control (Montgomery, 2010).

In this study, all patients were measured with medication on in order to guarantee that patients can tolerate the study. The medication on-state may have affected the results by decreasing differences between different DBS setting -states in some patients. It has been noticed earlier that both medication and DBS affect the surface EMG signals in PD but neither one of them is able to normalize the signals and muscle activation patterns (Sturman et al., 2004, 2007; Vaillancourt et al., 2004, 2006; Robichaud et al., 2002). It has been noticed that even with medication on, the DBS affects the agonist EMG burst characteristics during movement (Vaillancourt et al., 2004).

The patient group in this study was not restricted to such patients that respond to different DBS settings within a short time. Three patients did not respond to DBS with clinically observable motor symptoms (tremor and rigidity) in this study. These patients had received DBS treatment mainly because of difficult on–off-fluctuation in symptoms. Two out of these patients showed smaller changes in the surface EMG kurtosis and coherence of BB between different DBS setting -states than one patient. One could think, if a long-term EMG measurement could help in quantifying the muscle activation of patients with difficult on–off-fluctuation of symptoms. However, some of the DBS setting -states cause such adverse effects to the patients that the long-term measurement would not be ethically reasonable.

5. Conclusions

The results show that changes in the DBS-treatment parameters cause changes to the surface EMG signal features of BB during isometric muscle contraction. Although the correlation between the EMG features and clinical scores was weak, the EMG changes pointed to the optimal DBS settings in most of patients. It was noticed that, if the patient does not have differences in the tremor and rigidity score between different DBS settings, there can be differences in the surface EMG signal features. This indicates a need for further investigation on the DBS-induced muscle activation changes of these patients. In the signal features of TA, significant differences could not be observed in this study, which may describe different mechanisms of DBS in affecting the upper and lower limb muscle function. In general, surface EMG provides an objective estimate of the muscle activation changes due to DBS using quite simple measurement protocol. It can increase our understanding on the action mechanisms of DBS in PD. In the future, it may help in optimizing the DBS parameters in advanced PD in combination with other quantitative methods.

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