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The role of the sub-thalamic nucleus in the preparation of volitional movement termination in Parkinson's disease

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ABSTRACT

The sub-thalamic nucleus (STN) is relevant to the preparation of movement ignition but its role in movement termination is uncertain. Fourteen patients with Parkinson's disease (PD) received local field potentials (LFPs) recording at the left STN on the fourth day after deep brain stimulation surgery. They performed phasic and tonic movements of the right wrist extensor. Movement onset (Mon) and movement offset (Moff) of the electromyographic activities were used as triggers to determine an eight-second LFPs epoch for time-frequency analysis. Movement-related power changes were assessed by repeated measures analysis of variance with within-subject factors of Event (Mon and Moff), Period (ten time periods for phasic movement and six time periods for tonic movement), and Frequency (alpha, low-beta, and high-beta). There was significant triple interaction in both the phasic and tonic movements. By post-hoc analysis, high-beta event-related de-synchronization (ERD) appeared earlier (3 s prior to Mon) than those of low-beta and alpha for the Mon phasic movement. There was no alpha ERD for the Mon tonic movement. Alpha, low-beta, and high-beta ERD all appeared about 1 s prior to the Moff tonic movement. The current findings suggest that STN participates in the preparation of volitional movement termination but via a different mechanism from that in movement initiation. Unlike asynchronous ERD frequency bands present in movement initiation, a simultaneous ERD across wide frequency bands in STN may play a pivotal role in terminating volitional movement.

Introduction

Deep brain stimulation (DBS) of the sub-thalamic nucleus (STN) or the internal part of the globus pallidus has become a common surgical procedure nowadays for treatment of advanced Parkinson's disease (PD) or movement disorders (Alegre et al., 2010). The macro-electrodes used in DBS allow the recording of local field potentials (LFPs) and provide an opportunity for investigating the human basal ganglia (Chen et al., 2010).

STN is an important relay station of the cortico-basal ganglia circuitry (Alexander et al., 1990; Hamani et al., 2004; Montgomery, 2008) and its role in the execution or even in the preparation of movement is important. From the anatomic and physiologic points of view, STN is composed of three main parts: the limbic, associative, and motor regions. Among these, the motor region has tight connections with the primary motor cortex (layer V), supplementary motor area, pre-motor cortex, and globus pallidus (Hamani et al., 2004). Regarding STN activities in the pre-movement phase, recent articles reveal that event-related de-synchronization (ERD) at frequencies ≤ 35 Hz (for convenience here denoted as the beta band) in LFPs occurs prior to the onset of voluntary sEMG signals (Androulidakis et al., 2007; Kempf et al., 2007; Kuhn et al., 2004; Loukas and Brown, 2004). This implies that STN may not only be crucial for movement execution as previously believed but also for movement preparation.

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Moreover, from scalp electrode recordings, post-movement event-related synchronization (ERS) of beta activities has also been detected, although the implication of such phenomenon remains to be elucidated (Cassim et al., 2000). Movement preparation prior to movement onset (Mon) has been addressed in both scalp recordings of MRCP and from recent studies of STN in PD patients (Barrett et al., 1986; Dick et al., 1989; Ikeda et al., 1997; Kempf et al., 2007). However, there is no electro-physiologic information concerning the role of STN in the preparation of movement offset (Moff). When conducting brief movements like phasic wrist extension, the Mon and Moff times are too close to each other, which prevents separate analysis. This can be overcome by having the subjects sustain the movement long enough to allow for the separation of STN activities around the Mon and Moff.

This study examined the ERD and ERS of STN alpha and beta band frequencies during brief (phasic) and sustained (tonic) wrist extension movements by using the Mon and the Moff, respectively, as the trigger in PD patients on the 4th day after DBS. Since beta oscillation can be further classified into low-beta (13–20 Hz) and high-beta (20–35 Hz), and there may be different physiologic relevance of the two ranges of activities (Priori et al., 2002, 2004), power changes of these two beta bands along with voluntary hand movement were also examined. The aim was to provide a basic electro-physiologic framework for further investigating the inhibitory role of STN in PD patients.

Material and methods

Subjects and surgery

Fourteen PD patients scheduled for DBS were recruited and they provided informed consent. The hospital's Institutional Review Board Committee approved the study (DMR98-IRB-296). All right-handed PD patients (six females, eight males; mean age 61.14 ± 9.30 years; disease duration 6.25 ± 3.34 years, mean ± standard deviation) underwent bilateral implantation of DBS electrode in the STN. Their clinical details were summarized in Table 1.

The coordinates for implantation of the DBS electrode were calculated and measured based on magnetic resonance imaging (MRI). Intended coordinates for target points were localized in the STN, at 11–13 mm lateral from the midline and 2–3 mm posterior to the mid-commissural point. The depth of implantation, depending on each patient, was 4–6 mm below the anterior commissural–posterior commissural line, and the loci of STN were confirmed with microelectrode recording intra-operatively. The DBS electrode used was model 3389-40 (Medtronic, Inc., Minneapolis, USA) with four platinum iridium cylindrical contacts (1.27 mm diameter and 1.5 mm length) spaced 0.5 mm from each other. Four contacts were denominated 0, 1, 2, and 3 beginning with the most caudal location. Recordings of STN LFPs were conducted on the 4th day after the DBS electrode implantation. Patients were examined during their "off" period by overnight withdrawal of the anti-parkinsonian agents.

Paradigm

Patients were seated comfortably in an armchair with the right forearm and wrist placed flat on the armrest. They performed two different wrist extension–relaxation movements. In the phasic movement, patients rapidly lifted and dropped their right wrist (Fig. 1A) as previously described (Lu et al., 2008, 2010). In the tonic movement, patients dorsiflexed the right palm and sustained the posture for 7 s before placing the palm back into the original flat position (Fig. 1B). The time interval between each consecutive movement was about 7 s. For each type of movement, four experimental blocks were conducted, with each block lasting for 4 min with a one-minute break in between. Patients were asked to focus on a red button 1.5 m in front of their eyes during the performance of the movements.

Signal recordings

The STN LFPs were recorded bipolarly from the four adjacent contacts of each DBS electrode (contact pairs 0–1, 1–2, and 2–3) simultaneously. The mean and standard deviation (SD) of the power spectral density in the 13–35 Hz band in each nucleus were considered to obtain the threshold for significant spectral peaks (95% confidence interval, CI: mean ± 1.97 SD). Power spectral density values in the beta band exceeding this threshold were considered a significant peak (Giannicola et al., 2010). The contact pair with the highest beta power was selected for the ongoing experiment and signal processing.

The STN LFPs were sampled at a rate of 1 kHz per channel and amplified (×100,000) (Digitimer 360, Welwyn Garden City, Hertfordshire, England) with a bandpass filter of 1–250 Hz, digitized by an analog-digital convert (CED power 1401, Cambridge Electronic Design Ltd., UK). The signals were then recorded and monitored online using Spike2 software (Cambridge Electronic Design Ltd., UK).

The multi-channel surface electromyogram (sEMG) signals from the right extensor carpi radialis (ECR) and flexor carpi radialis (FCR) muscles were recorded through a pair of Ag–AgCl surface electrodes to monitor motor activity during the movement. The sEMG signal was amplified (×400), filtered at 10 Hz–1 kHz, sampled at 2 kHz, and recorded.

Table 1
Demographic data of the study patients with Parkinson's disease.

Subject	Age (year)	Sex	Disease duration (year)	Pre-DBS challenge improvement rate	Motor UPDRS drug off		Levodopa equivalent dose/day	Target coordinates[a] (Left STN)			Contact pairs (for signal processing)
					DBS on	DBS off		Lat	A–P	Ver	
1	61	M	5	14	24	43	750 mg	11	2.5	6	12
2	54	M	3	20	59	64	375 mg	11.5	2	4	23
3	67	M	10	61	56	64	750 mg	11	4	4.5	12
4	49	F	6	72	29	64	1042 mg	11.5	3	4	12
5	68	F	5	53	16	23	300 mg	11.5	3.5	4.5	12
6	55	F	8.5	60	26	33	625 mg	10.5	2.5	4	12
7	55	M	5	68	33	37	1219 mg	11.5	3	4	01
8	67	M	8	73	19	28	675 mg	11.5	3	4	01
9	75	F	7	39	33	39	613 mg	11	4	6	12
10	71	M	4	18	15	20	200 mg	11.5	4	4	01
11	50	M	2	40	13	25	613 mg	11.5	4	5.5	12
12	50	M	12	40	29	62	700 mg	11.5	4	4	12
13	75	F	7	9	35	Not available	300 mg	11	4	5	01
14	59	F	11	40	24	49	300 mg	11.5	3.5	6.5	12

[a] Each patient's target coordinates accorded to the anterior commissural–posterior commissural (AC–PC) line and mid-commissural point (MCP); Lat (Lateral, relative to midline); A–P (relative to MCP); Ver (Vertical, relative to AC–PC plane).

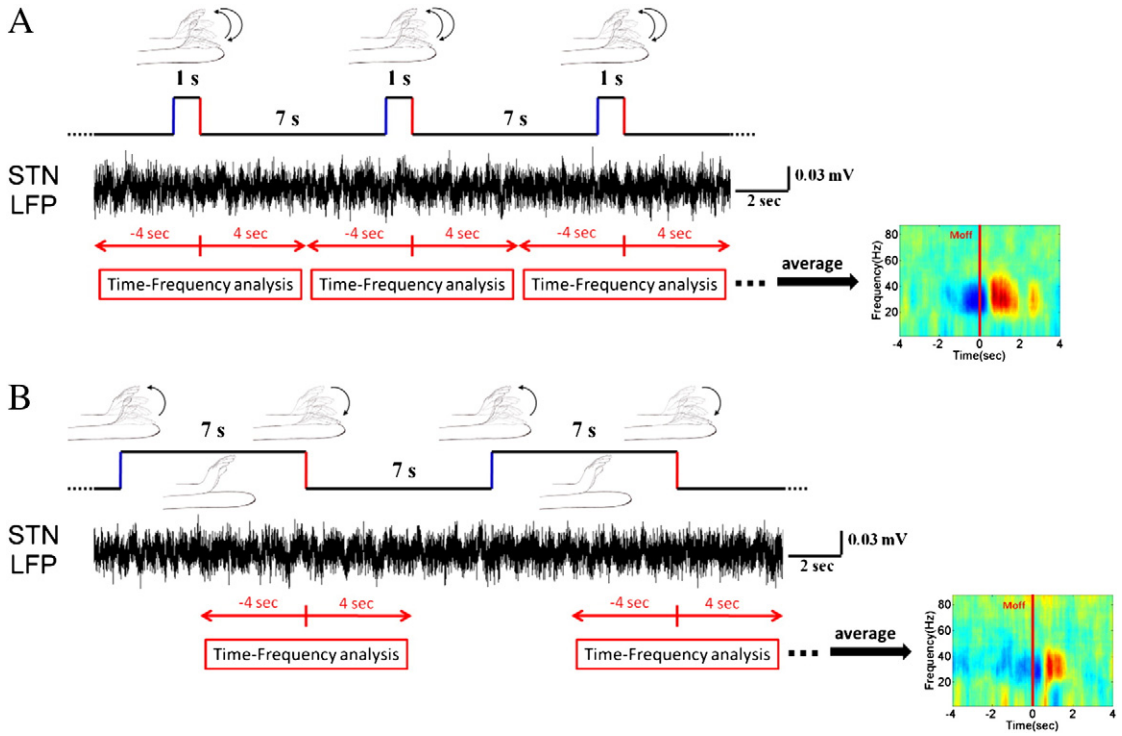

Fig. 1. Overview of the sEMG and sub-thalamic nucleus (STN) local field potentials (LFPs) analysis. (A) In the phasic movement, patients rapidly lifted and then dropped their right wrist. (B) In the tonic movement, patients rapidly dorsiflexed the right palm and sustained the posture for 7 s before letting the palm go into the original flat position. The figures showed examples of the signal processing using Moff (red line) as the trigger in both types of movement. sEMG activities were analyzed using the burst detection algorithm to determine the Moff automatically. The STN LFPs were then segmented into 8-second trails according to the Moff, with trail analyzed by time-frequency algorithm. The averaged time-frequency presented the power spectra in the timeline of movement. The analysis procedures for Mon (blue line) were the same.

Data analysis

The sEMG signal and STN LFPs were analyzed (Fig. 1). A burst detection algorithm (BDA) was developed to determine the transition points of movement representing the time points of Mon and Moff (see Appendix A). The STN LFPs were segmented according to the Mon and Moff of the wrist extensor sEMG bursts. These movement trials were then analyzed by time-frequency (TF) algorithm.

Time-frequency power analysis

The TF algorithm presented a variant of frequency in the timeline of movement using the discrete Fourier transformation (Halliday et al., 1995). The STN LFPs were divided into sections with a duration block of 256 data points and 1024 frequency resolutions. The spectra were estimated by calculating the median across sections overlapping in a constant window, which was shifted until the whole sequence was analyzed. The STN LFPs were analyzed over a frequency range of 1–85 Hz.

Movement-related power was analyzed for each movement trial with respect to both the Mon and Moff. With respect to the Mon, 8 s time durations ranging from 4 s before to 4 s after the Mon were extracted for both movements. With respect to the Moff, 8 s time durations (4 s before and after the Moff) were extracted for both movements. Movement-related power was then averaged across trials and displayed as percentage values in relation to the baseline period, which was defined as 100%, ranging from 3.5 s to 4 s before the Mon.

Statistics

In order to normalize the distribution of movement-related oscillatory activity between patients, movement-related power changes of all individual patients were analyzed using the Wilcoxon's signed-rank test, which tested the median in each time-frequency bin of the average trial for change different from zero. The results of spectral matrices were displayed as its Z-score value, which was threshold at two-sided p value of 0.01.

The main focus of the statistical analysis was to compare movement-related power changes in three broad frequencies during the phasic and tonic movements. Movement-related power changes were analyzed within the alpha band (7–13 Hz), low-beta band (13–20 Hz), and high-beta band (20–35 Hz) that were considered to maintain the main features of the spectral matrices (Foffani et al., 2005; Kuhn et al., 2006; Priori et al., 2004). The time course of the two movements was assessed by averaging power changes within the specific frequency band in defined time periods.

The periods of interest crossed the movement-event where the interesting segments were selected in ten consecutive periods (Periods 1–10) of 0.7 s, starting from −3.5 s prior to the phasic (^{P}Period) Mon/Moff and in six consecutive periods (Periods 1–6) of 1 s, starting from −3 s prior to the tonic (^{T}Period) Moff/Mon. In each frequency band, movement-related power changes were different from those of baseline in the respective periods assessed by *post hoc* Wilcoxon's signed-rank tests.

ANOVA was performed to assess power changes in the STN LFP (IBM SPSS Statistics 18, IBM Corp., USA). Movement-related power changes in the respective frequency bands were assessed by repeated measures ANOVA with within subject factors of Event (two levels: Mon and Moff), Period (ten levels: ^{P}Periods 1–10 for phasic movement, six levels: ^{T}Periods 1–6 for tonic movement), and Frequency (three levels: alpha, low-beta, and high-beta bands). If the data had no sphericity as assessed by Mauchly's sphericity test, a Greenhous–Geisser correction was performed to adjust the degrees of freedom. Relevant differences in movement-related power changes between time-frequency regions of interest were evaluated by *post hoc* two-tailed paired Student's t-tests. The mean values (±standard deviation, SD) were described in the text.

Results

The demographic data of the 14 subjects were shown in Table 1. The average UPDRS improvement to levodopa challenge test was 41.9% prior to surgery. The number of movement trials for analysis per subject was 121 ± 13.58 for the phasic movement and 58 ± 4.79 for the tonic movement. The mean duration of the sEMG burst in the phasic and tonic movements was 0.96 ± 0.04 s and 7.19 ± 0.34 s, respectively. The ERD or ERS was defined as the percentage power suppression (<100%) or increase (>100%), respectively, compared to the baseline period 4 to 3.5 s prior to the Mon.

Movement-related power change in the phasic and tonic movements

Movement-related power changes in both movements (phasic and tonic) with both time events (Mon and Moff) were shown in Figs. 2 and 3. Spectral changes at frequencies between 1 and 85 Hz were presented in a time frame ranging from 4 s before to 4 s after the Mon/Moff and were averaged across the 14 patients. Results were expressed as percentage power compared to the baseline period from −4 s to −3.5 s prior to the Mon.

Change of oscillatory activity during both movements in relation to the Mon

The square of sEMG signals recorded from the right ECR and FCR muscles and averaged across the 14 patients during the voluntarily phasic and tonic movements was shown in Figs. 2A and B, respectively. The Mon was defined by using BDA to detect the transitions of sEMG activities recorded from the right wrist ECR. The main feature of movement-related power changes in the frequency range of 7–40 Hz in the phasic and tonic movements was shown in Figs. 2C and D, respectively. Pre-movement ERD was found from ~2 s before to ~1 s after the Mon in both movements.

Post-movement ERS immediately occurred around ~1 s after to the Mon in the phasic movement (Fig. 2C) but not in the Mon tonic movement (Fig. 2D). The corresponding Z-scores were assessed by Wilcoxon's signed-rank test at threshold p value of 0.01 (Figs. 2E and F). The variability of power changes was reflected in the power and Z-score matrices where an increase in Z-scores showed significant change across patients for frequencies between 7 Hz and 40 Hz.

Change of oscillatory activity during both movements in relation to the Moff

The averaged square of sEMG signals recorded from the right wrist extensors during the voluntarily phasic and tonic movements with respect to the Moff was shown in Figs. 3A and B, respectively. The

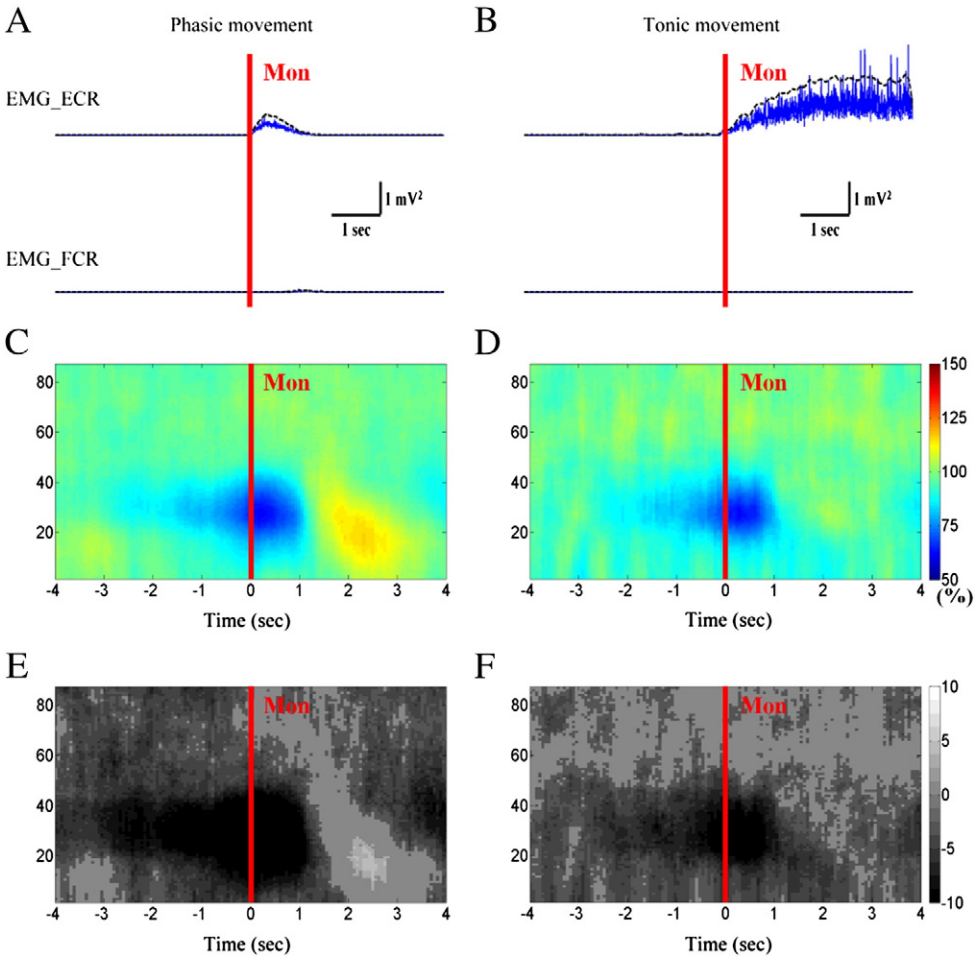

Fig. 2. (A–B) The average surface electromyography (sEMG) from the right extensor carpi radialis (ECR) and flexor carpi radialis (FCR) muscles for the Mon during the voluntarily phasic and tonic movements. The blue solid line and black dotted line indicated the square of muscle activity and the smoothening envelope using BDA, respectively. The vertical red bars denoted the Mon defined by the earliest change in the sEMG of ECR. (C–D) The power changes of oscillatory activity in relation to the Mon during the voluntarily phasic and tonic movements averaged across patients. The color changes represented power increases (>100%) and suppressions (<100%) expressed as percentages of the baseline period (from 4 to 3.5 s prior to the Mon). (E–F) Corresponding Z-scores were determined by Wilcoxon's signed-rank test at a threshold of $p = 0.01$. The ERDs appeared from −1.5 s to 1 s in relation to the Mon of the two movements, and occurred at ~1 s after the Mon of the phasic movement.

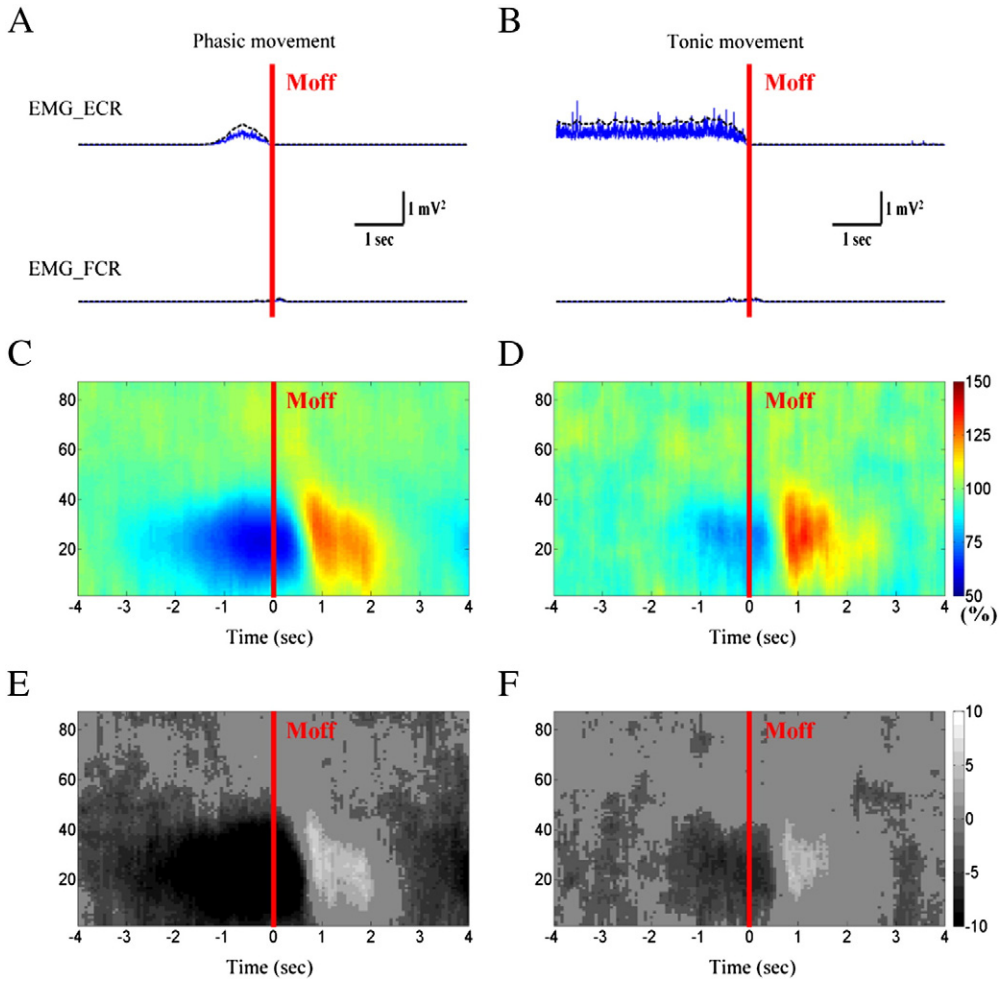

Fig. 3. (A–B) The average surface electromyography (sEMG) from the right extensor carpi radialis (ECR) and flexor carpi radialis (FCR) muscles for the Moff during the voluntarily phasic and tonic movements. The blue solid line and black dotted line showed the square of muscle activity and the smoothening envelope using BDA, respectively. The vertical red bars denoted the Moff determined according to the sEMG of the right ECR in the respective movement. (C–D) The power changes of oscillatory activity with respect to the Moff of the voluntarily phasic and tonic movements averaged across patients. The color changes represented power increases (>100%) and suppressions (<100%) expressed as percentages of the baseline period from −4 to −3.5 s prior to the Mon. (E–F) Corresponding Z-scores determined according to Wilcoxon's signed-rank test at threshold of $p = 0.01$. The ERD appeared ~2.5 s and ~1 s before the Moff in the phasic and tonic movements, respectively. The ERS occurred within the 7–40 Hz frequency range ~0.8 s after the Moff in the two movements.

Moff was defined using BDA to detect the relaxation in sEMG activities of the ECR muscle. The main features of movement-related power changes found in the frequency range of 7–40 Hz were shown in Figs. 3C and D. The pre-movement ERD over the frequency range of 7–40 Hz was prolonged and occurred earlier in the phasic movement, which persisted until ~0.8 s after the Moff. The post-movement ERS was greater in the phasic than in the tonic movements and appeared ~0.8 s posterior to the Moff. The variability of power changes was also reflected in the power and Z-score matrices, where an increase in Z-scores showed significant changes across patients at frequencies between 7 and 40 Hz (Figs. 3E and F).

Spectral changes of phasic and tonic movements in alpha, low-beta and high-beta bands

Time course of spectral changes in each frequency band

The power spectra between the baseline period and all time periods in each frequency band were tested by *post hoc* Wilcoxon's signed-rank test to analyze the time course of power spectral changes during the phasic and tonic movements.

The power in each frequency band was significantly different from baseline in most of the time periods except in ^{P}Periods 1, 7 and 10 for the Mon phasic movement. (Table 2). For the Moff phasic movement, there was a significant power change compared to the baseline period in alpha (^{P}Period 5), low-beta (^{P}Periods 4, 5, 6, and 8) and high-beta bands (^{P}Periods 2, 4, 5, 6, 7, and 8) (Table 2).

The power change in low-beta and low-beta bands compared to the baseline period was significantly different in ^{T}Periods 3 and 4 for the Mon tonic movement (Table 2). For the Moff tonic movement, there was a significant alpha power oscillation compared to the baseline period in ^{T}Periods 3 and 5. The power change in low-beta and high-beta bands compared to the baseline period was significantly different in ^{T}Periods 3, 4, and 5 for the Moff tonic movement (Table 2).

Movement-related power changes in the respective frequency bands in different time-frequency regions (periods) (Table 3; Figs. 4 and 5)

Phasic movement. There was a significant main effect for Frequency ($F = 9.886$, $p = 0.007$) and ^{P}Period ($F = 49.810$, $p < 0.001$), as well as a significant interaction between Frequency and ^{P}Period ($F = 22.197$, $p < 0.001$), and Event and ^{P}Period ($F = 8.875$, $p < 0.001$). The interaction among Event, ^{P}Period, and Frequency was also significant ($F = 3.980$, $p = 0.005$).

Tonic movement. There was significant main effect for Event ($F = 15.655$, $p = 0.002$) and ^{T}Period ($F = 23.938$, $p < 0.001$), as well

Table 2
The *p* value of power changes in terms of baseline period in each frequency band, by Wilcoxon's signed-rank test.

Phasic movement		^{P}Period 1	^{P}Period 2	^{P}Period 3	^{P}Period 4	^{P}Period 5	^{P}Period 6	^{P}Period 7	^{P}Period 8	^{P}Period 9	^{P}Period 10
Mon	Alpha	0.715	0.020	0.002	0.007	<0.001	<0.001	0.058	0.042	0.035	0.296
	Low–beta	0.241	0.009	<0.001	0.002	<0.001	<0.001	0.035	0.009	0.012	0.241
	High–beta	0.030	0.013	0.002	<0.001	<0.001	<0.001	0.670	0.002	0.035	0.463
Moff	Alpha	0.626	0.194	0.296	0.135	0.007	0.091	0.855	0.153	0.502	0.358
	Low–beta	0.542	0.079	0.135	0.009	0.002	0.013	0.119	0.035	0.241	0.296
	High–beta	0.268	0.042	0.068	0.001	<0.001	0.042	0.002	0.042	0.903	0.217

Tonic movement		^{T}Period 1	^{T}Period 2	^{T}Period 3	^{T}Period 4	^{T}Period 5	^{T}Period 6
Mon	Alpha	0.952	0.502	0.358	0.296	0.296	0.715
	Low–beta	0.808	0.173	0.001	0.002	0.241	0.268
	High–beta	0.296	0.035	<0.001	<0.001	0.808	0.049
Moff	Alpha	0.391	0.855	0.003	0.068	0.007	0.153
	Low–beta	0.326	0.194	<0.001	0.041	<0.001	0.142
	High–beta	0.358	0.119	<0.001	0.049	<0.001	0.142

The baseline period was defined as −4 to −3.5 s in relation to the Mon.
Gray shadow $p<0.05$, boldface $p<0.01$.
^{P}Period, period of phasic movement; ^{T}Period, period of tonic movement.

as significant interaction between Frequency and ^{T}Period ($F=9.548$, $p<0.001$) and Event and ^{T}Period ($F=14.339$, $p<0.001$). The interaction among the three factors was also significant ($F=3.984$, $p=0.016$).

Post hoc analysis between frequency bands for two Events (Mon and Moff) during Periods

Post hoc two-tailed paired Student's t-tests showed a significant difference in the Mon phasic movement between frequency bands (alpha vs. low-beta, alpha vs. high-beta, and low-beta vs. high-beta; $p<0.05$) during ^{P}Periods 4, 5, and 6 (Table 3).

For the Moff phasic movement, the alpha band significantly differed from the low-beta band in ^{P}Periods 1 ($p=0.047$), 2 ($p=0.008$), 3 ($p<0.001$), 4 ($p<0.001$), 5 ($p<0.001$), 6 ($p<0.001$), and 7 ($p=0.015$), as well as the high-beta band in ^{P}Periods 3 ($p=0.015$), 4 ($p<0.001$), 5 ($p<0.001$), 6($p=0.028$), and ^{P}Period 7 ($p<0.001$). There was a significant difference between the low-beta band and high-beta bands in ^{P}Periods 3 ($p=0.001$), 4 ($p=0.004$), 5 ($p=0.001$), 7 ($p<0.001$), and 9 ($p=0.021$) for the Moff phasic movement (Table 3).

There was a significant difference between frequency bands in the Mon tonic movement (alpha vs. low-beta, alpha vs. high-beta, and low-beta vs. high-beta; $p<0.01$) in ^{T}Periods 3 and 4 (Table 3).

For the Moff tonic movement, there was a significant difference between the alpha and high beta bands in ^{T}Period 2 ($p=0.048$), and significant differences between the alpha and low beta bands in ^{T}Periods 3 ($p=0.018$), 5 ($p<0.001$), and 6 ($p=0.033$) (Table 3).

Discussion

The feed forward role of STN in voluntary movement initiation has been illustrated in PD patients receiving deep brain stimulation (Kempf et al., 2007; Kuhn et al., 2004; Loukas and Brown, 2004). It is generally believed that beta range ERD will occur prior to the onset of voluntary movement. A similar phenomenon has been illustrated in scalp encephalographic recording (Cassim et al., 2000). Once a voluntary movement begins, it continues till termination. Thus, the neural function of movement termination warrants investigation. The main finding of the current STN recording is that different motion modes (Event) have different impacts on the studied frequency bands (Frequency) in different time periods (Period) relevant to either the start or termination of volitional movements.

Feed forward role of STN in movement termination — clues from different ERD patterns between Moff phasic and tonic movements

In the phasic movement, the sEMG includes at least three components: movement ignition, execution, and movement termination. Power change in the phasic movement using Moff as the trigger corresponds to STN activities responsible for all of these components, while the most front part of beta ERD represents movement ignition.

Table 3
Comparison of spectral changes between time-frequency regions of interest, by *post hoc* two-tailed paired Student's *t*-test.

Phasic movement		^{P}Period 1	^{P}Period 2	^{P}Period 3	^{P}Period 4	^{P}Period 5	^{P}Period 6	^{P}Period 7	^{P}Period 8	^{P}Period 9	^{P}Period 10
Mon	α vs. Lβ	0.636	0.508	0.009	0.010	<0.001	<0.001	0.339	<0.001	0.232	0.261
	α vs. Hβ	0.033	0.211	0.051	0.018	0.001	<0.001	0.016	0.002	0.041	0.075
	Lβ vs. Hβ	0.018	0.156	0.261	0.082	0.043	0.004	0.003	0.227	<0.001	0.001
Moff	α vs. Lβ	0.047	0.008	0.004	<0.001	<0.001	<0.001	0.015	0.139	0.975	0.415
	α vs. Hβ	0.083	0.064	0.015	<0.001	<0.001	0.028	<0.001	0.403	0.051	0.153
	Lβ vs. Hβ	0.146	0.240	0.001	0.004	0.001	0.387	<0.001	0.864	0.021	0.140

Tonic movement		^{T}Period 1	^{T}Period 2	^{T}Period 3	^{T}Period 4	^{T}Period 5	^{T}Period 6
Mon	α vs. Lβ	0.479	0.158	<0.001	<0.001	0.758	0.153
	α vs. Hβ	0.250	0.060	0.001	<0.001	0.084	0.077
	Lβ vs. Hβ	0.242	0.064	0.007	0.004	0.041	0.066
Moff	α vs. Lβ	0.705	0.078	0.018	0.571	<0.001	0.033
	α vs. Hβ	0.822	0.048	0.123	0.288	0.132	0.203
	Lβ vs. Hβ	0.513	0.105	0.554	0.240	0.447	0.837

Gray shadow $p<0.05$; boldface $p<0.01$;
^{P}Period, period of phasic movement; ^{T}Period, period of tonic movement.

Compared to that of the Moff phasic movement, the power of beta ERD, including low- and high-beta, is less of the Moff tonic movement (Fig. 5). This may be due to the elimination of the ignition and execution components of beta ERD in the Moff phasic movement.

On the other hand, an additive effect of beta power changes accumulating from different movement sub-components in the phasic movement has also been suggested. The beta ERD of the Moff tonic movement is not the extension of beta ERD arising from the Mon tonic movement because it commences near the Moff of tonic movement and there is an interruption between the preceding Mon tonic beta ERD and Moff tonic ERD (Figs. 2 and 3). There should be caution that relaxing the wrist from tonic extension may trigger forearm flexor muscle activity, to which the aforementioned phenomenon may be linked. Nonetheless, this possibility is unlikely since only trivial FCR EMG signals, in contrast to obvious forearm extensor EMG activities, are observed after the average (Fig. 3). Thus, the beta ERD of tonic movement termination comes mainly from the termination of wrist extensor activities.

In order to further confirm if beta ERD is caused by active movement termination in the Moff tonic, passive tonic movement in one subject was conducted. In completely different patterns from those of active tonic movement, the time locked beta ERD changes were disrupted by either the Mon or Moff as the trigger in the passive tonic movement (data not shown). In previous scalp recording movement-related cortical potential studies, two mechanisms have been proposed for the phase prior to movement termination (Rothwell et al., 1998; Terada et al., 1995). The "withdrawal mechanism" (Rothwell et al., 1998) posits the explanation that movement termination is due to the "shutting off" of the activated neural circuitry, whereas the "inhibition mechanism" (Terada et al., 1995) suggests that inhibitory neural structures are activated to terminate the voluntary movement. If the "withdrawal" hypothesis is correct, the electrophysiologic manifestations of the Mon tonic should just disappear or be quench as compared to those of Moff tonic. On the other hand, novel phenomenon should be turned out prior to Moff tonic in contrast with Mon tonic if the "inhibitory mechanism" is more appropriate. In the current study, the obviously different beta ERD patterns between Mon tonic and Moff tonic suggest that novel processes relevant to movement termination are elicited in STN. The findings gathered with different manifestation of alpha ERD (Table 2; Figs. 4 and 5) between Mon tonic and Moff tonic further strengthens the STN feed forward role in movement termination. It has been illustrated that putamen neurons are also crucial for feed forward or programming function for target acquisition in primates (Montgomery and Buchholz, 1991). The tight connection between STN and striatum (Moran et al., 2011) warrants future studies on the interaction of LFPs of these structures in movement termination.

The impact of different movement modes on different frequency bands (alpha, low and high beta)

The STN oscillatory activities contain a wide range of frequencies. It is necessary to know whether the aforementioned phenomenon occurs in respect to the beta band or if it is just a common phenomenon prior to movement termination. Since the PD patients in the current study have been examined during their "off" states, the focus is mainly on frequencies below the beta frequencies instead of high frequency changes that appear during "on" states (Chen et al., 2007; Eusebio et al., 2008). In addition, the beta oscillation is further classified into low- and high-beta (Priori et al., 2002, 2004) to examine if they are affected differently by voluntary hand movement.

Ignition of different movements may require different strategies in STN

In the Mon phasic movement, high-beta ERD appears earlier (from ^{P}Period 1, around −3 s prior to EMG onset) compared to low-beta and alpha, with a decrescendo amplitude trend towards alpha (Table 2; Fig. 4). The frequency main effect of Mon phasic movement (Table 3) illustrates the evolution pattern of significant differences among the three frequencies and confirms the above findings. The pattern is different from that of Mon tonic movement, in which no alpha ERD is observed with the apparent presence of low- and high-beta event-related patterns. The ERD starts to rebound to form ERS just after EMG onset in the Mon phasic movement (Table 2; Figs. 2 and 4).

In the Mon tonic movement, there is only trivial high-beta ERS and no alpha and low-beta ERS (Table 2; Fig. 4). The results imply that when conducting different movements, the STN strategies are different. High-beta is most crucial for conduction irrespective of Mon phasic or tonic movements as previously reported (Priori et al., 2002). There are no event-related changes of alpha oscillations in the Mon tonic movement, suggesting that alpha activities are less important for initiating sustained volitional posture. However, since the alpha ERD and ERS of Mon phasic movement may be contaminated by activities coming from the Moff phasic movement, the difference of alpha power changes between Mon phasic and tonic movements may be caused by an incomplete segregation of Mon and Moff in the phasic movement.

The less or absent ERS after Mon tonic may also imply that STN is less engaged in maintaining a tonic posture than conducting a phasic movement. Thus, there is less idling or deactivation required in the

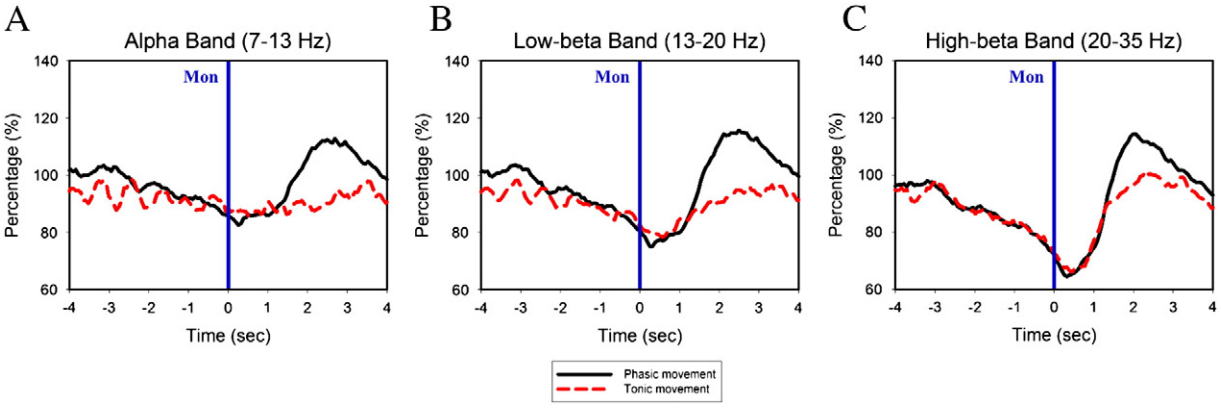

Fig. 4. Average power changes (n = 14) with respect to the Mon during the phasic movement (black solid lines) and tonic movement (red dash lines) were shown in the (A) alpha band (7–13 Hz), (B) low-beta band, (13–20 Hz), and (C) high-beta band (20–35 Hz). The figures showed the curve of averaged power changes 4 s before and after the Mon.

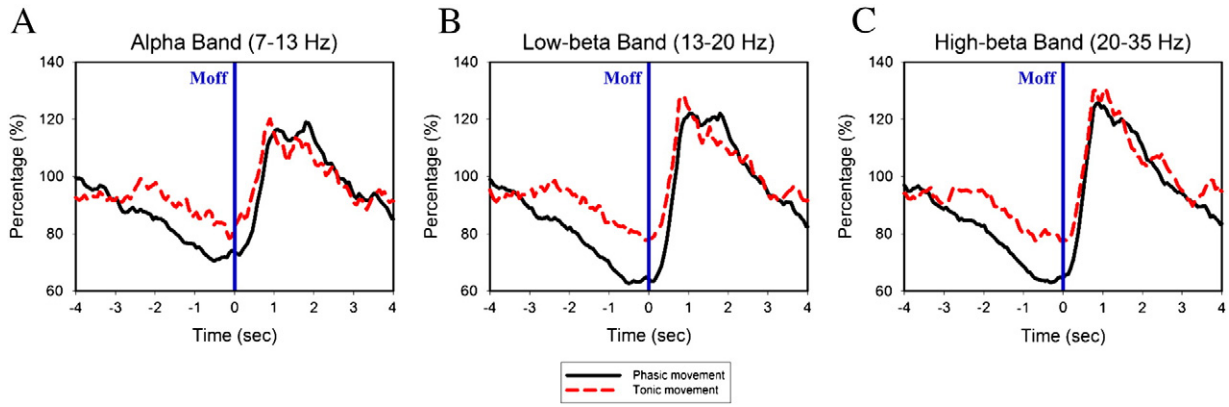

Fig. 5. Average power changes (n = 14) with respect to the Moff during the phasic movement (black solid lines) and tonic movement (red dash lines) were shown in the (A) alpha band (7–13 Hz), (B) low-beta band (13–20 Hz), and (C) high-beta band (20–35 Hz). The figures showed the curve of averaged power changes 4 s before and after the Moff.

former task than in the latter as seen in scalp recording (Cassim et al., 2000).

Movement termination requires simultaneous de-synchronization of different frequency bands (alpha, low-beta and high-beta)

In Moff tonic movement, the ERD of low- and high-beta power begins to appear at ^{T}Period 3 (1 s prior to Moff) with trough levels about 87.1 ± 7.4% for low-beta and 85.6 ± 7.7% for high-beta compared to baseline. The discrepancy between high- and low-beta, as seen in conducting either Mon tonic or phasic movements, perishes when conducting Moff tonic movement (Table 3; Figs. 4 and 5). Unlike that of Mon tonic movement, the alpha ERD and ERS becomes evident in the Moff tonic movement (Table 2; Fig. 5). The current results suggests that alpha ERD, in addition to low- and high-beta ERD, is important for generating tonic movement termination. The finding is a bit different from that of scalp recording event-related changes, which illustrates that only beta ERD/ERS is present for both the initiation and termination of a tonic movement (Cassim et al., 2000).

To date, this is the first illustration of alpha ERD and ERS developing in the termination of tonic movement, thereby extending the previous concept that alpha ERD in STN may be more relevant to cognitive task conduction or emotional processing but less relevant to pure motor action in STN (Kuhn et al., 2005a, 2005b; Rektor et al., 2009).

Another difference between tonic movement ignition and termination is that the alpha, low-beta, and high-beta ERD and ERS behave similarly, both temporarily and spatially, in terminating tonic movement (Table 2; Fig. 5). The ERD of the three frequency bands start simultaneously from ^{T}Period 3 (1 s prior to Moff). This is a bit later than that of high-beta ERD but the same as low-beta in the Mon tonic movement (Table 2). In physics terms, there is a serial relationship between high-beta and low-beta ERD and ERS in performing Mon tonic movement. Their relationship becomes more parallel in conducting Moff tonic movement. The study in Bereitschaftspotential suggests that the preparation of movement ignition may require less effort than that of movement termination (Terada et al., 1995). The current findings in STN may imply that wider frequency bands or neurons may be recruited at about the same time to shut off a tonic movement. In other words, more effort may be required to terminate a movement than to initiate it. However, initiating a movement may require an earlier arousal of high-beta ERD. The reason for this remains to be elucidated. In a previous study, high beta ERD in STN is more relevant to phasic voluntary movement and responses of low-beta are variable (Priori et al., 2002). The current findings are partially consistent with such findings and suggest that high-beta ERD is crucial for movement preparation.

The disappearance of the discrepancy among high- and low-beta bands in Moff tonic movement suggests that they are both necessary for movement termination. Another implication is that movement initiation and termination may involve different neuronal populations and culminate in different oscillation patterns for the two reverse movements. Priori et al. have illustrated that high-beta activities may abide within STN and be more relevant to the indirect pathway, while low-beta activities are relevant to the direct pathway of the cortico-basal ganglia circuitry (Priori et al., 2002). Based on their findings, the current results imply that movement initiation may rely more on the indirect pathway while movement termination may require the functional coordination between the two pathways. This may be the reason why high-beta event-related changes lead low-beta changes in Mon tonic but occur about the same time in Moff tonic movement.

The implication of ERS in STN

It is intriguing to observe that ERS of the studied frequency bands is not present in the Mon tonic movement but present in all other three conditions. The phenomenon is especially true during the Moff phasic and tonic movements. Post-movement beta ERS can be modulated by the application of levodopa and the presence of ERS may reflect partially the functional status of the basal ganglia (Priori et al., 2002). Higher post-movement ERS may be engaged in circuitry activities required for generating the next movement. This may be relevant to bradykinesia in PD patients (Priori et al., 2002). The absence of post-movement ERS in Mon tonic movement may be due to the absent or less requirement of engagement to generate the next movement in sustaining a posture. The current study does not detect any ERS in gamma range around movement onset as observed in other studies (Androulidakis et al., 2007; Kempf et al., 2007). Gamma ERS can usually be enhanced by the application of levodopa and is believed to reflect a physiologic processing status of PD patients (Androulidakis et al., 2007). It has been shown that discharge neurons in the STN tend to be locked to beta activities in the LFP (Kuhn et al., 2005a, 2005b; Levy et al., 2002) while the firing of neurons in both the upper STN and the bordering zona incerta tends to be locked to gamma activity in the LFP (Trottenberg et al., 2006). The current study selected the contact pair with the most robust beta activity for recording and this may distance the recording site from the gamma sources. This may be one of the reasons for the discrepancy between the current and previous studies (Aron and Poldrack, 2006). Since there are connections between STN and other cortical and basal ganglia areas, the influence of the current findings by signals conveying from these regions to STN remains to be elucidated.

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Appendix A. The Burst Detection Algorithm (BDA)

The Burst Detection Algorithm (BDA) is an automatic method for detecting the occurrence and completion time of movement by recorded surface electromyogram (sEMG). Together with the reduction ability of high-frequency noise and constant bias, BDA transforms sEMG into signal powers to further determine the transition point based on two horizontal thresholds. The detailed procedure of BDA is as follows:

Appendix A.1. Step 1. Normalizing signals

One of the factors that may influence the automatic computing processing is the mean value of sEMG, which is distinct among different patients. To get the normalized input V_n for automatic detection, sEMG signal V is computed into the zero-mean V_z and then transferred into positive signal V_z^2 by squaring all signals.

$$V_n = V_z^2 = (V - \bar{V})^2. \tag{A1}$$

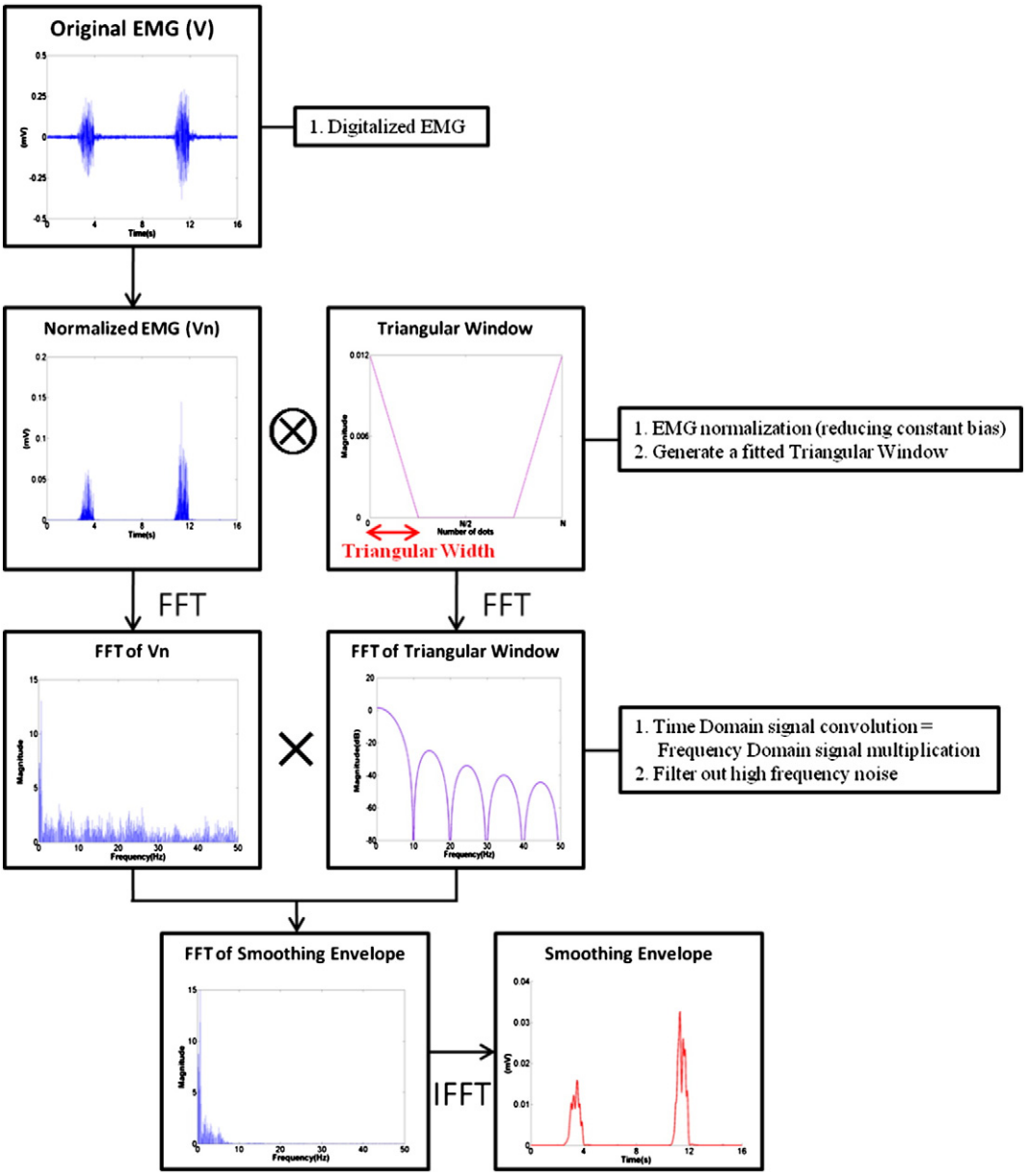

Fig. A1. The Burst Detection Algorithm (BDA) used a triangular window to smoothen the normalized signal in the continuous envelope.

Appendix A.2. Step 2. Smoothening the envelope signals

In this step, the normalized signals V_n are convoluted by a triangular window to reduce the high-frequency noise. The triangular window *T[n]* is represented by the following equation:

$$T[n] = \begin{cases} \dfrac{TW-n}{TW^2} & , \quad 0 < n \le TW \\ 0 & , \quad TW < n < N-TW \\ \dfrac{n-(N-TW)}{TW^2} & , \quad N-TW < n < N \end{cases}. \tag{A2}$$

In order to fit the normalized signals of the phasic and tonic movements, the triangular window *T[n]* is designed with two-sided waveforms whose length *N* is the same as the signals and the half-triangular width *TW*, based on 1 kHz sampling rate, is defined as 100 points (0.1 s) and 500 points (0.5 s), respectively, for each movement. The example of 100 points half-triangular width is shown in Fig. A1. The reserved signals then became smoothening envelope V_s with higher ratio of low frequency information.

$$V_s[n] = \sum_{m=-\infty}^{m=\infty} V_n[m]T[n-m]. \tag{A3}$$

Appendix A.3. Step 3. Detecting and checking isolated bursts

Defined as 0.4 times of the average value of smoothing envelope V_s, the first threshold th_1 is used to detect the start and end points of isolated bursts V_d. However, this threshold is quite small such that some short artifacts are selected as bursts. To eliminate these mistaken artifacts, every isolated burst is double-checked by the second threshold th_2, which is defined as 4 times the average value of the smoothening envelope. The preserved signals are selected by second thresholds as follows:

$$V_d = \begin{cases} V_s & , \quad V_s \ge th_2 \\ 0 & , \quad \text{otherwise} \end{cases}. \tag{A4}$$

The first and last points of each isolated burst higher or lower than the first threshold th_1 are defined as the movement onset (Mon) and movement offset (Moff) of smoothening envelope V_s, respectively. The two time points of sEMG are detected as:

$$\begin{aligned} T_{on} &= \text{first point}\{V_d\} \\ T_{off} &= \text{last point}\{V_d\}. \end{aligned} \tag{A5}$$

The Mon (blue stem with dot) and the Moff (green stem with square) of two movements are detected by BDA (Fig. A2), which shows that the phasic movement has different characteristics in duration and voltage than the tonic movement.

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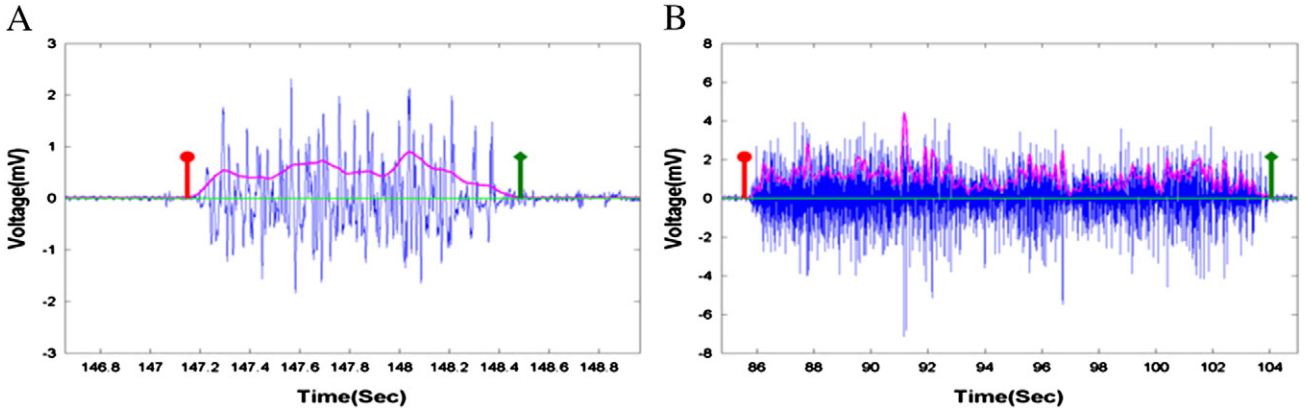

Fig. A2. sEMG burst detection of the (A) phasic and (B) tonic movements. The stem following the purple envelope was Mon (red stem with dot) and Moff (green stem with square).

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